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I Don’t Mean to Be Critical

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The FDA guidance on process validation issued in January 2011 has turned the quality and product development worlds upside down. As the industry attempts to translate the principles of the guidance to action a great debate is taking shape surrounding the identification and definition of critical process parameters. This may seem like an innocuous detail in the broader process validation scheme of things but closer inspection will reveal it is at the heart of the process validation maelstrom.

The three stages of the new guidance mandate the development organization to defend the identification and characterization of critical process parameters as the foundation of the process validation rationale. Yet the agency is careful not to predefine criticality as it pertains to process attributes and parameters. Rather, it states that their role in terms of process control should be evaluated using a risk-based approach: *“All attributes and parameters should be evaluated in terms of their roles in the process and impact on the product or inprocess material, and reevaluated as new information becomes available. The degree of control over those attributes or parameters should be commensurate with their risk to the process and process output. In other words, a higher degree of control is appropriate for attributes or parameters that pose a higher risk.”*[1]

While this approach may seem like common sense, it remains a radical departure from past agency direction. In fact, the Office of Generic Drug’s (OGD) position on the identification of critical process parameters has always been to assume that all parameters are critical if there is no development or characterization data to say otherwise. At a recent conference the OGD reiterated this position. Thus, as an industry, we find ourselves with diametrically opposed agency direction. On one hand we are directed to use a risk-based framework coupled with an understanding of how attributes and parameters work in our process to modulate the level of control along with the assigned risk; on the other hand, we are directed to assign all parameters as critical unless we can prove otherwise.

The trouble with this contradictory direction becomes apparent quickly as organizations attempt to implement the new guidance. Picture the number of parameters involved in each unit operation of any drug process. If all of these are de facto critical parameters that must be included as part of Stage 1 and Stage 2 then the number of lots required to demonstrate process predictability becomes untenable for any drug company or PAI manufacturer. Similarly, the concept of tracking and monitoring the behavior of these parameters as part of Stage 3 becomes a near impossible undertaking. Monitoring is of little value unless action and alert limits can be established to address process drift or radical change in a process. In the absence of process understanding, monitoring the behavior of default critical process parameters rapidly becomes an exercise in futility. Imagine a quality assurance professional faced with the dilemma of a commercial product

that satisfies the product’s release criteria but fails the Stage 3 action and alert limits for the default critical process parameter. In the absence of characterization data to define the role of the parameter or attribute as it pertains to process predictability and product performance, and no assignable root cause for the departure, there would be little alternative but to reject the lot.

To relieve this situation there should be several new areas of focus. The industry needs to understand this guidance is the first to explicitly embrace the goals and principles of the FDA initiative *Pharmaceutical CGMPS for the 21st Century - A Risk based Approach*, issued in 2004. The intent is to force the industry to adopt the principles of process understanding as the foundation for product quality, rather than fall back on the old model of inspection and testing. This requires a new, more cohesive linkage between product development technology transfer and validation organizations. Innovative companies are better positioned to make this paradigm shift as their current product development structure is more in line with establishing this level of process understanding. Generic and API manufacturers find themselves at a distinct disadvantage. It is not unusual for the process limits filed in an ANDA to have no supportive data at all. Similarly thin data backs up the establishment of the manufacturing batch record process limits. Bioequivalency lots are rarely manufactured at full scale since, in the absence of an In Vitro-In Vivo Correlation, there is always a chance the product will not be bioequivalent. Finally, historically, most process validation lots have been manufactured at nominal conditions so there is little precedence for making this leap in thinking.

If the industry and the FDA are to move forward several things must happen. First, all agencies dealing with market sectors of industry subsumed within the process validation guidance must put forth the same position regarding the new guidance. Second, it would be helpful to develop a common lexicon. I know the agency has been deliberate in not using the term critical process parameter, but doing so only slows the transition toward the new process-centric thinking of the new guidance.

The bottom line is that generics account for 78%[2] of the drugs sold in the U.S. and that number will likely increase as we deal with issues such as drug pricing control and national healthcare. The absence of a unified position in terms of agency expectations can only add to the confusion in the current U.S. pharmaceutical market and will keep industry from doing the heavy lifting necessary to embrace the principles of the new guidance.

References

1. Guidance for Industry - Process Validation: General Principles and Practices
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   Food and Drug Administration
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   Center for Biologics Evaluation and Research (CBER)
   Center for Veterinary Medicine (CVM)
   January 2011 - Current Good Manufacturing Practices (CGMP) - Revision 1
2. IMS Institute for Healthcare Informatics http://www.imshealth.com/portal/site/ims

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Links:
[1] http://www.imshealth.com/portal/site/ims