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More on Using Rinse Sampling Alone

Several months ago I discussed the option of using rinsing sampling alone for cleaning validation protocols. The purpose of this Cleaning Memo is to possibly explain why this could be a valuable option to consider, as well as why there may be objections to that approach. I believe the main reason why there appears to be a problem with this approach is related to changing technology – dealing primarily with the design of equipment. Regulatory agencies require that the equipment being used for drug manufacture be designed for cleaning. For example, CFR 211.63 states that "Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance."

In the 1980's, when the principles of cleaning validation were being developed, it was common for process equipment to be designed so that it could be disassembled for effective cleaning. Under that scenario, it made sense to perform swab sampling. After all, the equipment was taken apart and cleaned manually. Critical surfaces were readily accessible for swabbing. Since swabbing allows for the possibility of swabbing the worst case locations (those most difficult to clean, or most likely to have higher levels of residues after cleaning), it made sense that swabbing was a key part of a cleaning validation protocol.

What has happened in the meantime is that for many types of process equipment, the equipment is designed differently. The equipment is designed to be cleaned by an automated CIP (clean-in-place) process. Note that in this case, the equipment is still designed for cleanability. It's just that the cleaning process is different. Instead of being designed to be taken apart for cleaning, the equipment is designed to be cleaned without disassembly. All the good things that make equipment well-designed for cleaning by a manual process (such as gasketed and clamped parts for disassembly) are precisely those things that make equipment difficult to clean by a CIP process.

Unfortunately, there appears to be a belief by some that swab sampling is a requirement for a cleaning validation protocol. While swab sampling makes sense for equipment that is disassembled for cleaning, it does not necessarily make sense for equipment cleaned by a CIP cleaning process. The act of opening up a complex system, such as bioreactor which has been designed for CIP cleaning, to perform swab sampling may be more of a concern for possible contamination of the system than is reliance solely on rinse sampling.

The value of CIP cleaning can be illustrated with an example from the dairy industry. After all, the principles of CIP cleaning were first developed in the dairy industry before they were applied to the pharmaceutical industry. One of the main advantages of CIP cleaning was that switching from disassembly, manual cleaning, and then reassembly to an automated CIP process extended significantly the shelf life of milk. Why was this the case? It is believed that recontamination of the equipment during re-assembly was the culprit. If an analogy can be made to the pharmaceutical industry, there may be more concern about opening a system up to perform swab sampling (and then reassembling) than there is to depend solely on rinse sampling.

Of course, what this means if we depend solely on rinse sampling is that we are more reliant on our riboflavin coverage testing and good engineering principles to assure coverage of the cleaning solution over all parts of equipment surfaces. It also means that scientifically justified residue limits must be established for rinse

samples. And it further means that rinse recovery studies must be completed for sampling.

Another reason that there is resistance to rinse sampling alone is that there is a belief that regulatory agencies don't like rinse sampling. While the FDA guidance document on cleaning validation does state that swab sampling is "more desirable", both the FDA and the European (PIC/S) guidance documents say that both swab and rinse sampling are acceptable methods of sampling. I believe part of the reason that there is a belief that regulatory agencies don't like rinse sampling is that, particularly in the early days of cleaning validation (and even extending to the present), there have been pharmaceutical manufacturers who have misused rinse sampling. The main misuse has been the idea that if my incoming rinse water meets the compendial specs and my final rinse water also meets compendial specs, my system is clean. The ironic thing is that this is explicitly mentioned as unacceptable in the FDA cleaning guidance document (in 1993!!!!), and yet I still hear people who want to use this as the only criterion for acceptability of rinse samples.

The purpose of this Cleaning Memo is certainly not to require rinse sampling alone for cleaning validation protocols, but to indicate that it should be an option if it is used correctly.