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Differences between Cleaning and Process Validation

As those of you that follow my writings, webinars and seminars know, I am an advocate of applying the life cycle approach of the 2011 FDA Process Validation (PV) Guidance to cleaning validation (CV), where it is applicable and particularly where it offers advantages to make cleaning validation programs more efficient. Let me emphasize that in a formal sense, the 2011 PV Guidance applies only to manufacturing process validation. However, since cleaning is a specialized type of process, some of the principles of that PV guidance may be applied to CV. Realize that Stage 1 (Design) and Stage 3 (Continued Process Verification, or CPV) are steps that most pharmaceutical companies performed in some sense in the past. The validation runs for CV were never experiments; they were always preceded by some type of design/development work, and maintenance of the validated state (CPV) was also something most pharmaceutical manufactured pursued, through such activities as change control, routine monitoring, and trending of data. What is different in the 2011 FDA PV guidance is that these stages are now defined as part of the validation process.

The advantages of implementing selected principles from the 2011 PV guidance should be balanced by a consideration of what parts of the 2011 PV guidance may not apply to CV, as well as the rationale of why those parts are not applicable.

One area where PV and CV differ is in how data is handled, and the expectation of consistency of data. One of the main objectives of process validation is to demonstrate that both within a batch, as well as from one batch to another, the chemical properties are essentially the same. For example, potency assays for the active concentration may be measured at various points (times) within a batch to confirm uniformity. In addition, a certain uniformity of the active concentration is expected one batch to the next. The same may be true for physical properties, such as hardness (tensile strength), weight (mass) and dissolution time of tablets. For those types of measurements, it is reasonable to employ statistical measures of consistency (always remembering that the test of practical significance should be employed before considering statistical significance).

This is not to say that there might be certain areas where chemical or physical properties might vary slightly, such as the impurity profile of an active pharmaceutical ingredient (API). In that case, the issue is not unlike a cleaning validation residue value, where the key is that the value be below a specified limit.

For cleaning validation protocols, there is no expectation that residue values from different swab samples of a given equipment item be essentially the same. The reason for this is that the surfaces sampled are not the same population; they represent different types of surfaces because they are typically selected based on "worst case" principles (such as being sites that are "difficult to clean"). Furthermore, the key issue is not that the residue results are the same, but that they are consistently below the acceptance limit. An argument can be made that there should be more consistency from swab sampling at the same location in a given equipment item over multiple validation runs. That is, could I treat statistically the swab sampling results from swabbing the underside of the agitator blade over multiple cleaning validation runs? That is certainly a possibility. However, if swab sampling is only done during the validation runs, it is not likely that there will be enough runs to statistically evaluate that data in a meaningful way. However, the key difference between cleaning validation residue data and chemical analytical data for process validation runs is that I am expecting the data from the process validation protocols to be essentially the same; I do not have that expectation for cleaning validation residue analysis (although if my cleaning process is robust enough, the data may be the same in the sense that

the analyte might be non-detectable for all samples).

A second difference between PV and CV is that (generally) the manufacturing process I use for each drug product is somewhat unique. What I mean is that while a process for manufacturing tablets might be the same general process, the specifics of manufacturing parameters are different (they may be formulation dependent). For cleaning validation, it is more likely (although not necessary) that a firm would use the same cleaning process for all products made on a given equipment item; in this case the same cleaning process would mean identical process parameters (such concentration of cleaning agent, time, temperature).

The impact of this is that a company is more able to appeal to data on sufficiently similar cleaning processes to help determine that a given process is consistent (and validated). For example, imagine that a biotech company manufactured monoclonal antibodies, and that company has validated the cleaning process for three products. It now faces cleaning validation for a new product, so it may be able to appeal to data for cleaning of the three previous products as support that may result in reducing the number of validation runs required to demonstrate consistency for the new product. The key issue involves using the same (identical) cleaning process on a product that is similar to other products for which multiple cleaning validation runs has been performed. Generally, that approach will not work to the same degree for process validation where the manufacturing process parameters are different. The relevant knowledge base from similar processes may be more extensive for a cleaning process than for a manufacturing process.

These differences between cleaning processes and manufacturing processes are based on general differences, and might not apply in all situations. However, these differences should be considered in deciding what aspects of the 2011 PV guidance could be applied to CV. Furthermore, it is not a regulatory requirement that the life cycle principles be applied in a formal sense to CV. But, if I were to look in my crystal ball, I would expect that this would be a part of the CGMP for cleaning validation ten years from now.