Cleaning Memo for January 2016

Understanding Sources of Variation in Cleaning Processes

More and more as I present training classes I am emphasizing the issue of understanding sources of variation in a cleaning process. For me, the 2011 FDA process validation guidance has been one source of this emphasis. However, it should have been more obvious to me earlier. In its discussion of 2004 pharmaceutical manufacturing in the 21st century, the FDA stated "Quality and productivity improvement share a common element - reduction in variability through process understanding…." In my January 2005 Cleaning Memo, I addressed the issue of process understanding without really going into the reason for process understanding, and that is to *reduce variability*.

Reducing variability involves first understanding the sources of variation in a cleaning process. It then involves reducing the effects of that variability by either controlling the extent of variation or by designing the cleaning process to effectively deal with an extreme (worst-case) condition.

We'll deal with identifying sources of variation first. Here are possible sources of variation (not necessarily exhaustive); the specific ones applicable to your individual situation will depend on your understanding of your cleaning process.

- Operator (for manual steps in cleaning procedures)
- Specificity of cleaning procedures for manual steps
- Types of soils left behind after manufacture
- Manufacturing variations that might affect the difficulty of cleaning of soils
- Nature of surface (type and surface finish)
- Amount of soil left on certain surfaces
- Drying of soils during the manufacturing process
- Baking of soils (and possible degradation) during the manufacturing process
- Dirty Hold Time (DHT)
- Campaign length (number of batches or elapsed time)
- Pre-rinse (pre-wash) conditions
- Wash time
- Wash temperature
- Cleaning agent
- Cleaning agent concentration
- Rinse conditions
- Water quality (for pre-rinse, wash, and rinse)
- Times between various steps in the cleaning procedure
- Impingement (from a spray device, for example)
- Turbulence
- Coverage (contact of cleaning solution with all surfaces)
- Spray devices (including pressure)
- Drying conditions (of cleaned equipment)
- Storage of cleaned equipment (time and location)
- Clean Hold Time (CHT)

If these are possible sources of variation in a cleaning process, how does one reduce variability? There are basically two approaches. One approach is the set narrow ranges for various parameters. For example, can I narrow the range allowed in the wash temperature? Certainly for an automated cleaning procedure, I would prefer not to have a range as wide as ±20°C. Now it is probably not practical to control the temperature to a range of ±1°C. However, it is reasonable in many situations to control temperature to ±5°C. This approach of narrowing ranges of various parameters may be used for things like times, temperatures, concentrations, and times between steps. For certain parameters, the control of variability may be accomplished by specifying a either maximum or a minimum value. For example, for turbulence, there may be a requirement for a minimum Reynolds numbers, but not for a maximum Reynolds number. For DHT and CHT, maximums are usually set, with times less than that maximum considered as having no effect or being easier to clean.

It may not be practical to try to control the amount of soils left on equipment surfaces following manufacture (except perhaps by re-designing the equipment to allow better drainage), so other techniques might be used to reduce the effect of that variability. However, one way to reduce the amount of soils on surfaces is to utilize a pre-rinse with water or organic solvent. The temperature for this is typically ambient, probably because that is what is used in biotech manufacture to prevent setting of protein residues on surfaces. For other applications, a higher temperature may be more effective. The goal of the pre-rinse is to remove as much soil as practical with just flowing water (or solvent), primarily involving physical removal by the flowing stream of liquid. After the pre-rinse, the cleaning situation faced by the wash solution is generally less of a challenge.

The second approach to reduce variability is to design the cleaning process with a worst case variable in mind. To take a common example, if the difficulty of cleaning changes as the dirty hold time (DHT) increases, I design my cleaning process so that it is clearly effective at the maximum DHT, or perhaps at a time that exceeds the DHT. In this way, the cleaning process should be even more effective when used at shorter times than the maximum DHT.

Other cases where this second approach may apply is when I investigate in laboratory studies some of the parameters that I attempt to control to a narrow range. Let’s say I am controlling the temperature to a range of 55°C to 65°C. In a laboratory study, I would prefer to show that cleaning is equally effective at 55°C as at 65°C. In fact, I might also try to show that it equally effective at 50°C so that I can demonstrate the *robustness* of cleaning at the selected temperature range of 55°C to 65°C.

One special case of reducing variability is dealing with manual cleaning operators. Certainly the operator is the most important source of variation in manual cleaning processes. The approach to dealing with this situation is twofold. First is to have adequately detailed cleaning procedures (standard operating procedures or work instructions). The second is to train and retrain operators.

Another special case of reducing variability is by employing PAT principles. In PAT there is an immediate measurement of a parameter that is indicative of process step completion, and that measurement controls the time of that step. For example, in conventional CIP rinsing, rinsing is done for a fixed time (or volume of rinse water). Every time that procedure is used, rinsing will be for that fixed time or fixed volume. As a *monitoring* process, the conductivity at the end of the rinse is measured. In a PAT approach, rinsing is performed until a defined conductivity value is met. The time at which that conductivity value is met is recorded as part of the *monitoring* of the rinsing process. [See the October 2003 Cleaning Memo for more on PAT.]

Note that how you approach the issue of reducing variability in the cleaning process will depend on the specifics of your cleaning process. Next month we'll cover the related issue of reducing variability in the execution of *validation protocols*.