Cleaning Memo for September 2017
Another Issue for API Synthesis

Earlier this year I critiqued the APIC cleaning validation guide for small molecule API (drug substance) manufacture (Cleaning Memo of January 2017). That guide has many good points (and a few areas for improvement). One issue not addressed by that guide is dealing with processing of multiple lots of the *same* product (by "product" I mean either the synthesized intermediate or the synthesized API itself). The schematic in the APIC guide (Figure 1 on page 20) covers the appropriate approach where in the same equipment one is going from one intermediate to another intermediate or the final API in the *same* synthesis chain, from one intermediate to an intermediate or final API in a *different* synthesis chain, and from one final API to either a *different* final API or to *earlier* intermediate in a *different* synthesis chain.

The focus for this Cleaning Memo is what is required (or recommended) if I go from one product (either an intermediate or an API) to a second batch or lot of the *same* product in the *same* equipment. That is, what should be considered in this type of risk assessment? Unless there are some unusual issues, this situation of going from one product to another batch/lot of the same product should represent a *lower* risk as compared to going from one product to a different product. I might ask, what is the risk if I leave a small amount of the previous product behind on equipment surfaces, and the next product made in that equipment is another batch of that *same* product? Clearly, there may be lot integrity issues, and I may choose to have more robust cleaning to minimize concerns over batch comingling.

But, another concern is whether the residues from one batch *interfere* with the synthesis in processing of the next batch of that same product. Suppose my reaction is as follows:

ReactantA + ReactantB → ProductC

Does the presence of ProductC at the beginning of the next batch synthesis (where I am adding ReactantA and ReactantB) cause any side reactions to occur? In many cases the answer is probably "No", because as soon as I start my synthesis of that next batch, ProductC will be present.

However, there may be situations where what is happening in the synthesis of ProductC is slightly different. Let's suppose that the process involves two reactants to form a given product, and then without isolation of that product I then add another reactant to form ProductC. In this case, ProductC is not ordinarily present in significant quantities during the reaction of the first two reactants, and conceivably it could interfere with that initial reaction. This may require additional evaluation to determine whether significant quantities of ProductC left in the reactor would cause unacceptable side reactions (another way to look at this is to determine how much of ProductC can be left in the reactor without causing unacceptable side reactions in the subsequent initial synthesis).

Does this mean, particularly in the earlier example, that I don't have to clean at all? Perhaps, but I may want to do something to minimize gross batch intermingling. I may just do a solvent flush, perhaps just using the solvent that is used for that next synthesis step. This does not have to be a "full" cleaning process, nor is it necessarily required that the equipment be visually clean. In such a case, I would not even call this a cleaning step, but would use terminology such as a "solvent flush" or "process solvent rinse".

An analogy is what is done in drug product tablet manufacture for multiple batches (such as eight batches) of the same product. I may process eight batches of the same formulation on my tablet press, and only perform a validated cleaning process at the end of those eight batches. In between any two batches I will just vacuum or brush the equipment to remove gross amounts of powder. Such vacuuming or brushing does not result in equipment that is visually clean. However, it prevents the buildup of residues which could affect batch comingling and could affect the *functionality* of the equipment in the tablet processing.

In the same way I could use a solvent flush between batches of the same product in small molecule synthesis to minimize comingling of lots and to minimize the possibility of any unacceptable side reactions from occurring. Realize, however, that this analogy is not a perfect analogy. In the tablet manufacture, there is generally not a concern about the residue of the same product reacting with, and changing in some way, the next batch. With small molecule organic synthesis, the effect of the residue on the synthesis itself may, in some circumstances as mentioned earlier, be significant.

Clearly if this "solvent flush" approach is considered, I would still like to compare product *quality* for successive batches of the same product with only a solvent flush between batches. One thing I would look for is any change in the *impurity profile*, particularly looking for any trends and/or the presence of any unknown peaks in HPLC analysis. Note that I *may* see differences in comparing impurity profiles of "Batch 1" to "Batch 2". Why is that the case? It may be the case because "Batch 1" is likely to see some residues from the prior cleaning process, while residues from that "before Batch 1 cleaning process" are not likely to be a significant issue for Batch 2, Batch 3 and so on.

A second concern relating to the impurity profile is whether I see a change in the impurity profile from Batch 1 to subsequent batches of the same product due to the fact that degradation occurs during the time interval between batches due to such factors as heat, light, and oxygen. While degradation might also occur if the equipment is more rigorously cleaned between batches, the level of degradants in that situation would likely be significantly lower as compared to just using a solvent flush between batches.

Note that any addition of a solvent or process material *after completion* of the initial synthesis reaction may affect how this is handled. For example, if a different process solvent is added to precipitate the reaction product, the presence of that second solvent at the beginning of the next synthesis step of the next batch may be problematic. If it does cause concerns, then a process solvent rinse (that is, a rinse with the solvent used in the beginning of the next batch) would definitely be needed.

Clearly at the end of a series of batches of the same product, I would want to clean more rigorously. The extent of cleaning in that situation would depend on the product or products made in that next synthesis step. Both effects of residues of the cleaned product on that next synthesis itself and any health/safety issues if those residues transfer to the final API should be considered.

The issues discussed in this Cleaning Memo focus on *batch to batch* residue concerns in small molecule organic synthesis. Needless to say, this discussion illustrates the importance of issues other than patient safety being important for cleaning validation.