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Understanding the Cleaning Process in 2010 (and Beyond)

In January 2005 I wrote a Cleaning Memo entitled "Understanding the Cleaning Process". That Cleaning Memo was in response to the FDA report on risk-based approaches to pharmaceutical CGMPs. At the end of that Cleaning Memo, I encouraged 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." That encouragement is even more important now, based on the 2008 FDA draft process validation guidance (which reportedly will be finalized in the first quarter of 2011) that defines "design and development" as the first stage of the validation process.

Understanding what is happening in the cleaning process (which also includes what is happening in the equipment *soiling* process) is a key to using these new principles to more effectively and efficiently implement cleaning validation. One of the least quoted sections of the 1993 FDA cleaning validation guidance is in Section IV ("Evaluation of Cleaning Validation") where the statement is made that "Answers to these questions may also identify steps that can be eliminated for more effective measures and result in resource savings for the company." This statement, in which the FDA is suggesting "resource saving", is made in the context of questions such as "… at what point does a piece of equipment or system become clean? Does it have to be scrubbed by hand? What is accomplished by hand scrubbing rather than just a solvent wash? How variable are manual cleaning processes from batch to batch and product to product?" Now don't think for a minute that the FDA wants "resource savings" so that your firm can be more profitable. I don't know what the FDA's reason for this statement was in 1993, but in 2010 the reason is clearly that the FDA is concerned about costs of drugs to consumers.

So, when the FDA is encouraging the industry to look for "resource savings", why are some of us still doing things the way we did in 1993 when we had more limited information of what was happening in our cleaning processes? What are some things that we can do based on a better understanding of the cleaning process?

Well, one example is the ISPE RiskMaPP approach to dealing with highly hazardous drug actives (such as actives that might be genotoxic, mutagenic, or teratogenic). While I criticized (in my November 2010 Cleaning Memo) the RiskMaPP document for the way it critiqued previous methods of setting limits, the fundamental approach in that RiskMaPP document of setting health-based limits for highly hazardous actives (as opposed to previous approaches of using dedicated equipment or requiring that limits be set as non-detectable by the best available analytical technique) is an good example of using knowledge of the cleaning process to enable these highly hazardous actives to be manufactured in the same facility or on the same equipment (with appropriate controls in place).

Another example is understanding what is happening during the dirty hold time (DHT). The traditional approach has been to require a challenge of the maximum time during a validation protocol. However, it is clear (at least in some cases) that an increase in time does not change the difficulty of cleaning. In other cases, the difficulty of cleaning may increase with time up to a certain point (for example, when a liquid is "dry"), and then not change after that. An evaluation of how to approach the DHT will depend on our understanding of how the diffculty of cleaning might change over time. That means not only understanding the nature of drying, but also whether bioburden proliferates during the DHT and whether degradation of the active is

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accelerated during the DHT. Of course, the approach now should be to understand those factors, and design the cleaning process with those factors in mind, such that the challenges are addressed during the design/ development stage rather than during the qualification protocol.

A third example is dealing with campaign length, where so-called minor cleaning (such as vacuuming or a water flush) is performed between batches, and a validated cleaning process is only performed at the end of a campaign. The question comes up, what if the campaign is sometimes 5 batches and sometime 7 batches? Do my qualification protocols have to be at the maximum campaign length? Well, absent any information on the effect of campaign length on the diffculty of cleaning, it makes sense to perform a qualification protocol at the end of the maximum of 7 batches. If only production scheduling would cooperate by providing those number of batches for the required number of validation runs, it might be easy. However, scheduling is not always that nice; plus there might be a time when they want to run 8 batches in a campaign. What can be done?

Well, the secret phrase in the above paragraph was "absent any information on the effect of campaign length on the diffculty of cleaning". Is there information or data I can obtain from laboratory or developmental studies, or from "sufficiently similar" products or processes, that might allow me to determine the effect of campaign length on diffculty of cleaning? Particularly if I can demonstrate that campaign length has no effect on difficulty of cleaning, performing my qualification protocols after just one batch may be adequate. Again, this may also involve determining information such as bioburden proliferation and/or degradation of the active as a function of campaign length.

There are other approaches to understanding the cleaning process which were discussed in my April 2008 Cleaning Memo ("What Have We Learned in the Last Two Decades?") that also can be considered. The issue is this – if a pharmaceutical manufacturer is to thrive in the coming decades, the approach of new drugs with significant advantages is still the primary objective. However, low cost (but meeting current CGMP) production should be a secondary, but vital objective.

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