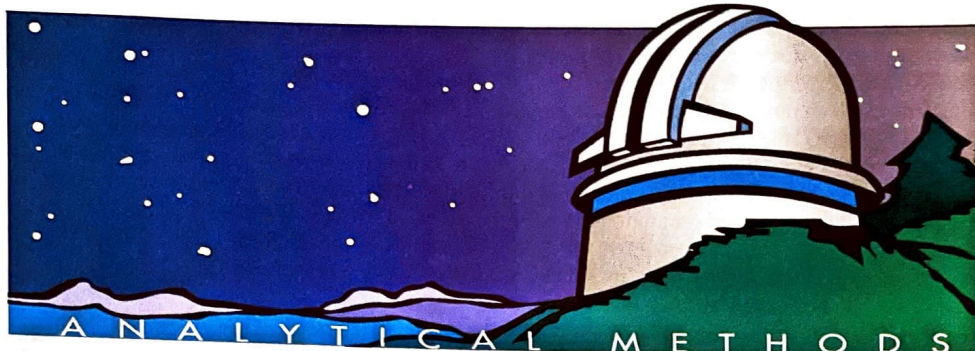


Validation **VIEWPOINT**



Cleaning Validation

Ira Krull and Michael Swartz

This month's column looks at validating cleaning methods for pharmaceutical manufacturing equipment. Krull and Swartz discuss general requirements and specific cleaning procedures, sampling types, and analytical methods.

Cleaning validation is the process of assuring that effective procedures are used to remove residue from pharmaceutical manufacturing equipment. The main rationale for requiring clean equipment is to prevent contamination or adulteration of drug products.

A proper cleaning validation program provides documented proof that a drug manufacturer can consistently and effectively clean a system or piece of equipment.

The required use of clean equipment is not new. Good manufacturing practice (GMP) regulations in place as early as 1963 stated that "equipment shall be maintained in a clean and orderly manner" (1). In 1978, updated GMP regulations included a similar section about equipment cleaning, which stated that "equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product" (2). More recently, the development of highly active drug substances, commonly called potent compounds, has placed more emphasis on cleaning validation to address issues of containment, cleaning, and decontamination (3).

Although several references about this subject are available (4–9), we will introduce the concept of cleaning validation in this month's "Validation Viewpoint" column and relate it to various method validation approaches summarized in previous columns.

GENERAL REQUIREMENTS

In two recent publications, the U.S. Food and Drug Administration (FDA) has outlined certain general requirements for compliance with cleaning validation regulations (see www.fda.gov/cder/guidance/index.htm). Written general procedures about how to validate cleaning processes still must be prepared.

Sometimes called a cleaning validation master plan, this document should address responsibilities, facilities, cleaning strategies, analytical strategies, residue limit justifications, and change control procedures (for more information, see B. Flickinger's "Charting a Course for Cleaning Validation" at www.pharmquality.com/validatn.html). The cleaning validation protocol should describe the equipment to be cleaned, methods, materials, extent of cleaning, parameters to be monitored and controlled, and analytical methods. The protocol also should indicate the collection and sample types (boil-outs, rinses, or swabs) and how they are labeled, stored, and transported to a laboratory for analysis.

During the cleaning validation process, users should evaluate various cleaning agents, the means of measuring residues, and the means for determining drug product-related residues. The accompanying sidebar lists some potential contaminants.

To monitor drug-product residues, companies generally test for the active ingredient. Endotoxin testing also could be performed. Measuring the residue of cleaning solutions can be problematic because they can contain

more than one active component. Analysts can either develop a test for the most abundant component or use a whole-product approach. In the whole-product approach, users must determine whether any residue is present without regard for its origin. A standard whole-product approach assay is to measure total organic carbon, which can reveal virtually every product and cleaning agent residue. High performance liquid chromatography (HPLC) is another commonly used technique (3).

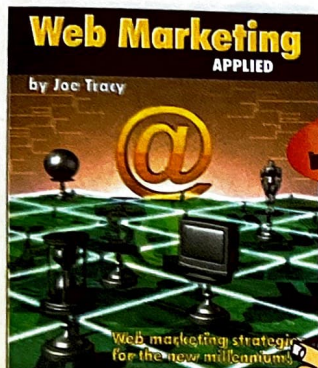
EQUIPMENT CLEANING

Another important consideration is how cleaning is best performed. Equipment can be cleaned by various procedures, including cleaning in place, cleaning out of place, and manual cleaning. Cleaning in place is performed by circulating cleaning solutions through the equipment. Cleaning solutions can be recirculated or drained immediately. When practical or necessary, systems that are cleaned in place should be disassembled during cleaning validation to enable workers to inspect and sample inner surfaces for residues or contamination. For cleaning out of place, whether manual or automated, equipment is removed and cleaned remotely. Although pharmaceutical companies generally prefer automated approaches, human intervention for manual cleaning is still necessary in some instances. Obviously, any time manual cleaning is implemented, personal hygiene is important.

POTENTIAL SOURCES OF CONTAMINATION

- Active ingredients
- Synthesis precursors
- Reaction byproducts
- Degradation products
- Excipients
- Organic solvents
- Microbes (*E. coli*)
- Endotoxins
- Cleaning agents (solvents and surfactants)
- Buffers
- Media
- Lubricants
- Particulates
- Filtering agents
- Residual rinse water
- Environmental dust
- Products of equipment wear

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SAMPLING METHODS

Sampling methods can include swabbing, rinsing, boiling, and direct extracting and should be used as appropriate to detect both soluble and insoluble residues. The sampling method used should be able to quantitatively measure levels of residues remaining on equipment surfaces after cleaning. From the FDA perspective, any direct method for sampling equipment surfaces is the most desirable.

The most common direct-sampling method is swabbing. Users obtain swab samples by wiping surfaces with solvent-moistened cotton gauze. Using swabs, analysts can evaluate equipment areas that are hard to clean but reasonably accessible. They also can determine levels of residue or contamination per surface area. Dried-out or insoluble residues can be sampled by physical removal. It is important, however, to determine that the sampling medium and the solvent used for extraction from the medium do not interfere with sample analyses. For example, the adhesive used in some swabs can interfere with sample analysis (see www.fda.gov/cder/guidance/index.htm).

In some cases, rinsing may be preferable to swabbing. Rinsing can sample a larger surface area as well as inaccessible equipment areas. However, if the residue or contaminant is insoluble in the rinse solution, the cleaning will be ineffective. During validation, therefore, analysts still must examine the equipment using the proverbial squeaky-clean test, not just the rinse solution used for cleaning.

Boil-outs are a variation on rinsing that involves the refluxing of a solvent to clean internal surfaces. Sometimes boil-outs are infeasible for piping and portable equipment. Sprayers and misting nozzles designed for cleaning equipment in place can facilitate the cleaning of hard-to-reach areas.

VALIDATED ANALYTICAL METHODS

Analysts must use validated analytical methods to detect residues and contaminants, and general method validation has been the topic of several "Validation Viewpoint" columns (10-12). The validation of analytical methods used to assay residues and contaminants uses the same principles as those used for validating finished products. In general, equipment-cleaning methods should provide consistent and reproducible results. The quantitation limit for each analytical method should be sufficiently low to detect the established residue or contaminant level.

If the method fails to detect residues or contaminants, it does not mean that they are absent from the sample. The analytical and sampling methods should be challenged to evaluate the level at which workers can determine the compounds of interest. A negative test may be the result of a poor sampling technique.

Analysts also should establish the recovery and specificity of the method. We have described quantitative schemes involving sample spiking to determine recovery elsewhere (13).

Appropriate documentation should be maintained to prove that critical parameters such as time, temperature, turbulence, cleaning agent concentration, and number of rinse cycles are achieved with each cleaning cycle.

Several types of analytical methods can be used to evaluate equipment cleanliness. In general, methods are classified as either residue nonspecific or residue specific. Residue nonspecific methods include total organic carbon analysis, colorimetric assays for protein residuals, UV-vis absorbance detection, and conductivity testing. As mentioned previously, total organic carbon analyses are commonly used because most contaminants contain organic carbon.

Total organic carbon analysis is relatively easy to perform and compatible with most sampling techniques; however, it is not very specific. One potential drawback to total organic carbon testing is that individual contaminants cannot be identified or quantitated. In addition, residues must be slightly water soluble to be detected.

Colorimetric assays, although still classified as residue nonspecific, are more specific than total organic carbon assays. Assays such as the biuret, Bradford, and Lowry tests can quantify proteins in the presence of other organic residues.

UV-vis testing usually can detect compounds in final rinse water samples. Conductivity testing, sometimes performed on-line, is

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useful for measuring inorganic and ionic residues. This technique can detect many buffer and media components and cleaning agents.

Residue-specific methods include U.S. Pharmacopeia (USP) purified-water assays, endotoxin testing, bioassays, thin-layer chromatography, and HPLC. USP purified-water assays include tests for chloride, sulfates, ammonia, carbon dioxide, calcium, heavy metals, oxidizable substances, total solids, pH, conductivity, and total organic carbon. Water assays commonly are performed on rinse samples and are useful for assessing the efficacy of a cleaning regimen. The main disadvantage of USP purified-water tests is that they detect a limited number of inorganic compounds, which also must be water soluble

Also, USP purified-water tests usually are limit tests; therefore, these tests provide no quantitative data.

Endotoxin testing, also performed on rinse water samples, can detect and quantify bacterial cell wall fragments. It can be quite accurate and precise to low levels but is susceptible to interferences.

Bioassays can be used to assess the specific biological activity of a given molecule. This method is the least commonly used residue-specific method for assessing equipment cleanliness because of its time requirements, expense, and high experimental error. Also, it is unlikely that many biologically active compounds remain active, even after a cursory cleaning.

HPLC is a commonly used, residue-specific assay that can detect and quantitate a broad range of compounds — from proteins and peptides to smaller molecules and detergents. It provides the required specificity, accuracy, and repeatability needed for cleaning validation testing.

SETTING RESIDUE LIMITS

The calculation of cleanliness for a piece of equipment is based upon the assumption that all surfaces are uniformly contaminated. In reality, this assumption is not always the case. Residue limits should be practical, achievable, verifiable, and based upon the most deleterious component (for more discussion, see www.fda.gov/cder/guidance/index.htm). Limits can be established based on the minimum known pharmacological or physiological activity of the active ingredient, and these limits must be scientifically justifiable.

Analysts can use several methods or formulas to calculate cleaning effectiveness. These formulas include the 10-ppm formula, the acceptable daily intake formula, and the $1/1000$ of therapeutic level formula (for more information, see reference 3 and www.fda.gov/cder/guidance/index.htm). The 10-ppm formula allows for no more than 10 ppm of cross-contamination between successive products. The acceptable daily intake formula allows no more cross-contamination than what the acceptable daily intake indicates. The $1/1000$ of therapeutic level formula allows no more than $1/1000$ of a pharmaceutical product's minimum daily therapeutic dose into a second product's maximum daily dose. Cleaning criteria usually are based upon the formula that results in the lowest number.

CONCLUSION

Many companies are experimenting with new technology and methods for cleaning and validation, especially given today's more potent and complex biotechnology-derived therapeutics. Emerging trends include more-specific assays, compound-specific (instead of whole-product) cleaning protocols, and increased automation. Many companies also have modified or are moving away from the use of cleaning agents. Water-based cleaning agents that are free of organic solvents or even hot water

alone have become more prevalent. Pressurized rinsing, visualization with fiber optics and video cameras, and more-specific and sensitive detectors for residue assay methods also are being evaluated.

But how clean is clean? By knowing the products, the manufacturing processes, and the ingredients used and their properties, validation experts can all but guarantee a greater probability of success. Simply knowing the basic principles of validation can go a long way toward helping you develop a successful cleaning validation program.

REFERENCES

- (1) *Code of Federal Regulations*, Title 6, "Good Manufacturing Practice Regulations" (General Services Administration, U.S. Government Printing Office, Washington, D.C., 1963), Part 133.4.
- (2) *Code of Federal Regulations*, Title 21, "Current Good Manufacturing Practices for Finished Pharmaceuticals" (General Services Administration, U.S. Government Printing Office, Washington, D.C., 1978), Part 211.67.
- (3) I.I. Valvis and W.L. Champion Jr., *Org. Proc. Res. Dev.* 3, 44-52 (1999).
- (4) S.W. Harder, *Pharm. Technol.* 8(5), 29-34 (1987).
- (5) J.A. Smith, *Pharm. Technol.* 16(1), 60-66 (1992).
- (6) G.L. Fourman and M.V. Mullen, *Pharm. Technol.* 17(4), 54-60 (1993).
- (7) A.O. Zeller, *Pharm. Technol.* 17(10), 70-80 (1993).
- (8) J.A. Shea, *Pharm. Dev. Technol.* 1(1), 69-75 (1996).
- (9) Brian Anglin, Ed., *Cleaning Validation* (Institute of Validation Technology, Royal Palm Beach, Florida, 1998).
- (10) I.S. Krull and M.E. Swartz, *LC-GC* 15(6), 534-540 (1997).
- (11) I.S. Krull and M.E. Swartz, *LC-GC* 15(9), 842-845 (1997).
- (12) I.S. Krull and M.E. Swartz, *LC-GC* 16(10), 922-924 (1998).
- (13) M.E. Swartz and I.S. Krull, *Analytical Method Development and Validation* (Marcel Dekker, New York, 1997), pp. 34-36.

The columnists regret that time constraints prevent them from responding to individual reader queries. However, readers are welcome to submit specific questions and problems, which the columnists may address in future columns.

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