Cleaning Memo for June 2019
Deviations and Nonconformances

Following up the last month's Cleaning Memo, this month we will cover another example where clarity in use of language might help. It deals with the similarities and differences between a "deviation" and a "nonconformance". How these are defined and how they are handled for cleaning validation purposes might vary among different companies, and those differences might be okay as long as the terms are used appropriately and consistently within that company.

As I use the term, a "deviation" occurs when a *procedure* is not carried out correctly. For example, if the wrong cleaning agent or the wrong cleaning agent concentration was used for a validated cleaning process, that would constitute a deviation – what should have been done (according to the cleaning process SOP) was *not* done or was done *incorrectly*.

As I use the term, a "nonconformance" is when the result of some *analytical data* (such as chemical, microbiological, or visual) is outside of a specified limit or acceptable value. For example, in a protocol my acceptance limit for the rinse sample for TOC is 1.2 ppm. My measured value is 2.7 ppm. That rinse result is considered a nonconformance because it is above my limit value.

Now there are similarities between deviations and nonconformances. Both are things that are "bad" and are things that cause headaches for cleaning validation scientists. I would like to avoid both. Furthermore, a nonconformance in meeting limits may be caused by a deviation in the execution of a cleaning SOP (although there may be situations where I exceed my protocol limit but there is no related cleaning process deviation, perhaps because the cause is poor design of my cleaning process). I also may have a deviation in the cleaning process during protocol execution that does not result in a nonconforming residue value, because my cleaning process was a robust design with significant overkill designed into the SOP. Note that in this last situation, I might have deviation in the cleaning process with no accompanying nonconformance of the residue value, perhaps because of a deviation in the analytical or sampling methods which led to lower residue values.

In the discussion above, while it is possible that a deviation (for example, in the cleaning procedure, in the analytical procedure, or in the sampling procedure) may cause a nonconformance in the measured residue value, it is *not* the case that a nonconformance in the measured residue value may cause a deviation. A clarification here is necessary; it may be the case that a nonconformance *caused* me to go back and investigate what was done in the cleaning, sampling and analytical procedures, and that investigation caused me to *discover a deviation* that I was not previously aware of. However, it would probably *not* be inappropriate to suggest that the nonconformance *caused* the deviation.

The next question is what to do when there is a deviation and/or a nonconformance. We will only discuss this in the context of a *protocol* (although the principles might apply to

other situations). There are several possibilities here. We can have a procedural deviation *without* a nonconformance for residue values, or a non-conformance for residue values *without* an identified deviation, or a procedural deviation *with* a nonconformance for residue values. For the first situation, we will want to find out the root cause of the deviation and select corrective actions (see discussion below) to keep that deviation from happening again in the future. Then we will want to determine the impact of that deviation on the validity of the protocol. Realize that it *might* be the case that the deviation did not affect the validity of the protocol (such as when the cleaning process temperature was slightly below the specified range); with the successful residue results we might accept that protocol run as a valid (and successful) run. On the other hand, if our conclusion is that the deviation might have helped in meeting the residue limits, then we might say that it is not a failed run, but rather an invalid run. In that case, we would still take corrective action to make sure that specific deviation did not occur again, and continue protocol runs until we had three successful consecutive runs.

The second situation involves no identified deviation with a non-conformance in residue results. Bad luck! Unless you can identify a lab error using your OOS (Out of Specification) procedure, the only reasonable conclusion is that you cleaning process was not robust enough to have consistent passing results (that is, this is a failed run). In this situation, it is probably best to go back to the design phase. This may mean actual changes in targets or ranges of some of the critical process parameters; for manual cleaning process it may also mean a better written SOP with associated better training.

The third situation (both an identified deviation and a nonconformance in residue results) might not be as bad as it sounds. Clearly, this may also be a case of an invalid run. If there is a good probability that the deviation was the *cause* of the nonconformance, then there is a strong possibility that the implementation of appropriate corrective action will result in successful protocol runs in the future.

It is important in all these cases that approved OOS (Out of Specification) and CAPA (Corrective and Preventive Actions) procedures be followed. Particularly for CAPA, it is important to note that there are actually three actions (not two) that are part of that process. They are:

> *Correction*, which is *fixing* what is wrong. For example, if the residue testing data is non-conforming, I will need to correct that problem with the equipment so it can be released for safe manufacture of another product. This *may* involve recleaning again with the same SOP and retesting to confirm acceptable residues. If a procedural deviation occurred, such as exceeding the dirty hold time (DHT) and I have not initiated any residue testing, I may decide just to clean twice with the cleaning SOP and test for residue after that. This latter situation would be considered an invalid protocol run; however, I would want to consider a corrective active to make sure I did not exceed the DHT in the future.
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> *Corrective Action*, which is taking steps to help make sure the *same specific deviation* does not occur in the future. Using the example of exceeding the DHT, I might

institute some program whereby I was alerted as the maximum DHT was approached. This would *not* help me with my "Correction", but it would help me avoid the same problem in the future.

Preventive Action, which is taking steps to help make sure *other* deviations or problems do not occur in the future. Perhaps during my investigation of a deviation, I identified other possible changes (not specifically related to the immediate deviation) that could be made to help ensure that my cleaning process stayed in a "state of control". These may be items that were considered for a root cause, but were rejected as the root cause for that specific deviation; but, I saw an opportunity to improve my cleaning process as part of "continuous improvement". Preventive actions are not necessarily associated with any deviation, but may be something new I have learned from current technical literature on cleaning processes that could be implemented to improve my process.

While this discussion of deviations and nonconformances reflects one approach to those terms, let me emphasize that other approaches are possible. In any case, there should be an attempt to assure consistency within a given company or facility.