A Change of COURSE for PHARMA MANUFACTURING

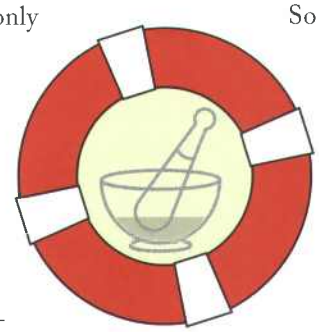
The FDA's Quality-by-Design initiative holds potential to transform the pharmaceutical industry's approach to drug development and manufacturing.

IN SOME WAYS, IT'S LIKE TRYING TO TURN A BATTLESHIP.

When the U.S. Food and Drug Administration (FDA) in August 2002 rolled out a significant new initiative known as "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century: A Risk-Based Approach," the Agency signaled a major change in direction. The approach contained several innovative concepts that the FDA believed would enhance and modernize the regulation of pharmaceutical manufacturing and product quality, and, by extension, the way that the pharma industry would operate.

Indeed, many believe that the methodologies laid out by the FDA—an approach that has now come to be known as Quality by Design, or QbD—have the potential to significantly cut costs and boost the strategic importance of manufacturing in the research-and-development (R&D)-intensive pharma industry.

But change comes slowly in pharma, a $700 billion-plus global industry in which product development lifecycles can easily last from seven to 10 years. And while FDA regulators say that they have been pleased with the industry's progress to date, pundits agree that industry implementation of the new FDA approach is only still in its early stages.



For the pharmaceutical industry, QbD represents "a 180-degree different way of producing products than they've been used to," contends John Avellanet, a biotech and pharmaceutical industry consultant whose firm specializes in quality systems and regulatory compliance issues. Consequently, he figures that full-fledged pharma industry understanding and adoption of the QbD methodology will require an additional 10 to 15 years. And for many of the industry's most tradition-bound participants, "it's going to be a struggle," adds Avellanet, who is managing director and principal at Cerulean Associates LLC, in Williamsburg, Va.

Slow turn

The QbD initiative comes as the pharma industry is facing numerous cost pressures, including growing competition from generics and over-the-counter drugs, expiring patents on many "blockbuster" drugs with fewer replacements in the R&D pipeline, and government and consumer pressures to make health care more affordable.

So as "Battleship Pharmaceutical" continues its slow turn to a new way of doing business, the industry stands to benefit greatly from the use of QbD methodologies.

Among other things, "the cost of manufacturing over the lifecycle will decrease, because there will be less rejects, batch rejection, product recalls and [lower] cost of compliance," says Dr. Moheb Nasr, director of the Office of New Drug Quality Assessment (ONDQA), Center for Drug Evaluation and Research (CDER), at the FDA. "There will also be

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"If you can prove that a drug or biologic characteristic has no impact on safety, efficacy or quality, then you can decide not to bother testing, tracking or controlling it any further."

cost savings in development, because based on Quality by Design, and using quality risk assessments, you will end up focusing your development on areas that are most critical to quality, safety and efficacy, rather than focusing on everything equally."

Other manufacturing savings will come through the use of automation, such as process analytical technology, or PAT, which will enable drug makers to move from batch manufacturing toward continuous manufacturing, Nasr continues. "That should speed up production, and eventually reduce the cost."

Essentially, QbD requires that quality be built into a drug product from the beginning, based on a thorough and scientifically based understanding of so-called critical quality attributes (CQAs) of the product, as well as the critical process parameters (CPPs) that can affect variability of those attributes during the manufacturing process. With this information in place, the pharma industry can then turn to modern technologies that can measure and provide real-time control of those critical parameters during manufacturing. The QbD approach also supports continuous process improvement and the establishment of modern, risk-based quality management techniques.

John Avellanet is Managing Director and Principal at Cerulean Associates LLC, Williamsburg, Va., a biotechnology and pharmaceutical industry consulting firm specializing in quality systems and regulatory compliance. Avellanet founded Cerulean in 2006.

This is a vastly different approach than that of the past, when manufacturing processes, once they were validated with the FDA, were essentially frozen in place. Quality control testing was done following production of a batch, and if changes were made to the process, FDA rules required a revalidation, which manufacturers saw as an expensive and time-consuming process.

As a result, critics say, change-averse pharma manufacturers have been slow to adopt modern manufacturing technologies and approaches such as PAT and continuous improvement methodologies that have been common for decades in other industries. Indeed, the use of Microsoft Excel spreadsheets and paper records is still common in the pharma industry. This has led to comparatively high levels of waste and manufacturing inefficiencies.

"Historically, [pharma] manufacturers have been very change-averse. They didn't want to mess with the process. They were almost forced to roll the dice on making the batches, and if a batch turned out good, they were happy, and if it turned out bad, typically they had to dump the batch," observes Dennis McKinley, Raleigh, N.C.-based industry sales manager, Life Sciences, for automation vendor ABB.

Gimme space

But now, as noted by McKinley and others, QbD is beginning to change that mindset, in part through the use of a "design space" concept. "What QbD is doing is bringing a lot more analytical and process information together in the R&D phase, potentially widening out the size of the design space that companies have to work with, and allowing them a little more flexibility in the process when the product gets up to the manufacturing phase," McKinley says.

Anjali Kataria agrees. "The new guidelines give leniency now to a new type of development manufacturing approach, which is to create a design space, and to identify all the parameters around that design space, so that you have a range that you're operating within, as opposed to a fixed point," says Kataria, who is founder and former chief marketing officer at Conformia Inc., a Sunnyvale, Calif.-based provider of process and product lifecycle software for the pharmaceutical industry. Kataria left Conformia recently to form a not-for-profit organization that will aim to be a clearing house for best practices in drug and food quality leadership, of which QbD will be a central component, she says.

Kataria notes that the design space concept has been used previously in other industry sectors, such as semiconductors, to provide manufacturing flexibility while still maintaining quality. Now, with QbD, she says, it is being ported to pharmaceuticals.

With the design space concept, an out-of-specification parameter that would have triggered a regulatory change process in the past may now be acceptable, says Kataria. Manufacturing may continue, she says, "if you are in a range that was deemed appropriate and acceptable when you submitted your design space, because you're indicating you know how to control your process within this space." The result is "a new way of operating on the manufacturing side, which does not create the need for a post-approval change process," Kataria explains. "It enables you to keep manufacturing."

The QbD approach is predicated on the use of scientific methods to identify and understand CQAs and CPPs that are critical to the quality of a drug product.