Critical Gaps

DEVELOPING AND OPTIMIZING CLEANING PROCESSES

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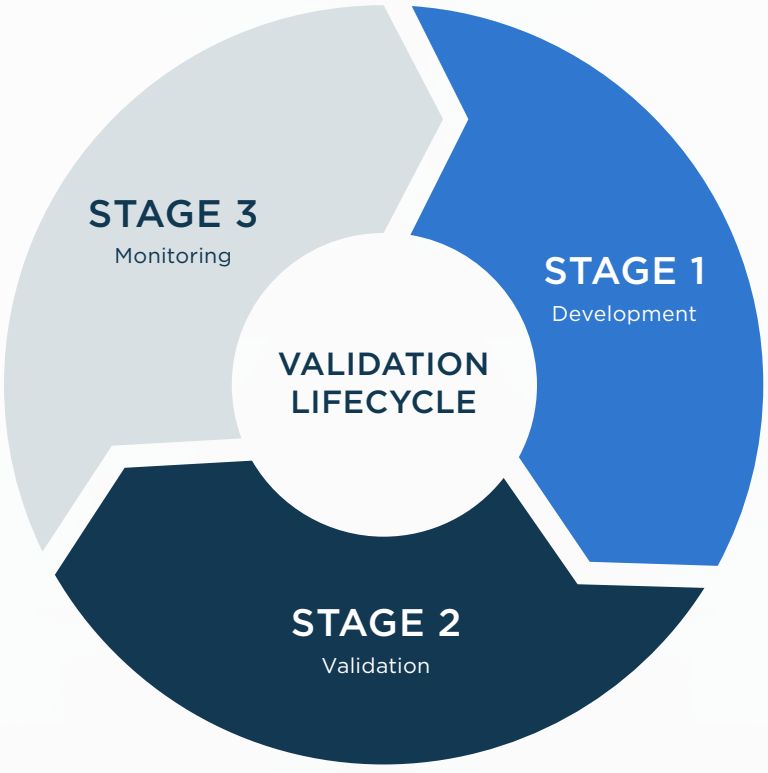
An Introduction to the Cleaning Process

Equipment cleaning in manufacturing companies is often not given the same emphasis as other processes. It can be viewed as a task that does not make the company money, as well as a process that takes away from labor and utilities.

However, effective and compliant cleaning processes are absolutely critical to preventing contamination on equipment surfaces and, ultimately, ensuring patient safety. Issues with equipment cleaning routinely show up on FDA 483 observations and warning letters. Manufacturing companies struggle with poor cleaning processes and the resulting failures including visual, chemical, and microbiological. These failures reflect adversely on the company's reputation, and cost the company the labor, effort, and time they were so desperately trying to save in recleaning equipment, lost production, and investigating the cleaning issues. Most importantly, these failures can have potentially harmful effects on patients.

There is another way to approach the cleaning process: a methodical and common sense one. Truly use the first step in the cleaning validation lifecycle—developing the cleaning process (see Figure 1). Companies often jump right into validating a cleaning process without even thinking about developing it, let alone optimizing it.

Figure 1: Validation Lifecycle



A TACTful Approach to Cleaning Validation

Cleaning validation is one of the most misunderstood areas in manufacturing companies. It is sometimes viewed as a mixture of magic and science, but in truth there is a method to the process. Cleaning validation can be broken down into two main pillars: the carryover acceptance criteria determination and the cleaning process.

For the acceptance criteria, determining what the targets are for the product, cleaning agent, and microbial carryover limits is critical. For product and cleaning agent carryover limits, the industry and regulatory agencies expect that safety-based limits with terms such as Acceptable Daily Exposure (ADE) and Permitted Daily Exposure (PDE) are calculated or rationale is provided for why they are not being used.

Once the carryover limits are determined, the targets are set for the cleaning process. Developmental cleaning should begin in the lab on representative equipment materials of construction (MOCs) or coupons. Cleaning focuses on critical cleaning parameters (CCPs) which are identified by the acronym **TACT**.

TIME: includes dirty and clean hold times, rinse, wash times

ACTION: type of cleaning process such as impingement, soaking, rinse, ultrasonics, manual

CHEMISTRY: cleaning agent(s), concentration

TEMPERATURE: rinse, wash temperatures

A TACTful Approach to Cleaning Validation

In the lab, the representative product(s) is used to soil the coupons in a defined manner. The soil or residue is held for a set time to represent the dirty hold time (DHT).

A cleaning process is simulated that represents the targeted manufacturing equipment cleaning process. The results of the coupon cleaning can be evaluated visually and through water break free testing (looking for a break or occlusions when rinsing the coupon's surface after cleaning). If the product analytical test method exists including swab or rinse recovery, it can be used after coupon cleaning to generate objective data on the cleanliness of the preliminary cleaning methods.

These lab studies can be repeated fairly quickly changing the CCPs to evaluate different parameters. Different cleaning agents tailored to the type of product residue can be trialed using various concentrations. One practical tip is to start simple and add complexity only when the data demonstrates the need. If water alone works for cleaning the product residue, use water.

There is one guiding principle to proper cleaning validation: More complexity doesn't equal more compliance.

Another key item is to document all the manufacturing equipment product contact MOCs including unique elastomers that may be on tanks and vessels. As part of the development phase, compatibility of any planned cleaning agents vs. all the MOCs needs to be researched or tested to ensure there are no issues.

Once the lab trials are complete, evidenced by the identification of preliminary CCPs, the next step is to implement them on the actual manufacturing equipment to further develop and optimize the cleaning processes. One practical technique to do this is to develop the cleaning processes under a cleaning verification protocol.

What is Cleaning Verification?

Cleaning verification is nearly the same as cleaning validation. It has the same product, cleaning agent, microbial acceptance criteria, validated analytical methods and release criteria.

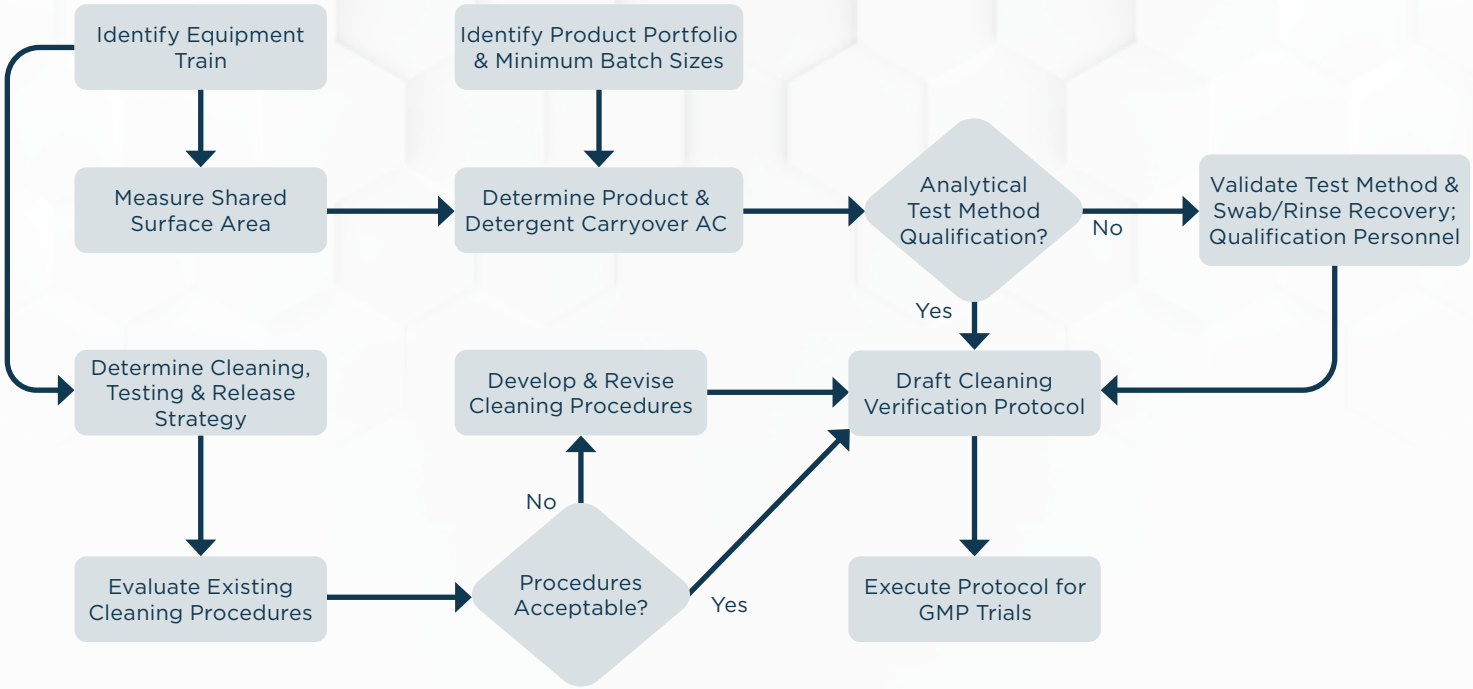
The one key difference is that each cleaning verification trial or process needs to be sampled and tested to ensure it meets the acceptance criteria. Cleaning verification also allows the cleaning process to be altered each time in order for it to be optimized based on the visual and test results. Figure 2 below shows the inputs into a cleaning verification protocol.

The number of trials or cleaning events needed for the cleaning verification process is dependent on the results and how they relate to the carryover limits. If the results are well below the limits, the next question is if the cleaning process is optimized.

An optimized cleaning process typically includes the shortest cleaning and drying times possible to achieve acceptable visual, product, cleaning agent, and microbial test results. Additional times can be added to the optimized cleaning steps if variability in the cleaning process is expected, especially if manual cleaning processes are used. After optimization, a report is typically drafted that outlines the CCPs that will be validated in the next stage using defined cleaning processes outlined in cleaning recipes or standard operating procedures (SOPs).

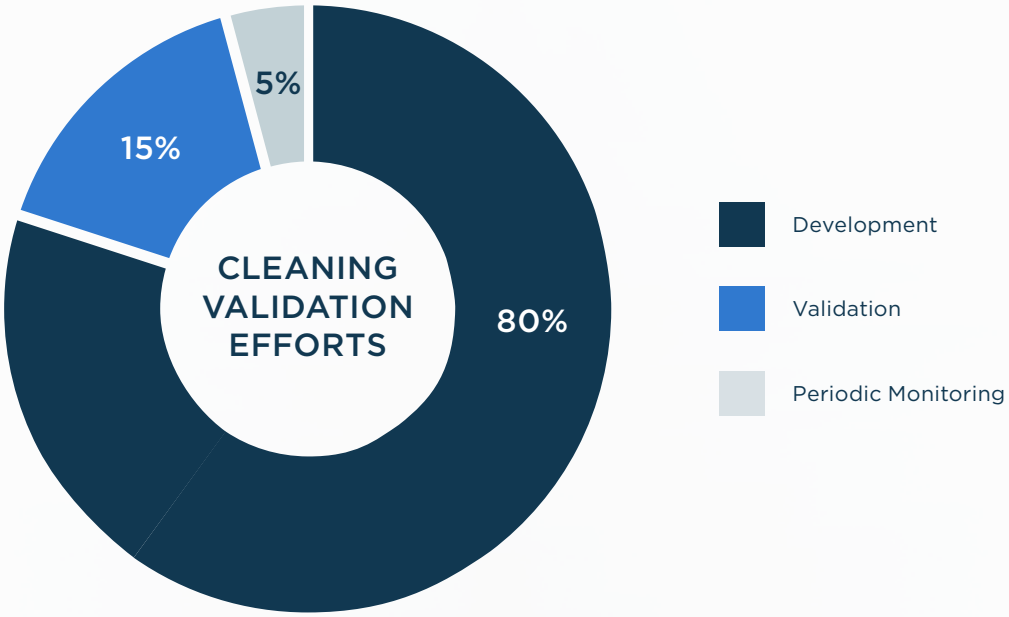
What is Cleaning Verification?

Figure 2: Cleaning Verification Inputs



Overall, cleaning development is the most critical phase in the cleaning validation lifecycle and ironically, it is given the least amount of attention. Figure 3 shows the targeted amount of effort for the cleaning validation lifecycle stages.

Figure 3: Cleaning Validation Lifecycle Targets



Case Study

To further illustrate the practical application of performing effective cleaning development, a recent project is detailed.

A biopharmaceutical client was experiencing manufacturing deviations for visual failures in a filling manifold. This manifold was rinsed after use and then decontaminated prior to full cleaning in an ultrasonic sink. The full cleaning included another manifold rinse, ultrasonic cleaning in one sink and soaking in two other sinks with rinsing in between. No development work was conducted on the products in question.

After receiving the project, the first step was to initiate lab studies involving the representative products. The lab studies used Type 316L stainless steel coupons that were spiked with known levels of product and allowed to dry for defined times. Rinsing trials were conducted using defined flowrates and temperatures. The coupons were visually examined and swab tested using the validated Total Organic Carbon (TOC) analytical method for the products. The lab results allowed for preliminary CCPs to be developed and to proceed to the next step, developmental trials involving the manufacturing equipment.

Through numerous trials under a developmental protocol, it was discovered that the initial flushing of the filling manifold was critical to ensure no residue remained prior to decontamination. If any residue remained on the equipment product contact surfaces, it would be essentially baked on and much more difficult to remove in the subsequent cleaning processes. After optimizing the initial equipment flush step, the residue remaining after decontamination could easily be removed in the subsequent cleaning process. In fact, the original cleaning process was cut in half by eliminating the second manifold flush step and second ultrasonic sink step completely.

The cleaning process that was developed was subsequently successfully validated. The end result was a cleaning process that was optimized (shorter, less water, and easier to execute) and more compliant (no more visual failures). Additionally, the equipment load was revised to better represent the needs of operations: a true trifecta and demonstration of performing effective cleaning development activities.

Conclusion

Implementing an effective and compliant cleaning process is critical to preventing contamination on equipment surfaces, as well as ensuring patient safety.

Despite historically being given the least amount of attention, the development of the cleaning process is the most important phase in the cleaning validation lifecycle. Routine issues with equipment cleaning can lead to lost production time, wasted employee resources, adverse effects on the company's reputation, and potentially harmful effects on patients.

Instead, investing in the development of the cleaning process from the very beginning will save time, money, and labor. By utilizing critical cleaning parameters as well as a cleaning verification strategy during development, manufacturers can effectively optimize their cleaning process while removing some of the complexity from their operation and remaining compliant.

About the Author: TJ Woody

TJ Woody, Director of Cleaning Validation, leads the Cleaning Validation team at Azzur Group and has 30+ years in the pharmaceutical and biopharmaceutical industries—both working for and within manufacturing companies.

His last 15 years have been dedicated to all aspects of cleaning validation from development through validation to periodic monitoring. TJ's hands-on approach takes the theoretical on cleaning topics and makes it compliant and practical for clients.

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