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The Performance Conundrum

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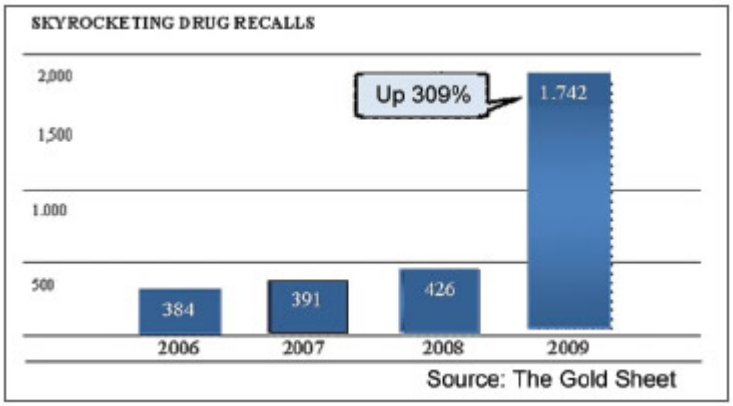
In my last editorial I spoke about the challenges facing the FDA and industry with regard to the effectiveness of the current regulatory structure. If we were to take a step back and look at our performance as an industry along with the effectiveness of the FDA's regulations, I think we definitely have some work to do. Last year the industry set a new record for drug recalls, issuing 1,724 recalls in 2009 versus 426 in 2008.[1]



Granted, nearly 1,000 of those recalls were from a single repackager, but even discounting these, the number represents an increase of nearly 50%. This is further affirmation that the system is broken. Looking at some of the underlying causes of this increase, several factors emerge. First, the rise in Abbreviated New Drug Application (ANDA) filings for generic drugs has increased the population of manufacturers that are striving to be first to file, but are not necessarily complete in terms of their manufacturing optimization. Second, the market pressures that are forcing consolidation on a large scale across the U.S. are challenging established quality management systems, resulting in organizational confusion and creating the potential for reduced oversight and increased product issues. Finally, the FDA has stepped up its scrutiny of manufacturing practices, taking a stricter interpretation of cGMPs and exposing the weaknesses in some companies' manufacturing and quality systems.

The FDA recognizes that industry cannot be held solely accountable for this downward spiral in product safety and compliance. The current system of oversight and regulation could not keep pace. In response, the FDA has launched a new program called TRACK, which stands for Transparency, Results, Accountability, Credibility, and Knowledge-sharing. Borrowing a page from the Operational Excellence playbook, the agency has established performance metrics for over 100 different program offices within the agency. Metrics are available for all interested parties, both internal and external to the agency, to review on a regular basis.

So what does this mean for us as regulatory professionals? I think there are several things to keep in mind when approaching the challenges of new product filings and filing amendments. First, the technical component of our filings may undergo a new level of scrutiny. For ANDAs, this means the product development report and supportive data for the Manufacturing Batch Record (MBR) limits and ranges. Historically this has been an area of weakness because of the pressure to be first to file. Disregarding these areas of increased scrutiny may make it more difficult to make improvements downstream. By this I mean, in the absence of rigorous data in the original filing, what may have been considered a CBE-0 or CBE-30 amendment may become a CBE-90 or Prior Approval. You could argue this goes against the concept of continuous improvement that has been the mantra of the agency's new commitment to scientific understanding. However, I believe this is not inconsistent with the agency's position. There have been far too many highly publicized cases of generic drugs causing adverse reactions to dismiss the risk. For NDA filings, the emphasis will be on the thoroughness of the product and process development activity. The question of adequately powered experimentation will creep back into the evaluation criteria. This is not a trivial shift in thinking. If you look at the history of industry's and the agency's cooperative effort to specify appropriate sample sizes for determining powder blend drug content uniformity, there has never been a satisfactory resolution. Now the onus is on both parties to balance the risk and the need for greater understanding, something we both did poorly in 2009.

On the positive side, I believe greater agency transparency along with having common metrics through the TRACK program will make it easier for industry to anticipate and prepare for agency concerns. This is critical if you consider that failure by both industry and the agency in 2009 could easily drive a philosophy of overt conservatism. Risk could become a four letter word, which could drive industry backward in terms of product approvals. We experienced this for nearly a decade in the late 1990s when the agency became increasingly risk averse. This did not manifest itself in terms of NDA review time or approvals but rather in the Investigational New Drug (IND) phase of product development. By raising the bar at the IND level, the agency was able to maintain its review and approval metrics while driving their risk down as far as possible. As a result, the industry saw fewer new products reach the market and was chastised for its lack of innovation in pursuing new molecular entities.

So what can we expect in the years to come? I believe the role of the regulatory professional is going to change. Involvement sooner in the development lifecycle will become essential to efficiently bring new products to market. Understanding the uncertainty inherent in the discovery, formulation, and process development phases will be important to properly manage risk in any new regulatory filing. I also believe falling back on the most conservative interpretation of an amendment or a filing will no longer be the de facto position from a regulatory perspective. Understanding the scientific rigor of the last filing and that of the proposed change will be essential to successful submission. Finally, extending the same risk management tools to the regulatory process that were used in the product development process will reap huge benefits in terms of anticipating the agency's concerns and understanding our true regulatory risk. In an era of greater transparency there will be no place to hide, so we should build in the tools and metrics to ensure that both can be successful.

Reference

1. 1. Drug Recalls Surge, Parija Kavilanz, CNNMoney.com [1], Aug, 2010

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Links:
[1] http://CNNMoney.com