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Selecting the Number of Validation Runs for Equipment Grouping

I must be getting crabby now that I'm on Medicare. This month's Cleaning Memo is on another subject where I see some bad ideas that won't go away. This concerns the number of validation runs (PPQ runs if you like the new FDA process validation terminology) required for equipment grouping where the equipment in the group is identical. Under the assumption that I must do a minimum of three validation runs for a protocol, my view has been that in an such an equipment grouping approach, I would do three validation runs unless I had a rationale for doing more than three. What I am seeing (and have seen) is that some people suggest (or require) three validation runs on one equipment item in the group, and then one confirmatory run on every other equipment item in that group.

Let me illustrate the difference with examples. First, let's make sure we all understand the situation. I have multiple equipment items that are identical by IQ (installation qualification) and OQ (operational qualification). [I generally modify that somewhat by saying that the requirement is they be identical for cleaning purposes by IQ and OQ. They may different in a way that does not impact the cleaning process. However, for this example, I am assuming they are identical in every way by IQ and OQ. That is not to be taken so far as to say the IQ and OQ were performed on different dates, and that makes them different.]

So, let's suppose I have three identical equipment items. My view has been that I will do a total of three validation runs on any combination of equipment items. The combination I prefer is one run on each of the three items. However, if scheduling is such that this is not practical, then I would accept two runs on one item and one run on a different item (meaning that no validation runs were performed on one item). I would even allow for all three runs to be on one item; but that would not be my preference because of the possible perception that I was really "cherry picking", and in fact I knew that I was more likely to get good results on this one particular equipment item.

What I sometimes see in this situation (of three identical equipment items) is a requirement that three validation runs be performed on one equipment item (in order to satisfy the "rule of three" for validation purposes), and that one validation run is performed on each of the other two items in the group. That is, a total of five validation runs are performed.

Using this same approach (three validation runs on one equipment item and one validation run on every other identical item in the group), one would perform a total of seven validation runs there were a total of five equivalent equipment items. I have also seen a situation where the proposal (NOT my proposal) to deal with about 100 identical equipment items was to perform three validation runs on one item and one validation run on each of the other 99 items.

Is such an approach acceptable? My answer is yes, it is acceptable. Is such an approach required? My answer is a definite NO. If I have clearly established that the items are identical, what is the value in doing at least one validation run on every member as well as three validation runs on one item? Unless there is something unusual about the situation, it appears to be a waste of resources. It also tends to call into question the basis for establishing the equipment group, that is, that each member of the group is identical by IQ/OQ. Do I really have confidence that the items are identical? If not, and I consider them as different, then my approach should

not be three runs on one item and one run on every other item. Instead, it should be three runs on every item (at least on the assumption that I do a minimum of three runs for each validation).

But, you might say, based on the FDA Process Validation guidance, aren't we getting away from the requirement that we do three validation runs (or a minimum of three). Yes, that is true to an extent. However, if you believe that, why the requirement that I must do three runs on one item and one run on every other item? Doesn't a risk-based approach say that I might be able to do less (that is, a total of three runs, using any members of the group for those three runs).

Another analogy for addressing this situation is what we do for small parts. If I am processing a number of small parts in a parts washer (or even by manual cleaning), do I require that for validation purposes, I perform three runs on one specific part and one run on every other identical part? If I am washing valves, and I have six identical valves, I have never heard a company say, "We'll do three runs on one valve and one run on every other valve, for a total of eight validation runs". Even if only three validation runs are done and all six valves are cleaned in one cleaning process, it is generally not the practice that I must sample every valve in each of three validation runs.

The purpose of an equipment grouping approach is to utilize process understanding and a risk analysis to focus efforts on those cleaning validation activities that improve compliance and improve efficiency. While the focus on efficiency from the company perspective might be to make the company more profitable, a more realistic view is to maintain profitability. Regulatory authorities should also have a view to more efficient processes from the perspective of costs of drug products to consumers. For clarification, I am not saying to sacrifice quality and safety for the benefit of more efficiency. What I am suggesting is to use process understanding and a risk analysis to make the process more efficient while maintaining or improving quality and safety. One way to do this is to approach equipment grouping on this basis, rather than trying to utilize a "checklist" mentality.

A final clarification. Why do I suggest doing three validation runs on any combination of three equipment items in an equipment grouping approach for identical equipment? Maybe one run or two runs on any combination of equipment items would suffice? Shouldn't I be more flexible, and allow a company to select the number of runs (based on the approach in the FDA Process Validation guidance)? My response is that I would do three runs (and not one or two) based on business considerations. When I do a grouping approach, I am putting more "eggs" in one "basket". Because I am applying these validation runs to a larger "basket" of equipment items, I would prefer to do a little more than I might otherwise do in order to minimize business risks. Remember that any cleaning problem on one member of the group calls into question cleaning validation for all members of the group.