Cleaning Memo for January 2019
The Value of a Protocol Worksheet for Manual Cleaning

In a protocol for pharmaceutical cleaning validation, there are generally many worksheets associated with that protocol. For example there might be a worksheet for entering sampling locations and ID numbers, with the time and date of sampling, along with the initials of the sampler. There might be a similar worksheet for analytical results, including analytical results for actives and cleaning agents, microbial results for bioburden, and results for visual examination. However, one worksheet that is particularly important for *manual cleaning* is a worksheet for the *execution* of the manual cleaning process. This worksheet is *an independent verification* that the manual cleaning process was performed correctly.

The worksheet would be completed not by the cleaning operator, but by a second person (perhaps from a validation or quality assurance department) who observes the manual cleaning process from the beginning to the end. That observer uses a worksheet with a list of specific actions or steps to be taken by the cleaning operator. That list of specific actions should closely follow the specific actions given in the SOP of the cleaning process to be validated. As each action is done correctly, the observer checks off that the action was completed correctly (or not), perhaps giving any additional comments as to what was not done correctly or possible ways to improve the written cleaning SOP.

You might ask why an independent verification is necessary, since the cleaning operator himself or herself documents that the cleaning process was done correctly in the cleaning log. Shouldn't the cleaning log be enough? Well, let's step back and remember that we are talking about a *manual* cleaning process. An independent verification has value in several situations in a protocol. For review, the purpose of the protocol is to establish that *if the cleaning process is done correctly*, I will obtain acceptable residue results. What happens in a manual cleaning process if I don't have an independent verification that the cleaning process was done correctly and I end up with *failing* residue results? Where do I look for the root cause of the failure? Was it the analytical group who did something wrong in the lab? Was it the sampler who made a mistake? Did the cleaning operator not follow the SOP? Or, was the cleaning process just a poorly designed cleaning process? All those are possibilities, but inevitably a sharp eye is usually cast on the cleaning operator. Besides the operator saying "I followed the SOP correctly", how can that that last concern be investigated?

Well, one way is to have an independent verification to confirm whether the cleaning process was done correctly or not. In a sense it protects both the integrity of the protocol and the *integrity of the cleaning operator*. If there are failing results and the observer confirms that the operator did everything correctly according to the SOP, then that should eliminate the operator as the root cause. The investigation should perhaps focus elsewhere, including the design of the cleaning process. If there are failing results and the observer notes where the operator performed a step incorrectly or omitted a step, then that helps identify an attributable cause, and the cleaning protocol run can be considered

not a failed run, but rather an *invalid* run. Of course, the fact that it is invalid may be small consolation, because that operator (and perhaps all operators) has to be trained again with an emphasis on what went wrong; then a new protocol run can be performed.

There are two more possible outcomes in addition to those two. The third situation is that the results are passing and the observer confirms that the cleaning process was done correctly. In that case, everyone is happy. The fourth situation is that all results are passing, but the independent observer notes that the operator did something wrong or different. Whoops! No one is smiling in this situation, because this is something like the situation where I get failing results and the operator did something incorrectly. There may be some cases where I might be able to say that the incorrect action by the operator did not affect the validity of the protocol. For example, suppose the SOP called for a 1% concentration of the cleaning agent, and only a 0.5% concentration was used. While I might accept that as a valid run, I would still have to do some retraining (and perhaps a change to the SOP to clarify how 0.5% cleaning agent is prepared). There may be other situations where the incorrect action of the operator may have made the cleaning process more robust. For example, using the same example of the cleaning agent concentration, it might be that the operator prepared a 2% concentration instead of 1%. In that situation, the higher concentration might have been the cause of the acceptable residue results.

With all these possibilities, you might think it would be preferable to emphasize better cleaning process design *and* better training of manual cleaning operators, and just skip having an independent verification of the cleaning process. Certainly better design and better training is *very desirable*. The purpose of the independent verification is to deal with situations where the cleaning protocol doesn't go as planned. It can be considered part of the "belt and suspenders" approach used in many aspects of pharmaceutical manufacturing. Certainly that type of independent verification can be helpful in a *manual* cleaning protocol.

Some might object that "Of course the operator will perform the cleaning SOP correctly if another person is closely watching the operator. But when the protocol is complete and cleaning is done routinely, who's to say the operator performs the SOP correctly". My answer to that possible objection is that as a validation specialist, I want to protect the integrity of the validation protocol, and having an independent verification can help with that. It gets back to what I said earlier, that the purpose of the validation protocol is to confirm that *if the cleaning process is done correctly, then I will get acceptable residue results*. If after completion of the protocol, the operator does not perform the cleaning process correctly, then the responsibility (or burden) for that falls with the production supervisor (or the production department). But that issue of correct performance of the cleaning SOP on a routine basis is something that is a possibility whether or not an independent observer is present during the validation protocol runs.

Some might be wondering whether an independent observer is needed for an automated cleaning process. If the cleaning process is a fully automated process like CIP cleaning, then it is *not* necessary to have an observer confirm that the operator selects the correct cycle and pushes the correct button(s). For an automated CIP skid, all those things, as

well as information like times, temperatures, pressures, flow and conductivity, are captured by the CIP skid itself. Therefore, if something goes wrong with the residue results, those operational parameters can be checked to confirm whether there was a problem with the cleaning process itself. If there are manual aspects to automated cleaning, there may be value to an independent observer confirmation. For example, in a parts washer the loading configuration may be something to be independently observed. For things like transfer panels for CIP cleaning, if there is an automated confirmation of correct placement (or if incorrect placement is not possible), there may be little value in having an independent observer confirm correct placement.

Finally, the question sometimes comes up as to whether an independent observer using a manual cleaning worksheet should tell the operator immediately when the operator is doing something *incorrectly*. There are two views on this. One is to immediately tell the cleaning operator of the mistake, so that it can be corrected without compromising the protocol, or so that the protocol run can be discontinued. The other is to let the operator continue, with the view that if a mistake was made at one step, let's try to see if the operator performs other steps incorrectly (trying to capture all the mistakes the first time rather than finding another mistake in a second protocol). Both views have some merit.

Let me be clear that a second person verification of correct performance of a *manual* cleaning process is *not* a regulatory requirement. However, most regulatory guidances emphasize the *variability* of manual cleaning processes and the need for more attention paid to such processes. A cleaning process worksheet used by an independent observer is one way to help address that extra attention.