September 2009
"Design Space" for Cleaning Processes

"Quality by Design" (QbD) and "Design Space" are currently two hot topics in pharmaceutical manufacturing. If you justify a project with these concepts, you are more likely to get it funded. Certainly design of manufacturing processes, including cleaning processes for process equipment, is a very desirable thing. In the past, I have heard some cleaning validation personnel tell me that "Process engineering designs the cleaning process, and they pass it off to us and we validate it." That may have been acceptable in the past, but with the new process validation paradigm from the FDA (see last month's Cleaning Memo and my January 2009 webinar), that probably will no longer be a prudent approach. Design of the cleaning process is becoming part of the cleaning validation process. [A side note here. I realize the FDA process validation guidance formally applies only to process validation. However, it is an inescapable conclusion that it will (or should) also be applied to cleaning processes.]

So, the question addressed in this Cleaning Memo is "How can I apply the concept of design space to cleaning processes?" There definitely are some differences between manufacturing process design and cleaning process design. For example, in working on design space for a manufacturing process, as a general rule the design space for each manufactured product is different. Now, I will admit that the parameters looked at in the design space for a manufacturing process might be the same for a given of manufactured product. In other words, the *parameters* that are important in the design space for the manufacture of Tablet A might be the exact same parameters that are critical for the manufacture of Tablet B. However, the *acceptable values for those parameters* (the design space) may be different for Tablet A as compared to Tablet B. The same thing may be true for a fermentation process. The critical parameters for Fermentation A may be the same as critical parameters for Fermentation B, but the acceptable values for those parameters are likely to be different for those different fermentation processes.

Isn't the same the case for cleaning processes? Are the design space parameters of time, temperature, concentration, etc. different for the cleaning of Product A as compared to Product B. Yes, that might well be the case. However, what is different for cleaning processes is that, if Product A and Product B are made on the same equipment, most manufacturers will not want to clean Product A and Product B with *different* cleaning processes. That is, those manufacturers prefer to have *one* cleaning process that is effective for *both* Product A and Product B. If one product requires a more stringent range of values for those critical cleaning process parameters as compared to the other product, this means the cleaning process for the other product may be an extreme overkill. In this is the case, the idea of design space is *not* that we select *ranges* for parameters and maintain control within those ranges to make sure the cleaning process is effective. Rather our goal is fixed parameters for the cleaning process; then for design space we verify, for *each* product to be cleaned, that those fixed parameters represent a significant *margin of safety* in providing effective cleaning. In other words, for a new product, I don't necessarily explore the entire design space for cleaning that new product. I could just demonstrate that the existing (fixed) cleaning process does not represent a challenge to that new product. In one sense, that is what (in principle) is already done. However, what is currently done may not be done formally and may not represent an adequate challenge.

What kinds of things might define the critical quality parameters of a design space for a cleaning process. Here is a possible list (which is not necessarily exhaustive):

- Nature of residue on surface
- Nature of surface
- Cleaning step times
- Cleaning agent concentration
- Temperature of the cleaning steps
- Action (in manual cleaning)

Note that I did not include the parameter "action" for an *automated* process, such as a CIP process. That was deliberate, because for automated cleaning processes in a fixed configuration, it will be difficult to *vary* "action". Sure I can get better coverage by adding additional spray devices, but once I establish adequate coverage, I am not going to deliberately block one spray device to show the design space. In manual cleaning processes (such as scrubbing or wiping), I can to an extent control the "action" to demonstrate a design space. Note also that the cleaning agent selected is not in this list, because it cannot be varied in a meaningful way.

How can this work in practice? Well, the nice thing about the new FDA process validation guidance is that it permits lab and scale-up (pilot plant) studies to support our cleaning validation. These would be key studies to help demonstrate that the design space of a new product "fits" with (or doesn't fit with) the existing fixed cleaning process. For example, let's assume I have a fixed CIP process for a biotech finished drug product (with a protein active). I am developing a new biotech finished drug product with a different protein active. As part of my design studies, I might consider the variables that would significantly affect the cleaning process. For example, I might select the nature of the residue on the surface (dried is a worse case), the washing step time (shorter is a worse case), the cleaning agent concentration (lower is worse case for cleaning), and temperature of the wash step (lower is worse case for an alkaline cleaner).

In my lab studies, I would compare the effect of a worse case variable against the target value for that variable, to see of there is any difference in my desired critical quality attribute (a clean surface, as measured by visual examination and/or by swabbing and analyzing TOC). I might take a look at the each of those three variables independently, or I might just do one study where each variable is a "worse case". In the study, I would compare the result from my "worse case" run against the "target case" run. If the cleanliness of the coupon were the same, I would tentatively conclude that my target range of values for my critical parameters was adequate to clean the new product. I might confirm this in a pilot study (perhaps on a clinical batch) before concluding that the existing cleaning process was adequate to cover the "design space" for the new product.

What if I performed a study with my worse-case parameters and determined that the target values cleaned adequately, but with the worse case values for those parameters, the cleaning was not effective? In that case, I might conclude that my existing cleaning process is *not* robust enough to deal with my new product. Of course, this stresses the importance of how one selects those worst case values.

Some of you might be wondering whether this is exactly what is done for product grouping, where I might perform lab studies to determine the worst case product. And the answer is a partial "Yes". In lab studies for grouping purposes, I generally try to stress the cleaning process to determine which product is most difficult to clean. A common way this is done is to stress only one parameter (typically time of the washing step) to determine which product takes the longest time to clean (with the temperature and cleaning agent

concentration the same). What is *different* in a grouping study is that I stress the time with each product until I get a "failure". By contrast, in the "design space" study described above, I don't have to stress the parameters on the new product to the point of failure. Now clearly if you have two objectives in your lab study (design space acceptability and grouping determination), then you will either conduct two separate studies, or else design the one study to accomplish both ends.

The purpose of the Cleaning Memo is not to lock anyone into only one mode of addressing design space for cleaning processes. Rather the objective is to make clear that design space studies for cleaning processes, where one cleaning process is to be used for a variety of manufactured products, may be different from the design space for product manufacturing processes.