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Meeting The Global Compliance Challenge

Bikash Chatterjee

There can be no doubt that the last decade for the pharmaceutical and biotech industry has been full of extraordinary change. Regulatory changes culminating in the FDA's 2004 guidance *A Risk-based Approach to CGMPs* underscored the reality that as an industry we needed to evolve. In the U.S., the FDA has undergone an unprecedented transformation in an effort to shed its overhead-intensive compliance baggage and move the industry toward more effective product development. The recognition that change is essential is not limited to the FDA. There has been a global push to drive toward an asset of rules and standards that represent a balanced summation of what we consider reasonable best practice. The International Committee for Harmonization (ICH) developed its portfolio of standards; culling input from the world's best and brightest in terms of pharmaceutical product development. There is universal agreement that the ICH guidelines Q7, Q8, Q9, and Q10 set the standard from a product development and compliance perspective for competing in the western markets of the U.S. and Europe.

This has been a long and arduous journey for the industry and we are by no means nearing its completion. As a Lean Six Sigma Master Black belt, I understand all too well the importance and challenges associated with changing organizational thinking. The FDA recognized this first in examining their own ability to evaluate the risk benefit profiles of new therapies being brought to market, and second in examining the industry's ability to defend its own work. Mired in regulatory overhead, the cost benefit ratio of bringing new therapies to the marketplace was drifting south. As costs escalated and the agency's aversion to risk reached new heights, the pharmaceutical industry found itself with longer and longer development timelines to market. This may have not been apparent when looking at NDA review times, but when extended to IND and ANDA cycle times the trend was unmistakable. Clearly it was time for a paradigm shift.

Further complicating this situation is the changing market landscape. The growth of the drug delivery market in the U.S. has changed the technical and regulatory landscape significantly. In looking at the overall drug delivery market in the U.S., the forecasted market size in 2009 is estimated at approximately $80 billion escalating to over $150 billion by 2011. In the current market, over 50% of the market is dominated by modified release, implants, and transdermal systems with the majority share belonging to modified release delivery systems. Changing market dynamics, patent extension strategies, and technology innovations will have a profound impact on where the demand is in the marketplace. It is forecasted that the market is going to shift to a new emphasis on targeted drug therapies. The evolution of PEGylation, nanotechnology along with polymer and liposome technology solutions, is expected to comprise almost 50% of the overall U.S. market by 2011.[1]

This convergence between CFR 820 regulatory world and the CFR 210/211 world presents unique challenges for development, compliance, and regulatory organizations. The roadmaps are similar philosophically but the milestones and metrics are very different. This convergence has been aided to some extent by the adoption of Six Sigma[2] and Lean Manufacturing programs within the manufacturing environment. The motivation for this diversion has been driven by both a need to comply with the new regulations emphasizing Quality by Design, and partially by the need to improve and maintain business performance. The industry's infatuation with operational excellence has been tenuous. Big Pharma and biotech along with large medical device and diagnostic companies have made the investment in operational excellence principles, particularly on the factory floor, but have been slow to move these principles to the product design phase.

The rest of the industry has not been able to make the shift with generic companies dabbling at best with isolated Lean programs.

The 2004 guidance not only raised the bar for the industry, but for the FDA as well. Suffering from ever restrictive budget cuts for the last decade, the agency found itself terribly underpowered to live up to their end of the bargain for ICH Q8, Q9, and Q10. In response, the agency began hiring and training its inspectors in statistical analysis and the basic principles of Six Sigma.

So, armed with this newfound knowledge, the FDA is ready to support this paradigm shift. However, the path to transformation has had another monkeywrench thrown in. The U.S. markets have been undergoing unprecedented contraction with consolidation amongst big Pharma in particular complicating the industry focus. Coupled with an extension of the supply chain to the global marketplace, our ability to focus on best practices has been significantly hampered. China has had some highly publicized missteps starting with adulterated pet food to the most recent tragedy with the contaminated Heparin API supplied to Baxter that resulted in so many fatalities. India raised eyebrows when the FDA sanctioned Ranbaxy in September 2008 from importing 28 drugs to the U.S.[3] These problems will not simply go away. We are talking about an educated management structure in emerging markets that is well aware of the regulations for manufacturing drugs for the U.S. and Europe. However, I believe the difference lies not with the knowledge gap but with understanding of the consequences. The difference between knowledge and understanding has always been at the heart of every regulatory professional's anxiety.

As compliance and regulatory professionals, we are faced with a perplexing situation: to manage multiple changes simultaneously in the compliance landscape. The emerging markets are here to stay. China supplies 80% of the world's APIs and over 40% of the U.S. market's APIs. ICH Q7A is a fixture. The portent of the drug delivery market is very real. Nanotechnology and similar bleeding-edge technologies are changing the rules on how we assess safety and efficacy. We are not alone in this realization. China just recently issued its GMP 10 regulatory guidance in January. This new guidance is the most sweeping of all GMP guidance and represents a national step forward towards parity. The guidance mirrors the U.S. and EU philosophy for compliance and is a complete departure from previous quality mindsets within the SFDA in China. China is predicted to become the fifth largest pharmaceutical market in the world by 2010.[4] There can be no doubt any long term strategy will include China somewhere in its supply chain.

So how do we as compliance professionals manage the risk of this rapidly changing environment? Ironically, I believe the answer lies in the basic tenets of ICH Q8, Q9, and Q10. The concepts of Quality by Design (QbD) and integrated risk management as a foundation for our quality management system strip away the impediments we have come to know when it comes to defining process and product predictability. This is not a trivial realization. Recently, the FDA engaged a high-profile consulting firm to conduct a survey of why the industry has been so slow to adopt QbD as its product development philosophy. As we figure out the recipe, so too will the emerging markets follow.

After a recent trip to China, I returned more impressed than ever with the rapid level of development within the major markets there. The maturity of the infrastructure in place, ready to support global commerce, was something I was not expecting. However, this new guidance draws a line in the sand that will be very hard for their markets to meet. Until they do, every decision to include the emerging markets will raise the ante from a compliance perspective. The next decade for compliance professionals will be one based on understanding—not just knowledge—as we attempt to interpret and apply the principles which underscore our regulations in a marketplace that will know more change than stability.

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Bikash Chatterjee *is the president of Pharmatech Associates, Inc. He has been involved in the bio-pharmaceutical, pharmaceutical, medical device, and diagnostics industry for over 20 years. His expertise includes site selection, project management, design, and validation of facilities for both U.S. and European regulatory requirements.*