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The Changing Paradigm for Cleaning Validation

One definition of paradigm is "A set of assumptions, concepts, values, and practices that constitutes a way of viewing reality for the community that shares them, especially in an intellectual discipline". Applied to cleaning validation, a paradigm is those "assumptions, concepts, values, and practices" that define the way we do cleaning validation. We are currently in the midst of a *paradigm change* in cleaning validation. I'll explain that change in a minute. However, first a little of *my* history with paradigm changes.

My first exposure to paradigm changes occurred when I was in college and took a class where we had to study the history of science. The book we used was Thomas Kuhn's *The Structure of Scientific Revolutions*, which has just been published. This is a book I still have in my library, because it provides a useful paradigm to explain how science works.

Basically what Kuhn argued was that science usually operates within a paradigm (he called this "normal science") to explain the way the world works. As long as scientists accept that paradigm, they explore the world within that framework and use that framework to explain their observations. However, as scientists work within a paradigm (framework), they eventually come up with observations that are not well explained by the existing paradigm. As a result, they may tweak the paradigm so that the paradigm and the observation fit together. Eventually there become enough things that are not well explained by the existing paradigm, that a new paradigm is proposed which accounts for the data better. As that new paradigm is adopted by scientists, a scientific "revolution" occurs.

One example of a paradigm change in science is the change from a Ptolemaic view of the planets and sun (geocentric) to a Copernican view (heliocentric). The Ptolemaic view was based on observations of the sun and moon rising. It made sense initially. However, as more data was collected (and particularly as mathematical models were made), the observed data didn't fit the model. Changes were made to the model (such as adding epicycles to the motion of other planets to explain their retrograde motion). Eventually, when a new model was proposed that explained those aberrant observations and did so in a much simpler way, scientists changed to the new Copernican model of the solar system.

Okay, you might be saying that sounds fine, but how does it apply to cleaning validation? Well, until recently we have worked under a paradigm of cleaning validation that said that cleaning validation was the three (or more) validation runs that demonstrated the consistency of the cleaning process. We operated (performing cleaning validation) using that model. But, we knew we had some problems. We all knew (as was pointed out by our statistician friends) that three runs in a protocol did very little *alone* to demonstrate consistency of the cleaning process. However, without a replacement paradigm (we cannot operate in a vacuum), we continued to operate in that paradigm. Yes, we talked about QbD (Quality by Design), but did not fully integrate it into a validation model. I (for one) also taught that some worst cases did not need to be evaluated (or fully evaluated) in a formal protocol if prevalidation work addressed it appropriately.

Now for the revolution. Last November the FDA published their draft guidance on process validation. What that document did was redefine process validation. Process validation now consisted of three stages: design/ development, process qualification, and ongoing process maintenance (the term the FDA uses for the last stage

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is actually "continued process verification"; however, since "cleaning verification" is a useful term to describe certain cleaning activities, I am reluctant to have that new term adopted). What they are now saying is that what demonstrates effectiveness and consistency of a process is what you do during design and development (including lab studies, scale up studies and commercial scale manufacture), what you do during process qualification (the protocols) *and* what you for maintenance (such as routine monitoring, trending, and change control). All of that is part of validation. [Now I know the FDA document formally applies to *process* validation; however, I believe the practical application should also cover *cleaning* validation, since cleaning is just an example of a specialized process.]

I believe it might take a few years, but we have begun the move to this new paradigm for validation. This new paradigm definitely presents a more holistic view of process/cleaning validation. While it might look like more work, there are also opportunities to leverage lab and scale-up studies, as well as leverage validation of similar processes, to actually simplify the overall process. However, there will be changes, particularly in documentation (for example in cleaning validation master plans) as we move to this new paradigm. Our focus, however, should not to be to worry about retrofitting previous validation work, but to make plans and begin to perform cleaning validation using the new paradigm. I also realize that the FDA's change produces a disconnect with other regulatory guidelines internationally. However, I (for one) believe that this new paradigm is where we're going, so we should start planning now to be there. And if I'm right, this new paradigm (once we get over the upfront costs to redesign our cleaning validation programs) should allow for significant efficiencies in approaching cleaning validation.

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