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Defining Three "Consecutive" Runs

Another question I commonly get is "What constitutes three consecutive runs for cleaning validation protocol purposes?" The basic approach to answering this question is to use the same principles one uses for process validation. If I am validating a blending process in a certain manufacturing vessel, do the three validation runs have to be one after the other, with no intervening product being processed? Or, in between the three manufacturing processes for the validation, am I allowed to blend other products? Most people would agree that the latter is appropriate for process validation. The rationale behind this is that the *first three* processes should be evaluated. If I were to evaluate, for example, only lots 1, 3 and 7 for blend uniformity, I might be asked whether I was selecting certain lots because I knew I could get better results, or that I selected them because they are all on the first shift. For this reason, the general practice is to require that once I have started the first validation run, the next two process runs should be included as the additional two runs needed to make a total of three consecutive validation runs.

This same principle should be applied to cleaning validation. Once I have started my first cleaning process for the validation protocol, then the next two cleaning events *which qualify under the protocol* should be the two additional validation runs to make a total of three. If I am doing cleaning validation on the cleaning of Product A, what this means is that once I have started the validation of one lot of Product A, there may be other products that are made (for example, Product B or Product C) before I get to the second lot of Product A for cleaning. And, there may be other products manufactured and cleaned between the cleaning of the second lot of Product A and the cleaning of the third lot of Product A. What would *not* be allowed would be to start the validation with one lot of Product A, and then to skip one or more lots of Product A before I started cleaning of the second validation lot.

The question may arise as the effect of the interspersing of other products between the cleaning events for a specific validation. Well, there are two possible responses. One is that interspersing other products reflects a real life situation. Certainly the process should be rugged enough to *not* depend on the previously made product (that is, the product made before the cleaned product). In addition, those interspersed products themselves should have cleaning validation on them so that the equipment is appropriately clean following those cleaning process (if not, this is a serious deficiency as far as *comprehensive* cleaning validation is concerned). Finally, those interspersed products are important for setting limits for the validation protocol, but they should not be such that they would affect cleaning of the subsequently made product.

Are there any exceptions to this? One possible exception is where the criteria for a run for the validation protocol cannot be achieved by three consecutive runs. For example, suppose I had a process which involved manual cleaning, and one of the criteria for the three runs was that each cleaning run should be performed by a different person. Perhaps the scheduling was such that I could not include three consecutive runs in the protocol without using the same operator twice. If this is the case, perhaps one could make a case for skipping a lot. However, even in this case it would be better to either reschedule operators so that I could utilize a different cleaning operator on each of the three consecutive runs or to perform four consecutive runs, with two of the runs having the same cleaning operator. Either of these alternatives avoids the issue of appearing to select runs to get better results.

Another possible exception might be in medical device manufacture, where I am trying to have different runs reflect the possibility of changes in the cleaning process as the ultrasonic solution is used. For example, I might want one run to be with a fresh solution, one run to be with a solution where 50% of the daily device load has been cleaned, and one run at the maximum number of cleaned devices for that day. Clearly in this situation, I would want to make sure devices were cleaned in between the three validation runs so that it represented a significant challenge to the ultrasonic cleaning process. However, in that case, it may not be appropriate to include every cleaning done in between the three runs included as part of the validation protocol. Perhaps to alleviate concerns here, it may be possible to include as intermediate runs cleaning process of devices which are not the worst case, or some similar strategy. It should be realized that this is being done for compliance reasons.

If situations like the above possible exceptions are present, it is also better to address the strategy upfront in the protocol, so the basis for the selection of the three runs is seen as a planned process, and not an attempt to avoid situations which might cause failures.

It should also be pointed out that if the three "consecutive" cleaning runs follow one another without any intervening cleaning of a different product, that situation is okay too. Certainly for dedicated equipment that is the only situation one faces. However, in multi-use (multi-product) equipment, the three consecutive runs may be "interrupted" by manufacture and cleaning of a different product.