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“Continued” vs. “Continuous” Process Verification

“Continued process verification” is a term used in the November 2008 FDA Process Validation Guidance. “Continuous process verification” is a term used in ICH Q8 (R2) Pharmaceutical Development. They sound similar, but are they really referring to the same thing? I believe it is clear they are two different concepts; however, because they sound similar, we must be careful about their use and make sure we use each correctly.

“Continued process verification”, as presented by the FDA, is a part of process validation. Specifically it is the third stage of process validation, following “design and development” (the first stage) and “process qualification” (the second phase). In this third stage, things are done to provide ongoing assurance that the process stays in a state of control. Activities covered by “continued process verification” include things like routine monitoring of process parameters, trending of data, change control, retraining, and CAPA (corrective and preventive actions). In part, this concept was included to replace the concept of “revalidation”, whereby one or more validation runs were repeated on a regular basis. I believe the rationale was this – “What is more relevant for determining that the process is still in a “state of control”: a single confirmatory validation run performed once a year, or the various ongoing activities such as routine monitoring, change control and the like?” Given the choice between the two, I would maintain that the ongoing activities were more relevant, and would more likely discover a problem on a more timely basis. Note that some may argue that both are needed, the ongoing activities and the yearly confirmatory run. While I would argue that this is the case for manual cleaning procedures, for automated cleaning processes the yearly validation run provides little added assurance of control (provided that the ongoing routine processes demonstrate control).

What then is “continuous process verification”? It is defined in Q8 as “An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.” The important word here is “alternative”. “Continuous process verification” is not a “part of” process validation (as in the FDA description of “continued process verification”). Rather “continuous process verification” is done in place of process validation. I believe this concept is related to PAT (Process Analytical Technology), where the conventional process validation concepts are not applicable. In PAT we are verifying each time that the quality attributes are being met.

I also believe this concept of “continuous process verification” is related to the medical device distinction between validation and verification. The FDA’s medical device QSR (Quality System Regulations) states “Where process results cannot be fully verified during routine production by inspection and test, the process must be validated according to established procedures”. This is also reflected in the GHTF (Global Harmonization Task Force) document on process validation SG3/N99-10 (2004) that calls for processes to be verified if it is verifiable each time and such verification is sufficient to assure quality. Otherwise the GHTF document calls for the process to be validated.

So, why do I bring up these terms on a web site devoted to cleaning processes and cleaning validation? The reason is that in cleaning validation we also have a concept called “cleaning verification”. Cleaning verification is a one-time activity whereby for a unique or seldom performed cleaning process, we determine acceptability of that cleaning process (that specific event). From a compliance perspective, that determination of acceptability applies only to that specific cleaning event. Cleaning verification may be used in cases such as

cleaning for clinical material trial materials, cleaning after deviations, or cleaning where there is infrequent production.

The important thing is to make sure we understand the terms consistently, and not intermix the terms. In other words the FDA's "continued process verification" is distinct from "cleaning verification", and in no way excludes the acceptability of "cleaning verification". In my comments submitted to the FDA about the 2008 process validation guidance, I pointed out that perhaps a better term for what they were describing might be "ongoing process control" or "continued process control", just to try to avoid the confusion with how "verification" is used for certain pharmaceutical cleaning processes and within the medical device community. However, I also realize that the same term can be defined differently for different technologies, so I am not expecting any change in this usage by the FDA.

However, it should be recognized that the concept of "cleaning verification" is consistent with the ICH Q8 definition of "continuous process verification", because in cleaning verification the determination of acceptability is performed for each and every cleaning event. However, there is no element in cleaning verification of "continuous", because it generally is applied to unique cleaning events. That said, it should also be recognized that a cleaning process which is repeated on a regular basis could conceivably be verified each time, provided of course that determination of acceptability is adequate. As a practical matter, however, most pharmaceutical companies would prefer to validate a process which is repeated on regular basis, primarily based on efficient use of resources.

Okay, where does this leave us? Just with the concern that in using terms like "cleaning verification", "continued process verification" and "continuous process verification", we must be aware that just because the term "verification" appears in all three terms, they are not equivalent. Care must be used in making sure that the definitions are clear, and the application of those terms is appropriate.