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**Cleaning for Manufacture of Clinical Trial Materials (CTMs)**

The issue of cleaning validation for the manufacture of CTMs frequently comes up in seminars I give. There are two basic topics that are of concern to people cleaning in such a situation. They are the necessity of doing cleaning validation, and the issue of setting limits when the next product (to be manufactured in the same equipment) is unknown at the time of cleaning.

The answer to the first question is usually very simple. One of the features of cleaning validation is that you will perform three consecutive cleaning events (the Performance Qualification, or PQ). The issue with manufacture of a CTM is that rarely will you make three batches in a row so that you can clean it using the same cleaning SOP for validation purposes. It may be that you make three batches, but the batch size will vary, or there may be other minor modifications to the manufacturing process and/or the cleaning process. Therefore, it is impractical to validate cleaning in such a case.

However, it is still necessary to clean the equipment and demonstrate that the equipment is suitably clean for manufacture of the next CTM in the same equipment. Therefore, what is done is cleaning verification (I'm using "verification" in a narrow technical sense to contrast it with cleaning "validation"). In cleaning verification, you still want documented evidence with a high degree of assurance the equipment is suitably clean. So you will still sample (by swabs, by rinse solutions, and/or by visual examination) and analyze for residues to determine how clean the equipment is. However, the data that you develop, while it may be suggestive of the results you might obtain if you repeated the cleaning process, can only be utilized to support the effective cleaning of that one cleaning event it is associated with (the validation element of determining the consistency of the cleaning process is absent).

The second concern that arises with cleaning for CTMs is that, in many cases, at the time of cleaning evaluation, you don't know the next product that will be made in the cleaned equipment. Since appropriate residue levels can only be determined based on batch size and on the dosing of the next product, this can be problematic (the element of predetermined quality attributes that is expected for validation is absent). While it's problematic, it is not an intractable problem. There are two ways to handle this.

**Option 1:** One is to clean the equipment, measure the residues left after cleaning, but not release the equipment for use until it has been determined what the next product to be manufactured in that same equipment is. At that time, a calculation can be performed (based on batch size and dosing of that next product) to determine whether the found residue is at an acceptable level. If the residue is at an acceptable level, the equipment is released only for manufacture of that next product. If the residue is not at an acceptable level, then it is necessary to reclean the equipment, resample the equipment surfaces, and determine again whether the found level of residue is acceptable based on the batch size and dosing of the next product.

**Option 2:** The second option is to estimate the worst-case batch size and worst case dosing of the next product. Worst-case batch size is the smallest size, and worst case dosing is the largest daily dose of the drug product. Remember that the dosing of the next drug product is not directly related (at least for cleaning validation purposes) to the nature of the next drug product or the level of the API in that next drug product.

Therefore, it may be possible to determine the worst-case batch size and worst case dosing frequency based on the history of what CTM products have been made in the facility and/or based on the development program of that company. If a “worst case” next product batch size and dosing is selected and then utilized to calculate an acceptance criteria for cleaning, then meeting that residue level can only result in a “tentative” release of that equipment. Once the next product to be manufactured is selected, it is still necessary to determine whether the actual batch size and actual dosing of that next product fits within the “worst case” previously selected. If so, then the equipment can be released for manufacture. If not, then you should revert to Option 1 above.

Either approach can be utilized in a manufacturing facility for clinical trial materials. Such an approach should be spelled out in a cleaning validation master plan or cleaning validation policy.