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How to Completely Avoid Doing Cleaning Validation

Some of you might have thought the title of this Cleaning Memo was some kind of April Fools joke. Others might have thought it was dealing with single-use (a.k.a. disposable) equipment. Well it's actually about doing "cleaning verification" in place of "cleaning validation". Cleaning verification (a "one-time" determination of cleaning effectiveness) is commonly used for situations like cleaning for clinical trial materials and cleaning after deviations. But, can it be used for something that I am manufacturing on a regular basis, where there is an opportunity to perform cleaning validation? My answer is "Yes". Why is that the case? Shouldn't we follow the general rule that "If it can be validated, it should be validated"?

Well, let's look at the purpose of cleaning validation. The ultimate purpose is to demonstrate that equipment which has been cleaned can be safely used for manufacture of another product (or a batch of the same product). How can I demonstrate that my equipment is suitable for manufacture of a product? One way is to perform cleaning validation. That is, I demonstrate that the under certain assumptions regarding the nature of the next product (primarily batch size and daily dose), that my cleaning process consistently produces equipment with acceptable residues from the cleaning process. Once I validate it in my qualification runs, I then only have to perform validation maintenance ("continued process verification" per the new FDA process validation guidance). That validation maintenance generally does not require that I perform extensive testing of residues on surfaces on a continuing basis.

What happens if I am determining the effectiveness of my cleaning process using cleaning verification (not to be confused with "continued process verification")? I am going to perform extensive testing of residues on surfaces after every execution of a cleaning process. If I do that, haven't I demonstrated that the equipment can be safely used for manufacture of another specified product? In other words, I have achieved what is essentially the same objective.

Okay, I may have convinced you that cleaning verification achieves the same objective of equipment surfaces that are suitable for manufacture of another product. What about the rule that "If a process can be validated, it should be validated". After all, if I am making a product once a month, it is certainly feasible that I can validate that cleaning process. My answer is that that rule is appropriate for manufacturing process, but may not be applicable to cleaning processes. How is that the case? In a manufacturing process, it is generally accepted that one cannot "test" quality into a product. In other words, I just don't depend on the product meeting finished products specifications. If I am only making one batch, there is a Human Drug CGMP (September 1997) about validation for a "bio-batch". That document states:

> "At early clinical stages, where a single batch of drug product may be produced, and where significant formulation and processing changes may make batch replication difficult or inexact, only limited process validation may be possible. In such cases, limited validation, especially for such critical processes as sterilization, should be derived, to the extent possible, from product and process analogs. In addition, data obtained from extensive in-process controls and intensive product testing may be used to demonstrate that the instant run yielded a finished product meeting all of its specifications and quality characteristics. It is expected that more comprehensive process validation will be conducted as additional uniform batches are made under replicated conditions
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> You may apply these principles to the bio-batch process and cleaning validation. We would expect

adequate cleaning to have been performed and documented and that in-process and end product testing would show instant lots to meet specifications."

In other words, for the manufacturing process I need "intensive" product testing and "extensive" in-process controls, but for cleaning I need only perform and document that I have "adequate" cleaning. In other words, there is a distinction made here between manufacturing processes and cleaning processes. Why is that the case? The FDA doesn't give an answer, but I will give you my answer. For a manufacturing process, if I mess up and the product doesn't meet my specifications, then the product must be destroyed or otherwise disposed of. For a cleaning process, if I clean and the equipment surfaces don't demonstrate acceptable residues, what happens? I certainly don't destroy or dispose of the batch of product immediately preceding the cleaning process (the exception to this is if failure of the cleaning process causes me to investigate whether that failure was related to something unusual in the manufacturing process). What happens for a "bio-batch", where I am using cleaning verification, is that I clean the equipment again and measure residue again (until I eventually get acceptable results). In other words, the implications of an ineffective process are different for a manufacturing process as compared to a cleaning process. If we extend this principle (implications of an effective process) to processes that are done repeatedly, I think you can understand why I say cleaning verification may be used for cleaning processes that are performed on a repeated basis.

But, you may ask, why do cleaning verification when I can do cleaning validation and not have to perform extensive testing of equipment surfaces on a continuing basis? The answer is partly a business decision and partly a scientific decision. For example, if I am cleaning drug products with a "highly hazardous active" in multiproduct equipment, I may decide that the risk of inadequate cleaning (even though it is a validated cleaning process) is an unacceptable risk in terms of patient safety (and consequently profitability). Another reason I may choose to verify every cleaning event is that it may be easier to meet acceptance criteria because I only have to set limits based on the product made next in that cleaned equipment (and not on every possible "next product"). This may be a particular benefit where analytical method limitations do not allow me to measure at the calculated limit based on all possible products being the next product. I also don't have to limit myself to the minimum batch size of the next product; in a verification mode I can utilize the actual batch size of that next product batch for my limits calculation. This avoids the situation where my limits are very low because the manufacturing instruction for a product gives a range of batch sizes. In that case, I am not "stuck" with the minimum possible batch size; I use the actual batch size if I am in a verification mode.

If I operate in a cleaning verification mode, I would prefer to have residue data for the cleaned equipment before I start production of the next product. However, I may start production of another product before that data are available, realizing that I am doing so "at risk". If the residue data are unacceptable, I may have to reject that product which was manufactured in that inappropriately cleaned equipment.

Issues such as dirty hold time are also not applicable in a verification mode. I must demonstrate acceptability of the cleanliness of the equipment under whatever the dirty hold time might be. However, clean hold time is a valid issue. Just because I demonstrated that the residues were acceptable at the end of the cleaning process does not mean that storage conditions are necessarily acceptable. So, some thought needs to be given to how to address this situation.

Some of you might object and say that regulatory authorities expect cleaning validation to be done. That is true, but it is not a regulatory requirement (at least for the FDA). Here is what is stated at the beginning of FDA cleaning validation guidance document:

> "Note: This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does no confer any rights, privileges, benefits, or immunities for or on any person(s)."

Newer guidance documents will generally have more elaborate wording, such as this from the 2011 process validation guidance:

> "This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations."

What is the appropriate regulation for the FDA for cleaning validation? One of the main citations for cleaning validation issues is 21 CFR211.67(a), which states:

> "Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

I would argue that cleaning verification for a cleaning process that is done repeatedly may meet this GMP requirement.

Remember, that in cleaning verification, I am still going to establish limits as I would for cleaning validation (but those limits will be based on the actual parameters of the next product). I will still perform analytical method validation and still do recovery studies. And I will still select appropriate sampling methods, including worst case locations for swab sampling. So it is probably not the case that costs will be reduced. However, I do avoid some of the issues of validation maintenance (such as trending of data and performing an annual cleaning validation review).

Some of you might not accept these arguments. That okay; you will continue to perform cleaning validation. For some of you (such as a generic drug product manufacturer that produces dozens of products on shared equipment), the thought of doing cleaning verification on every cleaning event just doesn't make sense. However, for some of you (particularly those who are already performing cleaning verification every time where cleaning validation is possible), these arguments may resonate.

Let me also clarify that even though I have stated publically many time that the FDA process validation guidance can (and should) be applied to cleaning processes, I have always modified that by saying it should be applied "as appropriate" for cleaning validation. Those of you that have attended my webinar on the FDA process validation guidance, as well as those of you that have heard my recent training seminars, realize that I make this distinction. And the arguments presented here should also clarify some of the differences between manufacturing processes and cleaning processes.

The purpose of the Cleaning Memo is not to advocate for cleaning verification in place of cleaning validation for cleaning processes that are performed repeatedly. It is to illustrate why it might be an acceptable alternative.