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Revisiting "Cleaning Verification"

This is a follow-up to my November 2009 Cleaning Memo on "continued process verification" and "continuous process verification". You might notice that I am putting the term "cleaning verification" in quotes. The reason is that for cleaning validation purposes, "cleaning verification" has a very specific meaning. It is not just any verification that is done. For example, some people like to talk about a "revalidation" run (yearly, for example) on a cleaning process as a "verification" run. That may be appropriate (although I prefer the terminology "confirmatory" run), but it is not what I mean when I talk about "cleaning verification". Other people like to talk about "verifying" the residues in a cleaning validation protocol. That also may be appropriate (although I prefer the terminology "measuring" the residues), but it is also not what I mean when I talk about "cleaning verification".

So, what exactly is "cleaning verification"? I would define it something like this: "A one-time process for determining the effectiveness of a cleaning process for a specific cleaning event. " In this sense, "cleaning verification" should be contrasted with "cleaning validation". "Cleaning validation" is a process for determining the effectiveness and consistency of a cleaning process for defined products and equipment. If cleaning validation is considered in light of the new FDA Process Validation guidance, the validation process is (in one sense) never complete. You design the cleaning process, and then you qualify it (qualification involves what we used to call "validation runs"). Then you maintain the state of control through what the FDA refers to as "continued process verification" (not to be confused with "cleaning verification"). What I mean by cleaning validation never being complete is that the control measures for each batch following the qualification run(s) add to the supporting data for saying the cleaning process is validated.

While cleaning validation is never done, "cleaning verification" is a one-time activity. It may be repeated multiple times for an "equivalent" cleaning process, but here is what I mean by "one-time" activity. The data that is generated from a "cleaning verification" study is applicable only to that one cleaning event it is associated with. From a scientific perspective, data on one cleaning event may suggest that you will get similar data if you were to repeat that cleaning event in the future. However, from a compliance perspective, the data developed on one cleaning event does not apply to future identical cleaning events for which cleaning verification is to be done. For those of you wondering if three "cleaning verifications" on the same cleaning process constitutes "cleaning validation", my answer is generally "No" (at least not without additional support evidence). This was discussed in my Cleaning Memo of August 2008. I believe it even more so following the redefinition of "process validation" in the November 2008 FDA Process Validation guidance.

So what is done in "cleaning verification"? Many of the same things that are done in cleaning validation protocols (or qualification protocols, if we want to adopt that terminology). You have a cleaning SOP; however, as compared to a cleaning SOP to be validated, there may not be a lot of design and development for the "cleaning verification" SOP. You establish limits for critical residues. However, in contrast to cleaning validation protocols, for "cleaning verification" protocols it is only necessary to consider the residues in light of the immediately manufactured next product. You need to have analytical methods and sampling methods. However, as compared to cleaning validation protocols, the analytical method may just be a "pass/fail" method, as opposed to a method which measures the exact amount of residue in the samples. Recovery studies are also required, but the recovery study for a pass/fail analytical method is slightly different.

In a "cleaning verification" protocol, there may be deviations in the cleaning process that occur. However, these may not be fatal to the "cleaning verification" exercise, because the key thing is whether acceptable residue data is obtained. Furthermore, if a "cleaning verification" protocol fails (that is, the residue limits are exceeded), then it is perfectly acceptable (from a compliance perspective) to clean again and test for residues again. This process may not be desirable from a manufacturing efficiency perspective, but it is (or should be) allowed. This is one reason cleaning process SOPs associated with "cleaning verification" protocols may be "over-designed" (to the extent that they are "designed"), so that passing residue results are obtained the first time.

When can "cleaning verification" be used? It certainly can and should be used for any one-off cleaning situation, like a one-time manufacture of a clinical trial material or like cleaning after a deviation (such as a clean hold time that has been exceeded). It can also be used for any cleaning process which is done infrequently, such as cleaning after a batch manufactured only once a year.

For cleaning processes repeated frequently, it usually is an expectation that cleaning validation be done. There is an old rubric that says "If a process can be validated, it should be validated". Now part of the reason for that is that validating a frequently repeated process usually makes good economic sense. However, there does not seem to be a good logical reason why "cleaning verification" couldn't be done for every cleaning process that could be otherwise validated. After all, in process validation for the medical device industry, it is a well established practice that if a process cannot be 100% verified each time, then the process should be validated. The clear implication is that validation is not required if you do 100% verification. So it may be something to think about for pharmaceutical cleaning processes. I realize that this goes against "Quality by Design" principles. However, let's not lose sight of our objective. Our objective is not to use QbD principles; our objective is to produce safe and effective products meeting quality specifications.

One last comment about "cleaning verification". While "cleaning verification" is in contrast to cleaning validation, it still should be considered part of your cleaning validation program. In other words, it should be included in your cleaning validation master plan, cleaning validation policy, or cleaning validation quality standard (or whatever you call your high level cleaning effectiveness document). Under that high level document, you might have separate procedures for "cleaning validation" and "cleaning verification". However, they should be tied together at the top. If you prefer to call "cleaning verification" something different in your documents, that certainly is okay provided that a clear definition is given. (I will point out that "cleaning verification" as I have described it is presented to the FDA Basic Drug School when I train that group.)

The purpose of this Cleaning Memo is to neither encourage nor discourage the utilization of "cleaning verification". The purpose is to make sure we understand what it is, and how to utilize it appropriately.