Published on *Controlled Environments Magazine* (http://www.cemag.us)

The Devil Is In The Details

Bikash Chatterjee

Consolidation on a massive scale amongst the elite of the U.S. pharmaceutical industry raises questions about how to remain competitive, and profound changes to the marketplace can be seen on all fronts. On the regulatory side, the FDA's transformation from an overhead-intensive approach to quality to one based on scientific rigor is well underway. What this will ultimately mean to brand and generic pharma is still unknown, but there can be no doubt that the levels of scientific rigor and document traceability will need to be higher than ever before.

The latest weapon in the competitive arsenal is to leverage low cost APIs and development and manufacturing capability in emerging markets, the so-called BRIC nations of Brazil, Russia, India, and China. On closer view, the real challenge to fully reap the benefits of these low-cost resources lies in minimizing risk, rather than blindly pursuing what looks like easy money. Within the context of regulatory exposure, that entails converting legislation into a measurable action plan. The recent spate of high-profile enforcement actions in the U.S. serves as a bitter reminder of how difficult it is to translate theory into practice.

The U.S. Food and Drug Administration (US FDA) is responsible for enforcing one of the world's most stringent sets of quality requirements. And the newer markets are struggling to correctly interpret regulatory guidance documents and manage overall compliance risk exposure.

India has the largest number of accredited facilities outside the U.S., with nearly 100 pharmaceutical manufacturing facilities approved by the US FDA to source pharmaceuticals. Even before any approval can be given for a pharmaceutical product, these facilities are monitored periodically to ensure that the good manufacturing practice (GMP) standards set by the federal regulator are followed. If there are excursions from these standards the agency moves toward immediate action. Over the years, Show Cause notices have been sent out to several Indian manufacturing facilities, including Ranbaxy, Wockhardt, Sun, Lupin, and Cipla, after manufacturing deviations were found during inspection of their overseas facilities. Despite the benefit of exposure and experience with the US FDA regulations, the risk of non-compliance is ever present.

Ranbaxy, now a subsidiary of Daiichi-Sankyo of Japan, is one of India's leading drug exporters to the U.S. Most recently, the US FDA went so far as to suspend the certification of Ranbaxy's formulations manufacturing facility, Paonta Sahib, for not following its own standard operating procedures (SOP). What followed was a ban on importing products manufactured there, inflicting huge losses to Ranbaxy.

The challenge for China is even greater. Faced with a new set of GMP guidance documents, titled GMP 10 by China's State FDA (SFDA), the technical interpretation and implementation of the guidance documents is daunting.

The discussion regarding Airborne Molecular Contaminant (AMC) control is an excellent example of the gap between the level of definition established by the guidance and the practical challenges in establishing a compliant system design. In my travels to China I have received repeated inquiries as to how to perform Heating, Ventilating and Air Conditioning (HVAC) cleaning and maintenance. In the U.S. and Europe this is rarely an issue. HVAC design is based upon multiple design criteria, such as target air changes per hour, required pressurization cascade, static and dynamic particulate control, and cleaning and environmental monitoring strategies. Filtering and duct sizing considerations are based upon demonstrating an escalating level of control and cleanliness as defined by the operational and process requirements for the area.

These design considerations are universal to the BRIC nations as well. However, the challenge in these countries is the availability of qualified component suppliers, installation contractors, and third party certification companies. In the U.S. and Europe the ductwork supporting controlled environments is not typically cleaned, because it is installed and commissioned in a manner that will ensure cGMP compliance and operation. This is in part achieved because the suppliers of each component are very familiar with the requirements of the industry and can provide defensible Certificates of Authenticity (COA) if required. In addition, both U.S. and Europe have wellestablished third party testing and certification firms that can be engaged to ensure compliance against the design criteria for the room. China has few, if any, of these elements. Compounding the problem is the fact that the European Union (EU), SFDA, and US FDA guidance documents do not line up completely, making establishing a clear compliance strategy difficult.

So why should the regulatory compliance professional care about the HVAC design and installation? I believe the time has come and gone where a regulatory strategy can be blind to the socioeconomic factors that affect our ability to demonstrate regulatory compliance. It is impossible to truly understand the compliance risk of an expansion strategy without including the culture and business mores of the expansion nation. I am sure it is possible to complete the paper exercise of commissioning and qualification as part of a facility validation. But, given the scenario we just discussed, what have we really done to demonstrate **regulatory stability**? With the new complexity associated with regulatory affairs comes the need to delve deeper into the underlying basis for our compliance claims. In other words, the devil is in the details.

The concept of AMC is a good example of the hidden risk that cannot be addressed with conventional compliance thinking. The sources of AMC can be varied. Many of our GMP best practices—such as triple bagging to protect the product as we move through escalating room air quality classifications—protect the product but also the room environment from potential AMCs that may be present in the material entering the room. While in pharma this is an infrequent issue, it becomes a consideration when we enter marketplaces with locally sourced materials that do not have the same stringent controls seen in U.S. suppliers. It has been a primary design consideration for the semi-conductor industry since the inception of large-scale wafer fabs. This critical risk recognition allowed the industry to leverage low-cost nations such as Malaysia and Singapore with relative immunity.

This dynamic interconnection between design, process and quality is the new paradigm shift captured in ICHQ8, Q9, and Q10 that we are trying to embrace as an industry. The complexities of the new global marketplace are changing the risk profile of the regulatory function.

On the positive side, there has never been a better time, from a regulatory philosophy perspective, to define our own best practices in this regard. The FDA's shift to a risk based foundation for demonstrating process stability means we can define what is or is not critical. This changes the rules of how we as regulatory professionals may determine what is a CBE-0 or CBE-30.

On the negative side, our current approaches to establishing process stability are not always designed to capture the underlying risk that comes from global expansion, making the role of regulatory compliance that much more difficult.

Like other industries that have been successful in expanding highly complex processes and products to emerging markets, our success will depend upon our ability to identify the critical details that link the product and process design with true compliance risk and then integrate them as part of our comprehensive regulatory strategy. Anything short of this will leave us vulnerable to compliance and quality risks that will undermine any attempts to fully leverage a global strategy.

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.*