# Cleaning Memo for May 2018
## "Concurrent Release" for Cleaning Validation

I am generally an advocate of applying the principles of life cycle validation given in the FDA's 2011 process validation (PV) guidance to a life cycle approach for cleaning validation (CV). As I have written before, there are many similarities between CV and PV, as well as some significant differences (see the Cleaning Memo of August 2012). One difference I have not written about before is the concept of "concurrent release".

I'll start with a discussion of concurrent release as given in the FDA's PV guidance. Here is the FDA's *definition* of concurrent release as given in that 2011 guidance:

> "Releasing for distribution a lot of finished product, manufactured following a qualification protocol, that meets the lot release criteria established in the protocol, but before the entire study protocol has been executed."

The idea here is that *ordinarily* a product is not released *during* the Stage 2 (qualification) protocols. Only after *completion* of the PPQ runs and establishment that a process is validated can the products manufactured during those protocols be released. However, there may be "special situations" where concurrent release of individual batches may be appropriate. There is no need to discuss those situations in this Cleaning Memo (refer to Section V of the guidance for that detail), except to note that the PV guidance "expects that concurrent release will be used rarely".

Okay, how do we apply this to CV? The first thing to note is there is a difference between what is released in PV and what is released in CV. In PV we are releasing the *batches* made in the Stage 2 (PPQ) protocols. In CV we are *not* releasing the batches made, but rather are releasing the *equipment* for subsequent manufacture of the same or a different product. Ordinarily, what happens in CV has no impact on the batch of product just made and cleaned. [One exception might be a situation where I obtain non-conforming results in the CV data, and as part of my investigation, I find that there may have been some kind of change (not previously detected) in the manufacturing process of the batch of product just cleaned.]

In the discussion that follows, I am assuming I will perform three protocol runs for my cleaning process. So, for equipment release do I have to wait to complete all three runs with acceptable results before I can release any equipment from each of the three runs? Certainly not! That just doesn't make sense, nor is it even possible in most cases. Clearly the test data on the first protocol run should be adequate to release the equipment for manufacturing of another product (either another batch of the same product or a batch of a different product). In this situation it is not unlike "cleaning verification" (see the Cleaning Memo of February 2010). I prepare a one-off cleaning protocol, such as is commonly done for infrequent production or after a deviation/non-conformance. I then use the protocol data for each of the three runs to release the equipment for another batch or product following each individual run.

Ideally I should have all the protocol results for a given protocol run before I release the equipment for subsequent manufacture. Note that if certain protocol data (such as microbial results) are delayed or not available at the time I would like to use the equipment, I may release the equipment "at risk". In that case the subsequently manufactured product cannot be considered for product release until that "missing" data has been obtained and product release has been authorized by QA.

If I am performing three CV runs and the first two have acceptable residue results, but the third has unacceptable residue results, what should be done? Clearly something may be wrong with the cleaning process. Unless I can somehow invalidate that third run (to make it an *invalid* run, and not a *failed* run), the cleaning process is not validated. If the third run is a valid failed run, then I need to make changes as part of my design/development effort and try again with three new protocol runs. However, such a failure of a CV protocol should *not* invalidate the release of the equipment following the first two runs. The data generated in the third run should not change my conclusion regarding the release of the equipment in those two instances. However, for the third run where I obtained unacceptable residue data, clearly I should clean the equipment again in a "cleaning verification" mode. That cleaning is preferentially done with the same cleaning process to avoid the need to calculate residue limits for a different cleaning agent. In most cases where I had such a failed run, repeating the same cleaning process is likely to result in passing data so that the equipment can be released for subsequent manufacture.

In all cases *product* release should be handled by PV principles and by QA procedures. Except in situations where a failure in a CV protocol suggests a problem in product manufacture or where equipment has been released at risk before all CV analytical data is available, CV does not directly affect what I may be doing for product release.

Note that in some cases, CV may be done on a product where PV was completed many years before. In those cases what is done in CV has no impact on product release (except for the exceptions mentioned in the previous paragraph). And there are some cases where PV and CV are done simultaneously. In that situation, there are three protocols runs for PV, with CV being done by a cleaning process on those same batches used for PV. And finally in some cases all three PV runs may be completed *immediately before* the starting any of the three CV runs. Note that during the PV runs in this third case there generally will have to be "cleaning verification" performed after each PV run to successfully release the equipment each time for manufacture of a subsequent batch or product.

A few cautions are in order relating to this issue of "concurrent release" of equipment. First is that I have used for illustration purposes that three runs are done for PV and CV. In its process validation guidance the FDA does not specify the number of runs, while the EU in Annex 15 still states that the number of batches should be based on QRM principles, but adds that "it is generally considered acceptable that a minimum of three consecutive batches manufactured under routine conditions could constitute a validation of the process". Secondly, there will always be special cases where what I have suggested could be the case probably will *not* be the case. So a careful understanding of what is done in CV, and also *why it is done*, is critical.