January 2011

More on Campaign Length

Last month I gave one example related to "understanding the cleaning process" that deals with campaign length. I said if there is adequate evidence that campaign length (defined as number of batches and/or elapsed time) has no effect on the difficulty of cleaning, then performing all qualification runs after just one batch may be adequate to deal with cleaning after any campaign length. For clarification, I am not talking about campaigns in biotech manufacture, where a fully validated cleaning is usually conducted after every batch in a campaign (probably for process consistency reasons, more so than for safety concerns about residue carryover). An example of a campaign that would be relevant for this discussion is manufacture of multiple batches (or lots) of a solid oral dose product on a tablet press (where perhaps only vacuuming of equipment is done between successive batches/lots).

What can happen during a campaign to make cleaning more difficult? The product may become dried or compacted on equipment surfaces, thus making it more difficult to clean. Bioburden may proliferate as a function of time, changing the nature of the residues to be removed. Actives may degrade due to extended exposure of the product to heat, light and/or air. This list of possible changes is not meant to be exhaustive, but rather illustrative. Vacuuming or water flushing between batches is partly an attempt to minimize possible changes. Measuring bioburden or degradation products and performing visual examination over a campaign (that is, after every batch in a campaign) can help determine whether these are significant problems. Such data may also provide clues as to whether time or number of batches is more critical.

What if the campaign length is truly variable? How can I determine how to proceed on the qualification runs? One option is to perform qualification runs after only one batch. The number of runs will be determined by company policy; however, for purposes of illustration, I will use three runs as the required number of runs. The residue data is collected after each of the three runs. That data is used to support the claim that "the cleaning process is validated". Despite the statement that "the cleaning process is validated", we should realize that under a life cycle approach, validation is never completed (at least until the cleaning process is discontinued), since ongoing process controls (what the FDA has called "continued process verification" in its draft process validation guidance) is one phase of validation. The next time I manufacture that same product (perhaps immediately after the three "qualification runs"), I then proceed to manufacture in a campaign mode, most likely with the number of batches in the campaign determined by requirements other than those of the validation group. Let's assume for purposes of illustration, that an additional three batches are to be made in a campaign mode (with minor cleaning between batches, and the previously validated cleaning process performed at the end of the third batch). After that "full" cleaning process, I collect my samples for residue testing. Once I obtain the results, I then compare the data after three batches (I have one run for this) with the data obtained after one batch (I have three runs for this). If the data is essentially the same (I will have to establish predetermined criteria for determining whether the data sets are the same or different), then I have a rationale for claiming that the studies I have performed support that the cleaning process is validated for cleaning after up to three batches.

What else can happen in this situation? Well, another possibility is that the residue data after three batches

passes my acceptance criteria, but is not "essentially the same" as the data after one batch. What this suggests is that there may be changes in the difficulty of cleaning as the number of batches manufactured increases. It probably is not possible, without additional data, to confirm that cleaning after three batches is validated. However, it is possible to release the equipment for subsequent manufacture based the fact that the residue data is below the acceptance criteria (that is, the acceptance criteria for residue levels, not the acceptance criterion to determine equivalence between data after three batches and data after one batch).

There is one additional possibility, that the data after three batches exceeds the residue limits. In this case, it is clear that cleaning is not only more difficult, but also unacceptable, when done after three batches. There are now two considerations. To release the equipment I must perform additional cleaning and retesting of the equipment (in a cleaning verification mode) to establish that it can be safely released for subsequent manufacturing processes. Second, I must consider whether the second and third manufactured batches can be safely released. This will depend on several things. For example, it might be affected by the nature of what residue criteria were not met. Was it the level of the active, level of the cleaning agent, or level of bioburden? If it was just the cleaning agent that failed, then that failure was not relevant to the quality of those two batches (since cleaning agent was not used in the process immediately before manufacture of those batches)? If it was a high level of the drug active, and if all product specifications were met, then I may only be concerned with batch comingling, which would be an issue anyway if all I was doing was vacuuming between batches. If the failure was bioburden, then I would want to more closely evaluate manufactured product for bioburden quality, particularly since any high bioburden levels could be transferred preferentially to a small portion of a manufactured batch. If the failure was due to a high level of degradants, then I should approach the manufactured product the same as for bioburden. In reviewing the data for release, remember that my acceptance limits were probably established based on transfer of residue to a different product as a worst case, not necessarily to the same product. Therefore acceptability of transfer to the same product may be considered as part of any evaluation of the acceptability for release of batches made prior to the failing residue data.

Another option for validating a campaign is to perform the required number of qualification runs (let's assume again that the number is three) on whatever campaign lengths are possible for those three runs. For example, the first campaign might be five batches, the second campaign might be four batches, and the third campaign might be six batches. If the residue data is acceptable after each of those campaign lengths, the some companies might consider that the shortest (four batches) of the three campaigns lengths is the validated number (using a criterion of "the shortest of the three longest acceptable campaign lengths"). Of course, it is then possible to extend this by performing an additional qualification run after at least five batches; success with that run would then allow the validated campaign length to be extended to five batches (based again on the criterion of "the shortest of the three longest acceptable campaign lengths"). However, if any campaign length gives failing results, then the effect not only on the validation effort, but also the equipment and product disposition must be considered.

This discussion of campaign lengths is not meant to exhaust all possibilities. However, it should provide a framework to consider other possibilities.