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Setting Limits Based on Process Capability?

As some of you might know, I am not generally a fan of setting residue limits based on process capability. Where this sometimes comes up is when a manufacturer sets limits based on standard dosing calculations (also called maximum allowable carryover calculations), but then the actual residue data measured is much below that calculated limit. For example, suppose I do a standard 0.001 dose calculation for a finished drug product, and end up with limits in a desorbed swab sample of 3.2 µg/mL. When I execute my protocol, the actual data I see ranges from 0.1 µg/mL to about 0.5 µg/mL. Could I be accused of setting my limits too loosely, and I really should have set my limits at 1.0 µg/mL. Well, that argument can be made. However, the issue in residue limits is whether my validated limit has any effect on the safety and quality of the next manufactured product. If the 0.001 calculation is an acceptable calculation for determining levels of residues of actives, then what practical difference does it make if my actual data is in the range of 1.0-2.0 µg/mL instead of 0.1-0.5 µg/mL?

Another way to look at this situation is to suppose we had two identical manufacturers making the same products. Both did the same dose-based calculation and determined the limit for cleaning was 3.2 µg/mL in a desorbed swab sample. Manufacturer A actually obtains results around 0.2 µg/mL, while Manufacturer B obtains results around 1.5 µg/mL. Is it right for me to accuse Manufacturer A of setting limits too loosely, while perhaps praising Manufacturer B for setting appropriate limits? Of course not! That would be equivalent to penalizing Manufacturer A for doing a better job in cleaning. We also should recall what the FDA has written in their Second Quarter 2001 Human Drug CGMP Note: Equipment "should be as clean as can reasonably be achieved, to a residue limit that is medically safe and that causes no product quality concerns (other than the fact of the contaminant's presence), and that leaves no visible residues." I encourage you to read the question and the FDA's answer in full.

Another issue with setting limits based on process capability is that a manufacturer may not have sufficient data on a new cleaning process to know truly what the process is capable of. The manufacturer may be able to calculate a dose-based limit, and then design a cleaning process to be well below that limit, without having sufficient data to know the process capability. Indeed, true process capability studies usually require at least 25 replicates to establish such capability. One possible reply might be that during the prevalidation studies, one could collect 25 or more swab samples and establish a limit as the mean plus 3 standard deviations. That may be appropriate if those swab samples were all from the same sampling location in 25 different cleaning events. However, to perform one cleaning event and then to take the average and standard deviation of the 25 different sampling locations is a misuse of statistics. Even to perform three cleaning events and take the average of 75 swab locations is still a misuse of statistics.

Let me make it clear that if my swab limit was 3.2 µg/mL, I would prefer to design a cleaning process that resulted in data closer to 0.2 µg/mL than to design a process with data closer to 1.5 µg/mL. But, from a compliance perspective, I would not require more rigorous cleaning with the higher residue data, nor would I accuse the manufacturer with the lower residue data of being lax in setting limits. Let me also make it clear that for any reason, including process capability, a manufacturer may set limits below what is calculated based on the 0.001 dose calculation. But the reverse is not true; in almost no case for finished drug manufacture would it be acceptable to set limits based on process capability if those process capability values were above the 0.001 dose limit.

But, those who argue for process capability do have a good point when it comes to evaluating *routine monitoring data after validation is complete.* Let's change our example. Suppose a manufacturer had a final rinse water limit of 1.4 ppm of an active. During validation, the data was consistently in the range from non-detectable (<0.05 ppm) to 0.3 ppm. Further suppose that this manufacturer routinely monitored final rinse water for the same active. Over time, the manufacturer should build up enough data to perhaps set action and/ or alert levels for the active in the rinse water. Perhaps those data indicate an alert level of 0.6 ppm. If on a given run, suppose the manufacturer had results of 0.8 ppm, exceeding the alert level of 0.6 ppm but below the validation limit of 1.4 ppm. Should the manufacturer be concerned? Well, the answer is "Yes", because the rinse water value for the active is significantly out of line with historical data. It does not necessarily mean that the batch should be rejected solely on the basis of the higher data point, because the actives level is still below that limit established in the cleaning validation protocol. However, it does suggest that something may be different, and an investigation into what may be different is called for. If nothing is discovered, and if the next batch drops back into the "normal" monitoring range, then the manufacturer may not be concerned. After all, a range of the "mean plus 3 standard deviations" does allow for the possibility that some batches will exceed that range. Furthermore, if on cleaning the next batch, the rinse water value for the active is 1.0 ppm, then lightning has struck twice in a row, and clearly something is different about my cleaning process. Again, it does not mean that any product is unacceptable, but it clearly calls for an even more thorough investigation. That investigation may turn up problems with the manufacturing process of the cleaned drug product, with the cleaning process itself, or with the analytical or sampling techniques. This situation described here is truly a case where process capability can be valuable in establishing controls to help assure ongoing consistency in a validated cleaning process.