June 2007
Issues in Campaigns

There are at least three different kinds of campaigns, and accordingly three different considerations in cleaning validation for those three situations. Those three situations are as follows.

> Case I: A campaign in which there is fully validated cleaning between each batch in the campaign.
>
> Case II: A campaign in which there is some kind of "minor cleaning" between each batch, but only fully validated cleaning at the end of a certain number of batches or after a certain elapsed time (or at the end of a campaign at changeover).
>
> Case III: A campaign in which there is no cleaning of any type in between each batch, but only a fully validated cleaning at the end of a certain number of batches or after a certain elapsed time (or at the end of the campaign at changeover).

Case I may be straightforward. The best example of this is in fermentation in biotech. There is a fully validated cleaning after each batch. The validation at the end of the campaign may be covered by the same validation that is done in between each batch. In other cases, there may be additional steps taken at changeover at the end of the campaign. This may include equipment changes (such as change out of soft parts such as gaskets), or it may involve additional cleaning and/or testing steps. For example, in fermentation for biotech, the company may choose to change gaskets, to clean with the validated cleaning process after gasket change (in addition to cleaning before the gasket change), and to sample the final rinse water of the second cleaning with a rinse water analysis using the specific method for the previous active.

For Case II, the general approach is to have a requirement such as "no more than X batches and no more than a total elapsed time of Y days, whichever comes first". The maximum batch requirement addresses the possibility of buildup of residue over time, perhaps affecting efficiency of cleaning and perhaps affecting production processing effectiveness. The maximum time addresses the possibility of difficulty of cleaning increasing with time, or the possibility of buildup of degradation products (due to exposure to heat or light, for example) with increasing time. In this case, it is generally the case that a worst case challenge for the cleaning process is to evaluate the cleaning after a maximum time or maximum number of batches. Note that the important item here is that the challenge addresses a worst case condition, which is not necessarily a maximum number of batches or a maximum elapsed time. If it can be demonstrated that the difficulty of cleaning does not change with time or number of batches, then cleaning after one batch may be equally a worst case as cleaning after five batches (for example). Of course, if the concern is buildup of degradation products, and if degradation products are measured in the protocol, then the maximum batches/time represents a worst case condition.

Also note for this situation where "minor cleaning" is utilized, I prefer not to call it "minor cleaning". Use of the word "cleaning" may suggest to the uninitiated that cleaning validation must be performed. My preference is to use terms like "water rinse" or "vacuuming", because for this situation there is no expectation that the equipment be even visually clean (so any type of validation usually does not make sense).

For Case III, where there is no intermediate cleaning of any type ("minor" or "major"), but only a fully validated cleaning at the end of a designated time or batch number or at the end of the campaign, the key issue is whether the number of batches or the elapsed time affects the difficulty of cleaning. The cleaning validation should address the worst case condition. Note that in comparison to Case II, it is more likely that elapsed time and/or number of batches will affect the difficulty of cleaning (because of the lack of the water rinse or vacuuming in Case III). For Case III it may also be the case that I operate in a cleaning verification mode because of the frequency of campaigns. For example, if the frequency of the campaign is every two years, I may decide it is prudent to operate in a verification mode.

Assuming that the worst case condition is in fact the maximum number of batches or the maximum time, the question arises for Case II and Case III whether all three validation runs have to be at the maximum. One option is to make sure all runs are at the maximum. However, this may be difficult because the scheduling is usually not controlled by validation concerns. Another option is to perform three runs, and only consider the minimum time and/or minimum number of runs as the validated conditions. A third option is to develop prevalidation data which helps supports the effectiveness of the cleaning processes at the maximum time or maximum number of runs; in such a case, only one run need be at the maximum time/number of runs.

Note that there are no hard and fast rules for dealing with campaigns. There may be variations in each case or situation which might suggest slightly different approaches. This is clearly a case where the FDA emphasis on understanding of the manufacturing process (including the cleaning process) will help decide the appropriate approach to dealing with cleaning validation issues for a campaign.