August 2008
Do Three Verifications Make a Validation?

The traditional approach to validation, including cleaning validation, is to perform a minimum of three validation runs. Of course, there is no statistical justification for three runs being acceptable. It is just something that pharmaceutical manufacturers and regulatory authorities have agreed on. In some regulatory documents (for example, the European PIC/S PI 006-03) it is written as a minimum of three runs. Based on previous communications from the FDA and the talked about (but not yet released) new FDA process validation guidance, the requirement for three validation runs is being replaced, probably by a statement that the manufacturer should decide on the required number of validation runs. Because of this, some manufacturers are changing their high level documents to read something like "three validation runs or a different number if appropriate". That "different number" may be more than three or less than three.

Verification protocols are protocols for one-off (unique or one time) cleaning events. Most companies would validate a cleaning process if that option were practical. However, for cleaning for clinical trial materials or for cleaning after deviations (such as exceeding the dirty hold time), a cleaning verification is appropriate. Some companies have chosen to treat verification runs such that if three verifications are done for the same product, the same equipment and the same cleaning process, then the cleaning process can be considered as validated (for that product and for that equipment). When this has been done, it is usually the practice that this be allowed (permitted) in the high level cleaning validation document for that company. Furthermore, when it is done, there usually is a validation protocol written at the same time the initial cleaning verification protocol is written to cover that possibility. Note that in this case, the three verification protocols may not or may not be performed, so there usually should be some kind of time limit for completion of the three verification protocols. If not completed on a timely basis, then the "umbrella" validation protocol should be closed out.

All of this is preliminary to getting to my main point, which is whether this practice is justified. Like a good consultant, my answer is "It depends". If the three verification protocols are runs without any other support data, then my opinion now is that it is not appropriate to consider the cleaning process validated. This is a change in my opinion. What has caused me to change my opinion is that in my training seminars on cleaning validation, I usually emphasize that it is not just the three validation runs that demonstrate consistency of the cleaning process. It is also all the prevalidation work (including design, lab studies, and scale-up studies) that helps support any claim about the consistency of the cleaning process. (Although not specifically related to this discussion, all work following the three validation runs also supports any claim of consistency.) Therefore, it is probably not appropriate to state that three verification runs (absent any pre-verification or other supporting studies) is a clear demonstration of consistency. For that reason, my opinion now is that three verification runs alone do not constitute validation.

A key word in that last statement is "alone". It is not likely that extensive pre-verification studies would be done for a cleaning process that might be used only once. There may be limited studies, but remember that in a verification mode, if a failure occurs, then it is perfectly okay to clean again and retest until the acceptance criteria are met. Certainly recleaning and retesting is not a preferred mode; I would generally prefer to overdesign the cleaning process in a verification mode such that I met the acceptance criteria after the first cleaning event. However, this is clearly a situational decision.

If I do not have extensive support data on that cleaning process on that product and on that equipment, another possibility is to leverage data on related cleaning processes. For example, if I were in biotech manufacture and had successful cleaning validations on a variety of proteins using a certain cleaning process, I might leverage that data and use that to support the contention that three verification runs on a new (but similar) protein using the same cleaning process and similar equipment would constitute successful cleaning validation. Another situation might be in tablet manufacture. I believe it is generally true in tablet manufacture that it is the difficulty of cleaning of the excipients that determines the difficulty of cleaning of the final formulation. If that is the case, then successful validation of a variety of formulations might be used to leverage the contention that a new, but similar formulation, is validated based on three verification runs. If this is done, then this should be something that is allowed in the manufacturer's high level documents.

The purpose of this Cleaning Memo is not to specify how to handle such verification runs, but rather to discuss issues relevant to how three verification runs might be considered as successful validation.