January 2005
Understanding the Cleaning Process

A key issue in the FDA's recent report on a risk-based approach to pharmaceutical CGMPs was that manufacturers should move to a better understanding of their manufacturing processes. A clear statement of this is on page 5 of that report: "Quality and productivity improvement share a common element – reduction in variability through process understanding…." This drive for better understanding of the manufacturing process is part of the basis of PAT (Process Analytical Technology), whereby the idea of validation becomes not "three consecutive runs" but rather "continuous validation".

While the applicability of this to drug manufacturing processes is more straightforward, it also has applicability to the cleaning process. Some possibilities for PAT for cleaning process control were covered in my October 2003 Cleaning Memo. How else is this concept of "process understanding" applicable to cleaning processes?

One commonly used technique is to determine if the cleaning process degrades the drug active, hence making it not analyzable by a specific analytical technique (such as HPLC) for residues of that active. This is a common assumption in biotech manufacture where the active is usually a protein. However, it may occur in other situations as well. How can this be confirmed for a better understanding of what occurs during the cleaning process? Well, there are some simple experiments that can be performed to document this. One is to sample the equipment surfaces in a scale-up run *prior* to the first rinse step. If no active can be analyzed in this process, then either the active is degraded (so it is not analyzable by the specific method) or the cleaning agent interferes with the specific analytical procedure. Another way is to actually perform a laboratory study in which a known amount of active is exposed to the cleaning solution for a time and temperature that simulates real life cleaning exposure. At the end of that time, the cleaning solution is cooled and neutralized (if the cleaning solution is not a neutral pH), and then analyzed for the active. A control should be the same amount of active mixed with an equivalent amount of neutralized cleaning solution. For this control, the effects of high (or low) pH and high temperature are minimized. The issue for the control may still be interference of cleaning agent components on the specific analytical procedure. If that is the case, other analytical tests may be required to determine whether the effect is primarily degradation or primarily interference with the analytical procedure (or a combination of the two effects). Of course, what one is hoping for is that the active survives the cleaning process and can be adequately analyzed by the specific procedure in the presence of the cleaning solution.

Another illustration of the benefit of "process understanding" involves understanding what residues are being cleaned in the cleaning process. Those residues may not just simply be the residues that were originally present on the equipment surfaces. For example, suppose I am in biotech manufacturing and during the cleaning process residues of stearic acid are formed. If I am cleaning with just sodium hydroxide, then I might not be too effective in cleaning those residues in that sodium stearate is an insoluble compound (even though sodium stearate, ordinary "soap", may be a good cleaning agent). A better option in such circumstances may be to utilize potassium hydroxide as a cleaning agent, since potassium stearate is water soluble. For clarity, it may be possible to clean effectively with sodium hydroxide; however potassium hydroxide offer a better route of effective cleaning.

Another simple example of process understanding involves a recent study that was mentioned in my October

2004 Cleaning Memo. This study was done by scientists at Merck and Drexel University, and the objective was to determine the worst-case product (most difficult to clean) by lab experiments measuring the change in conductivity of the cleaning solution over time. While the focus of the article was on selecting the worst-case product, a secondary feature of the study was that it also demonstrated that conductivity of the cleaning solution might be an effective PAT technique. What leads to this conclusion is that the authors were able to establish that at the time that conductivity leveled off, the spiked coupons were also effectively cleaned (as measured by TOC or ICP). This understanding of the dynamics of the cleaning process could lead to a control of cleaning processes not by time, but rather by achieving a certain conductivity end-point. Again, this is a case of a better understanding of the cleaning process possibly leading to a significant benefit in process control.

The point of this Cleaning Memo is not to limit types of process understanding that might benefit pharmaceutical and medical device manufacturers, but rather to encourage manufacturers to explore more fully what is occurring in a cleaning process, and then to use that knowledge to design more effective and more efficient cleaning processes, as well as simpler ways to validate those processes.