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Cleaning Validation for Continuous Manufacture

An internet search for "pharmaceutical continuous manufacture" will turn up a number of recent articles discussing the possibility of continuous manufacture to supplant batch manufacturing for pharmaceuticals. While for most companies this is in the future, it may be applicable in certain situations now. What does "continuous manufacture" mean for cleaning validation? Or, how might cleaning validation apply to a case where a pharmaceutical manufacturer is using a continuous manufacturing process. Realize in continuous manufacture, even though there are no definite "batches", there may be "lots" defined by criteria such as time.

As I see it, there are two situations to consider for addressing cleaning validation. One is where continuous manufacturing is done on only one product, and where production is only interrupted for things like equipment malfunction or equipment maintenance. However, once the interruption occurs (and whatever activity takes place during that interruption is completed), continuous manufacture of that same product starts again. A second situation is where I am making Product A on a continuous basis, and at the end of that campaign, I then interrupt production and start continuous manufacture of Product B.

We'll cover the first case first. In a sense, this is not unlike dedicated equipment. I don't have to worry about cross-contamination of the active into a different product. And the need for cleaning validation only comes into play if I clean the equipment during the interruption of the cleaning process. For example, if the interruption merely involves stopping the equipment for a fixed time with no cleaning, then there are no cleaning validation issues. Certainly I would be concerned about product quality just from the perspective of initial product on start-up meeting quality specifications, but that is not necessarily a cleaning concern.

What if during the interruption, I did what has been termed "minor" cleaning (such as vacuuming for dry products or a water flush for aqueous liquid products)? The issues are exactly the same as if no cleaning at all were done. I should not be concerned about cross-contamination of actives, and I shouldn't be concerned about residues of cleaning agents (unless for some strange reason I used a detergent). However, I am still concerned about product quality on the start-up of the continuous process after the interruption and minor cleaning.

Note that with minor cleaning I may be less concerned about product quality during a restart of the continuous process because of removal of product that may buildup and cause quality issues (such as in the case of vacuuming dry products). However, minor cleaning may also increase concerns about product quality on restarting a continuous process; for example, a water flush on a shutdown of a continuous process may lead to more concerns about product quality due to the dilution effect of water on initial startup product. Note in this paragraph when I refer to product quality, I am generally not focusing on safety dealing with residues, but about meeting product quality specifications.

Note also that this manufacturing interruption could be just an annual or semi-annual shutdown for maintenance. If maintenance is done on the equipment, then there may be concerns about residues from any chemicals used for maintenance (such as passivation chemicals). Certainly in that case I want some documentation that those maintenance chemicals are not affecting the safety or quality of the product once I start my continuous manufacturing again. However, if any cleaning is done (and particularly with a detergent), I am more likely to document that cleaning in a "cleaning verification" mode, since the possible residues left after the maintenance step may different from shutdown to shutdown.

Now let's take the second case, where I'm manufacturing in a continuous mode, but make Product A for a time, and then make Product B. In this case, I am clearly concerned about cross-contamination of actives

(active from Product A getting into Product B). How do I deal with this? One option is to perform a cleaning process after Product A (and before starting manufacturing of Product B). In a sense this is no different from batch manufacture in a campaign mode. I still need to evaluate the length of the manufacture of Product A and determine whether that time or volume affects the difficulty of cleaning of Product A at the end of the campaign. My goal is to establish a maximum manufacture length before I have to clean the equipment. This is not unlike what I would do for campaign length in a batch process, where I would establish a maximum elapsed time and/or maximum number of batches before I had to perform my validated cleaning process.

Another option in this case is to immediately switch from the continuous manufacture of Product A to the continuous manufacture of Product B. Clearly there will be significant commingling of the two products initially, and I might have to discard (or handle in a different manner) a certain initial portion of Product B due to this effect. However, I must determine (perhaps on a continuous monitoring technique for commingling) when 'good' Product B (that is, Product B with acceptable residues of Product A) is being made. Note in this case, when I move from Product A to Product B I might discontinue manufacture for short time and physically remove as much Product A from the equipment as practical. This will reduce the extent of commingling, and will allow for a lesser amount of the initial portion of Product B to be rejected.

Note that continuous manufacture (like use of single use equipment) may remove some issues related to cleaning and cleaning validation, but it brings up other issues related to clearly establishing product quality. In any case, issues relating to product safety and product quality must be carefully considered in a continuous manufacturing mode.