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Process Validation and the New Compliance Challenge

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The issuance of the new FDA Process Validation Guidance in January of this year is a significant event for several reasons. Fundamentally, the definition of what constitutes acceptable process validation differs dramatically from the conventional definition first put forth in the 1987 guidance. This guidance, more than any of the ICH documents or previous FDA guidance issued since the Critical Path Initiative in 2003, attempts to legislate the transformation envisioned by the agency. In 2004 the FDA issued its landmark FDA guidance Pharmaceutical cGMPs for the 21st Century— A Risk-Based Approach, which advocated a more scientific approach to demonstrating process quality. Since that time there have been many discussions regarding how to implement the principles of Quality by Design (QbD) and risk-based decision making. Few could argue that the adoption of these new principles has proceeded at glacial speed. There are many reasons the industry has been slow to embrace these new concepts, despite their potential benefits in terms of process predictability and business performance. The underlying challenge, beyond the development of organizational expertise and resource allocation, is the significant paradigm shift in compliance thinking.

Historically, the foundation of our industry's compliance philosophy was based upon the three quality pillars of inspection, testing, and documentation, while the 2004 FDA guidance advocates a product quality philosophy based upon process understanding and the scientific application of risk to maximize the potential for predictable product performance. To do this, the industry found itself supplanting industry standard practice—and the three-validation-lot rule of thumb— with a more descriptive methodology that required the industry to design and defend its approach to process and product development. This new, descriptive approach requires a thorough understanding of statistics, probability, and risk. Even if the development team were equipped to meet this challenge, the compliance organization often found itself lacking the necessary linkage between the old philosophy and the new philosophy. Consequently, the concept of risk-based process validation meant adding rather than reducing risk to the compliance equation in the minds of most quality professionals.

So now the agency has drawn a line in the sand with its new process validation guidance. If compliance professionals are to make the transition to the new guidance, there will have to be a clear roadmap to articulate, in broad terms, the necessary quality attributes for each stage of the new guidance. I would advocate the following deliverables to ensure a clear compliance position as the process moves through the three stages of process validation.

STAGE 1

Stage 1 of the new guidance requires identifying the critical process parameters that drive process stability. The guidance goes further to describe establishing the knowledge,

design, and control space for the process. This phase is intended to identify as many sources of variation as reasonably possible for the process and to establish the first correlation between process performance and product performance. Deliverables from this stage should reference some risk-based assessment of potential failure modes in the process based upon the product design. This assessment should easily map to the areas of process characterization performed. In addition this stage should begin the discussion regarding sample size, sampling technique, in-process testing metrics, and measurement system capability. To be complete, the Stage 1 activity should also clearly define and defend what parameters are not critical to the process stability. This understanding is essential to laying the common understanding for Stage 2 in terms of the compliance argument.

STAGE 2

This stage introduces a new concept called the Process Performance Qualification (PPQ). Right away this could cause confusion with Performance Qualification (PQ), performed historically as the last stage of equipment qualification. Understanding the components of the PPQ is essential to garnering buy-in. The challenge most compliance professionals will have with this stage is that the level of characterization will vary depending upon the thoroughness of the work performed in Stage 1. Risk is always part of any quality assessment; however, it is rarely quantified in routine quality decision making. In this case, based upon the Stage 1 risk assessment and final control space establishment the sampling justification and acceptance criteria will have to be justified.

STAGE 3

The last stage—and perhaps the most confusing for compliance professionals—will be the monitoring portion of the process. All Quality Management Systems (QMS) require product performance monitoring as part of their annual product review. However, the new guidance is asking for more than that. The agency will look for evidence of monitoring of critical input and output parameters as well, in keeping with the new philosophy of process understanding driving product performance. The reality of all new processes is that it is nearly impossible to anticipate what the variability will be from the six Ishikawa factors (man, machine, measurement, materials, methods, and environment), until routine manufacturing begins in earnest. So it is reasonable to establish a data gathering phase before establishing alert and action limits for any process correction. One new advantage of this three stage approach is that change control assessment will be more straightforward since the variables that are critical have been identified a priority and the need to revalidate should be much easier to determine.

CONCLUSION

There is no doubt that the bar has been formally raised for all compliance professionals with this new guidance. The transformation recommended by ICH Q8 and Q9 has now been formally required. If we are to be successful as an industry it will be essential that we learn to adapt to the changing role and requirements of the new compliance philosophy. If we cannot, the road ahead will be a difficult one for the agency and industry alike.

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