**October 2003**
**PAT and Cleaning Validation**

Surprise!! This month's Cleaning Memo is not what was listed last month. That topic, "Correlation of TOC with a Specific Analytical Method?" will be covered in November. The reason for this change is the release of the draft guidance from the FDA entitled "PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance". Since this was a topic I covered briefly in some seminars, I thought it useful to address how PAT could be used for cleaning processes.

PAT, an acronym for Process Analytical Technology, is (according to the FDA guidance) "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw materials and in-process materials and processes with the goal of ensuring final product quality". As illustrated by the FDA, it may involve processing to an end-point other than a time-based end-point.

How can PAT apply to cleaning processes? Traditionally the cleaning process has been defined as complete based on a time end-point (for example, "rinse for ten minutes"). That time end-point is usually determined in scale-up studies that measure some attribute of the rinse solution that is indicative of completion of rinsing. Conductivity is an example of an end-point when the cleaning agent is a highly conductive solution. The end-point of rinsing is a return to or near the baseline rinse water conductivity. In scale-up studies, a time is determined to be the minimum time to consistently be at or below that selected conductivity. That time is then written into the cleaning procedure.

If PAT principles were applied, it is possible to specify the end-point of rinsing not as a completion of a minimum time, but rather as achievement of that selected conductivity in the final rinse water. Will this be acceptable to regulatory agencies? It should be, provided that the defined end-point is selected and justified carefully. One might, for example, not just determine the end-point as reaching a certain conductivity, but rather reaching and staying at or below that conductivity for 60 seconds.

If reaching a certain conductivity end-point in rinsing is to be the technique to define the completion of rinsing, this does not mean (as clearly pointed out in the FDA guidance) that the time of rinsing is not important. Rather, a range of acceptable rinsing times (a "time window") should probably be considered in the rinsing procedure. In other words, if one found that ordinarily one could achieve an acceptable rinse conductivity in a time of ten to fifteen minutes, would one be concerned if this were achieved in only one minute? Or if it was achieved in as long as sixty minutes? Both of these extreme cases suggest that something is out of control with the rinsing process. In the very short rinse, it may be that there was no cleaning agent present in the wash solution (although if that was the case, hopefully it would be picked up by other process control techniques). The extremely long rinse time might have been caused by a clogged spray device, for example. In either case, a rinse time outside the "normal" window requires some investigation.

In one sense, defining rinse completion by conductivity and then verifying that the rinse time is within a window is a "backwards" version of what should be done under traditional processing, which is defining rinse completion by time and then verifying that conductivity is within a window. In both cases, we are measuring time and conductivity. However, in one case we use conductivity as the end-point and then verify that time is

acceptable; in the other we use time as the end-point and then verify that conductivity is acceptable.

This illustration of using conductivity in rinsing is just meant to be illustrative. There may be other end-points that can also be justified.

Another example of a PAT technique for cleaning processes is in the solvent cleaning of an API. For example, if methanol were used as the cleaning agent for an API train, the methanol may be recirculated through the equipment not for a fixed time, but to a fixed end-point as defined by some analytical technique, such as UV spectroscopy. As the methanol circulates and dissolves the active, the absorbance due to that active increases until it reaches a maximum. At that point, all the API has dissolved (of course, it is necessary to determine that a maximum has not been reached because of solubility limits). Once the maximum absorbance has been reached (and maintained for a fixed time), then that step is complete, and the equipment can be drained, and rinsing can commence. It may also be possible to set the number of methanol rinses not at a fixed number, but at a number required to obtain a certain UV absorbance.

It should be noted that PAT is a technique for controlling and defining the cleaning process. Cleaning validation for appropriate cleaning processes can then follow as it usually does.

The purpose of this Cleaning Memo is to promote the investigation of PAT for improving cleaning processes. It is highly recommended that the FDA draft guidance be carefully reviewed before implementing PAT for cleaning processes. However, the simple examples presented here are probably relatively straightforward in terms of implementation in a PAT framework.