Process Validation Guidance: Light at the End of the Tunnel

Those who embrace the new process validation guidance may separate themselves from those who do not.

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The draft of FDA's new guidance for Process Validation is big step forward in process-centric product development that would result in designing quality into the process. The new guidance is significant in that it attempts to divide the validation step into three discrete phases, integrating a characterization phase as a precursor to the demonstration and monitoring phases. This is a radical departure from what industry has perceived to be the role of validation in the overall product quality system.

For organizations that have been exposed to principles of Six Sigma and Lean Manufacturing, this structure will seem familiar. Understanding what drives process variation and—more importantly—process stability is at the core of these two approaches. Whether the end product of the exercise is tighter process variation or more predictable process velocity through the plant, it is essential that drivers for predictability be identified and controlled.

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In the past, we have relied upon regulatory guidance to tell us what to do. Whether we are building our sampling and testing plans or demonstrating aseptic process capability we have always looked to the FDA to prescribe what is good enough. This has been industry's relationship with the FDA since its inception. This new guidance, however, disrupts that dependent relationship significantly. The agency is asking us to define and defend what is adequate with regard to our process capability and predictability.

The consequences of this new edict in terms of process and product development time have yet to be understood. It is clear though, that industry is sitting up and taking notice. The Parenteral Drug Association (PDA) recently compiled a 122-page summary document containing over 400 comments from its membership concerning the new guidance. Many of the comments revolve around clarifying terms as they relate to the old paradigm of validation. Traditionally we have separated qualification and validation activities, underscoring the difference between verification against design criteria and verification of the control space. The new guidance is unclear as to the differences, but we have dealt with this before. This is not unlike the philosophical arguments revolving around the break between enhanced commissioning and validation activities. The industry has gone back and forth on this subject for more than 10 years.

In reviewing the comments submitted I could detect considerable evidence that we as an industry have already begun the shift in mindset. Overall, there is consensus that this is a major step in the right direction. For those organizations that have been actively working on a transition plan integrating the principles of ICH Q8 or Quality by Design (QbD) as part of their drug development lifecycle, this is a logical last step in the process. Many have struggled to integrate the concepts of risk management as prescribed in ICH Q9 and Q10 as part of their development and quality systems. Contrary to what many might think, integrating a risk management structure should not increase a program's risk but reduce it! This means backing up our decisions with data and aligning them with the basic tenets of drug safety,

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quality, integrity, potency and purity. Historically we have done this by testing against release criteria. This new guidance says that is not good enough anymore.

Within any new drug submission there is the Chemistry, Manufacturing and Controls (CMC) section that describes the critical components of the drug's development, tying together the rationale behind our formulation, specifications, sampling strategy, in-process and release testing with final validation testing. What has been missing has been the processes' relationship to these key attributes. The new paradigm affords us the opportunity to complete the puzzle.

We will now be required to defend our process and product development conclusions with a much higher level of confidence. This will lead to heartache in the short term as we attempt to align process and product development and compliance expectations and begin the education process with regard to risk. Being comfortable with looking at only those things that matter is a difficult concept to embrace in an increasingly risk-averse environment.

However, the end-result will be increased business performance through more stable product velocity through the plant, more consistent and reduced inventory and greater flexibility to respond to market opportunities. In an environment where generic filings in the marketplace are skyrocketing (more than doubling since 2002, according to the Generic Pharmaceutical Association), can industry make the transformation? That is the great challenge. The massive increase in filings has resulted in almost 1,400 non-approvable letters from drug manufacturers which must be dealt with by the Office of Generic Drugs (OGD), ballooning approval times from the mandated six months to closer to twenty-one months.

So one could argue that there is a disconnect between the industry and the FDA in terms of expectations. Couple this with emerging market manufacturers reeling from FDA injunctions and heightened scrutiny, and the old adage that we are a quality driven industry has never been truer. This new guidance reinforces the concept of quality by defining it in new terms and, if embraced by our industry, may prove to be the differentiator between those who can remain competitive and those who cannot.

About the Author

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