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What's Happening to Revalidation?

At the recent PDA annual meeting a representative of the FDA mentioned that in the upcoming FDA revised process validation guidance the term "revalidation" will no longer be used. What's behind this move? And will it apply to cleaning validation?

The latter question is probably easier to consider. Cleaning is a just another manufacturing process, and the principles of process validation certainly apply to validation of a cleaning process. The first question is the more interesting one, and the answers provided below are my best guess as to the rationale for the change. However, if you have kept up to date with the FDA's thinking for the last five years, the rationale is clearer.

First, "revalidation" for cleaning processes has meant one of several things. One is a yearly confirmatory protocol, usually a single run. This has been more common on fully manual cleaning processes (as opposed to fully automated cleaning processes) because of the concern about control and variability with manual cleaning processes. A second is a yearly review of all relevant data for a given cleaning process to document that the cleaning process is still in a "state of control". Relevant data may include routine monitoring data, change control data, deviations, training records, and quality records for products. A third use of revalidation is a validation protocol on a significant change in the cleaning process. It is perhaps this last use of revalidation that is of most concern. When I make a significant change in the cleaning process and perform a validation protocol, in one sense I am not revalidating the old cleaning process. What is really happening is that I am validating for the first time a new cleaning process (even though the new process may have many elements of the old process, if I have made a significant change, it really is a new process). So, it is reasonable that we drop the term "revalidation' for this third case.

What about the other two situations? They are still activities worth doing (or at least activities worth considering).What could the concern be? Well, it's probably related to concern about revalidation (or for that matter validation) being a one time activity. It is clear that what we typically call cleaning validation (IQ, OQ and 3 PQ runs, or at least traditionally 3 PQ runs) is not all there is to cleaning validation. Based on numerous regulatory documents, there is more to validation than this. One is the various design elements that go into selecting a cleaning process, including "prevalidation" studies. This is one reason why three validation runs, which has no statistical support for demonstration of consistency of a cleaning process, is still the most common requirement for cleaning validation (despite recent FDA changes, based on PAT, that three is no longer the "magic" number). The reason for this is that what demonstrates consistency is not just the three PQ runs, but also all the various prevalidation studies that were also done. (Note: Perhaps this is a part of the problem, in that we view these studies as before the validation and not part of the validation effort.) Furthermore, consistency is further demonstrated by the post-PQ validation data that is collected (such as the data reviewed for the yearly "revalidation" review).

Now, what is more relevant, to have a yearly review of data (a one time activity once a year) or a continuous review of data (such as trending charts and alerts)? By "continuous", what I mean is something more regular, like every batch, perhaps with a monthly summary. Certainly we don't want to wait until year-end when we could have discovered a potential problem much earlier by having a "continuous" data review. I actually believe that many companies do this continuous review, even though they still have a formal, "once a year"

data summary (since I am not aware of a situation where a pharmaceutical manufacturer evaluated data at the end of a year and was surprised by a problem).

What about the situation with manual cleaning? Isn't it still required to have a yearly protocol run? Actually, this is not a regulatory requirement, but it is a response that many manufacturers choose to address regulatory concerns with the variability of manual cleaning processes. For example, the PIC/S document states that manual cleaning processes should be "reassessed" on a more frequent basis. What does "reassessed" mean, for it is not clear from the PIC/S document itself? As I've said, one way to deal with this is to have a yearly "revalidation" run (or as I prefer to call it, a "confirmatory" run). Is this the best way to assure consistency for a manual cleaning process? Some might suggest it is all we can do for manual cleaning, because we don't have the automatically recorded process monitoring that is possible with an automated cleaning process. On the other hand, one thing that is often overlooked is the importance of a visual observation following cleaning as part of (or perhaps the main part of) routine monitoring for manual cleaning. Particularly in cases like a manual scrub where all surfaces are readily accessible for visual examination, this can be a powerful tool. I'm not suggesting here that visual examination alone should be used for measuring residues in a protocol (although that certainly is possible). What I am suggesting is that the major concern with manual operators is inconsistency in coverage of scrubbing (or brushing) the surfaces. If this occurs, then it usually can be picked up by visual examination after the cleaned surface is dry. It will be apparent as streaks of residue on the surface, with the streaks corresponding to patterns that would occur if overlapping, consistent cleaning actions were not used. Again, the purpose of visual examination in this monitoring function is not to say that the residues are below any calculated limit, but rather to be an indicator of inconsistent cleaning practices. As I generally repeat in my training seminars, the purpose of the validation protocol is to determine that the cleaning process, if done correctly, will produce residues below the acceptance limit. The purpose of routine monitoring (and this is true for either automated or manual cleaning processes) is to establish that the cleaning process is performed correctly (or to give an early warning that it may be performed incorrectly).

So, where does this leave us with the "revalidation" issue? First, if the FDA is abandoning the term for process validation, it would be prudent to also consider abandoning the term (although I realize that this might be a slow process for the industry). Second, when we make a significant change to a cleaning process, just refer to that as "validation". As with any other validation, the old cleaning process might have valuable data that helps provide assurance that the new cleaning process will perform consistently, so there is not necessarily a hard disconnect between the old and new processes. For example, the clean hold study that was done for the old process might still be applicable as a clean hold study for the new process (if the condition of the equipment at the end of each cleaning process and the storage conditions are essentially the same). Third, our focus on a "yearly" review should probably change to a "regular" review, which could be continuous (with perhaps a monthly summary). This is consistent with the FDA's emphasis on lifecycle approaches to validation (Design, Formal Validation Studies, and Ongoing Controls) as well as to continuous improvement for manufacturing quality and efficiency.