**Beyond Compliance: The Future of Pharmaceutical Manufacturing**

***FDA has announced its vision of pharma's manufacturing future. The Process Analytical Technology framework provides a roadmap that companies should follow as they prepare for a new age of highly-automated, IT-driven continuous production systems that are monitored in real time.***

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Engineers who manage pharmaceutical manufacturing plants know that compared to most industries drug making is decidedly low-tech. Most pharmaceutical products today are still prepared and tested in batch mode, even though more efficient continuous processing and monitoring technology is available.

The Food and Drug Administration wants drug companies to adopt continuous processing and online monitoring because the agency believes it will result in safer and more efficacious drugs. FDA's new mantra is "quality by design," in place of "quality by test."

FDA envisions the day when many pharmaceutical manufacturing processes can be remotely monitored in real-time, obviating the need for field inspections.

Pharmaceutical industry executives acknowledge that current manufacturing practices are inefficient – much of their equipment sits idle more than half the time – and that in the future their manufacturing plants will be highly-automated with continuous processing systems running 24/7 in smaller, less-costly facilities.

Both sides share a common vision of the future. The problem is how to get there?

Pharmaceutical executives worry that collecting real-time data from continuous online production will open the door to increasingly onerous regulations and lawsuits. It is difficult enough to comply with FDA's current regulatory regime. What will happen when inspectors remotely monitor production processes around the clock? And what legal liability might accompany this cornucopia of digital data? Will trial lawyers use the natural variance that occurs in every pharmaceutical manufacturing process to allege that drugs created in one production run are of lesser quality than those from another, and therefore were neither safe nor effective?

Clearly, government, industry and consumers have much to gain by moving pharmaceutical manufacturing into the 21st Century. But they have many hurdles to overcome in the process.

FDA officials realize that their past approach to interpreting and enforcing regulations has discouraged technical innovation and the incremental improvement that is common in most manufacturing environments. In the past, FDA inspectors exercised little discretion in determining which systems to inspect or how to apply regulations. Every production process, piece of equipment, electronic record and software program was deemed equally important and subject to vigorous enforcement and remediation. Even simple manufacturing changes might require bioequivalence studies or new clinical trials.

So no changes were made. In most cases, drugs that are under patent today are made in precisely the same way as they were the day they underwent human clinical trials, no matter what breakthroughs in production technology may have occurred since.

Despite punitive fines exceeding $500 million in 2002, quality breakdowns are increasing. FDA recalled 354 prescription drugs in 2002, 40 percent more than in 2001 and double the 1998 tally of 176. While some recalls are caused by mislabeling or other snafus, many are the result of manufacturing problems. According to the Wall Street Journal, five to ten percent of medicines fail to meet specifications and must be reworked or discarded.

Clearly the fines are not having their intended effect. While they may be an effective form of punishment, they have done little to improve quality, safety or efficacy. FDA officials are aware of the shortcomings of this comply-or-be-punished paradigm and want to play a more proactive role encouraging industry to embrace new technology.

Despite its more collaborative stance, industry should expect that the agency will become even more aggressive with repeat violators. FDA has adopted risk management in part to compensate for its limited resources. Critical production systems that pose the highest risk to human health will receive careful scrutiny. And the agency won't hesitate to levy big fines against companies that are slow to remediate.

FDA's inspectorate has not kept pace with industry growth. Agency officials admit they cannot visit every plant at least once every two years as mandated by law. There are more plants, more drugs of greater complexity, and two-thirds of the active ingredients used in more than 6,000 regulated compounds are manufactured abroad in faraway plants that are difficult to visit and inspect. As a result, the agency conducted 1,497 inspections in 2001, down from 2,072 in 1997.

FDA's new approach is based on the science of risk management – determining through statistical analysis and systems theory the likelihood and potential impact of an adverse event.

Industry will benefit from the new approach by cutting the cost of compliance. Manufacturers will be able to anticipate what FDA will inspect, and how rigorously. Extending risk-based analysis to the entire regulatory regime will enable industry to resolve disputes with FDA more expeditiously. In addition, risk management should allow industry to adopt new technology more rapidly, in some cases even retrofitting existing production lines with new equipment.

## Regulatory Overhaul

In August 2002, FDA unveiled its strategy to dramatically overhaul pharmaceutical industry regulation. As part of the two-year initiative, *Pharmaceutical cGMPs for the 21st Century: a Risk-Based Approach*, FDA working groups have released the following guidance documents describing the agency's new approach to regulating five key areas of pharmaceutical manufacturing. FDA's regulatory approach in each of these areas will be based on its new risk assessment methodology.

- *Part 11, Electronic Records, Signatures – Scope and Application.* FDA announced two major policy changes. Fewer electronic records will be subject to Part 11. And inspectors will have greater discretion in deciding which systems are subject to enforcement.

- *Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical cGMP*. FDA's science-based dispute-resolution process enables companies to counter the observations and claims made by inspectors whom they believe to be in error.

- *Sterile Drug Products Produced by Aseptic Processing: Current Good Manufacturing Practices*. FDA adopts a risk-based approach to inspecting the production, testing, facility controls, and electronic records management required in aseptic production.

- *Comparability Protocols – Protein Drug Products and Biological Products, Chemistry, Manufacturing and Controls Information.* FDA wants to encourage industry to modernize its production and testing processes. Comparability protocols are the path by which industry can show new equipment and methods do not change the compound being manufactured.

- *PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance.* FDA's roadmap for manufacturers who want to embrace new production and quality assurance technologies.

In order to comply with FDA's new risk-based cGMP mandates – and to begin moving toward the new manufacturing paradigm – *industry must develop an entirely new approach to manufacturing.* By 2006, the agency expects to see significant

progress towards the vision of continuous processing, including the adoption of new technology and quality management practices.

The agency's newly formed Pharmaceutical Inspectorate and PAT review and inspection teams will have expertise far beyond the current crop of FDA inspectors. Industry will benefit by avoiding inaccurate Form 483 letters written by inexperienced inspectors. By the same token, highly-qualified inspectors accompanied by product specialists from the PAT team can be expected to drill-down into production data and evaluate systems far more critically than their predecessors. Although FDA has developed a dispute resolution process for companies to present evidence contesting observations recorded in a Form 483 letter, the agency's special pharmaceutical inspectors can be expected to write much more insightful criticisms of the high-risk systems they identify and review.

## Working Within the PAT Framework

FDA's Process Analytical Technology framework provides a roadmap for pharmaceutical manufacturers to adopt innovative technology and quality management practices. It also lays out the agency's strategy for enforcing regulations in a way that encourages innovation.

FDA wants industry to adopt an integrated systems approach to achieving product quality. Industry is strongly encouraged to develop risk-management practices to improve product and process quality *because FDA will use risk analysis to target plants, products and systems for inspection.* Starting from today's inefficient, batch-oriented approach to manufacturing, testing and biannual inspections, FDA wants to:

- Ensure product quality through better manufacturing processes.
- Focus on product and process factors that affect performance.
- Engage in continuous real-time quality monitoring.
- Create regulations that evolve along with scientific knowledge.
- Implement risk-based inspections and enforcement to ensure drug quality.

FDA expects that industry will take a systems-based approach to the design, analysis and control of pharmaceutical manufacturing *by using automated sensors and IT-driven analytical tools to measure the quality and performance attributes of materials and processes*.

While FDA has de-emphasized the role of 21 CFR Part 11 in non-critical or low-risk systems, *it is greatly emphasizing the need to adopt sensors, automation and information technology* to improve critical or high-risk manufacturing processes and outcomes. Manufacturers should conduct risk-based assessments of their current

production systems – including the sensors, IT systems and electronic records they generate – and develop a strategy for evolving along with FDA to adopt the PAT manufacturing framework.

FDA has identified a number of technology and management tools that manufacturers should consider applying in their existing and new drug production lines. They can be broadly categorized to include:

- Multivariate data acquisition and analysis tools
- Process analytical chemistry tools
- Process and endpoint monitoring and control tools
- Continuous improvement and knowledge management tools

Each of these tools has a significant IT component and in most risk-management scenarios will need to comply with 21 CFR Part 11 regulations governing data collection, storage and presentation.

Moreover, it is expected that FDA will develop a new approach to inspecting manufacturing processes by monitoring real time data as it is generated by these online, continuous production systems. Manufacturers should begin to implement such systems on a pilot basis now so they can build the knowledge-base they will need in the future.

No matter how proactive its new approach, FDA will never become industry's best friend. A natural and healthy tension always exists between regulator and regulated. But the agency listened carefully to industry concerns as it developed its framework for the future. The ball is now in industry's court. The time has come to put the FDA's new regulatory guidance to the test.

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**Sidebar 1:**

**Drug-Making By the Numbers**

Today's typical pharmaceutical manufacturing plant is a scaled-up copy of the lab in which the drug was developed and first produced in small quantities for clinical trials. But what was relatively simple in a lab setting becomes enormously complex and inefficient on an industrial scale.

Large batch processes are inherently inefficient. Some materials take weeks to process and require human intervention to be sampled and tested, instead of being monitored in place electronically.

According to a study conducted by Raymond Scherzer, senior vice president of manufacturing for GlaxoSmithKline, the 16 largest pharmaceutical companies spend $90 billion annually on manufacturing, $45 billion on materials alone. Between five and 50 percent of materials are lost due to manufacturing inefficiencies. Saving just one percent on material costs would add $400 million a year to industry profits.

Lack of automation means drug-making is labor-intensive. Manufacturing labor costs are $22.5 billion a year industry-wide. Nearly every step requires manual intervention.

Manufacturing facilities are large and complex because drugs are prepared and stored as work in progress in large batches. Thus, facility maintenance and utility costs are $16 billion a year. Capital expense is $25 billion a year, 10 percent of total costs. More troubling: on average, the industry's batch equipment is used less than 30 percent of the time. Most equipment sits idle 70 percent of the time. Clearly, manufacturers have strong incentives to embrace the IT-driven future.

**Sidebar 2:**

**Pharma's Future**

- Small facilities
- Quality by design
- Online measurement and control
- Continuous processing 24/7
- Lights-out factories
- Zero human intervention
- Self-contained and fully-automated systems
- IT-driven factories
- Software and sensors
- Storage area networks
- Lower capital investment
- Manufacturing and R&D overlap
- Manufacturing scale-up is planned before clinical trials

**Sidebar 3:**

## ABCs of Risk-Management

### A. Impact Analysis – Weighing Risk vs. Probability

Every risk management, assessment and measurement process looks at risk in terms of the impact and likelihood of occurrence. These two factors can be separated for analysis, but they are like the front and back of the same hand. Risk analysis must weigh both the likelihood and the impact of an adverse event. The likelihood may be low but the impact could be very high, in which case the system may be very high risk.

When high risk systems fail they have a large and direct impact. For example, a high impact system failure may result in serious injury or death; it may harm or destroy the company's reputation or ability to function; or it may adversely affect a product's strength, purity or marketability.

Of course, a high risk system failure may also result in costly fines and the loss of license to manufacture.

### B. Systemic Risk Analysis – Everything is Connected

Risk is a systemic issue. You cannot separate the software application from the hardware, the user and the overall system. Systemic risk analysis includes the equipment, the environment and the human element.

For example, a well-tested software application may create a security hole because it was improperly installed, default security settings were not adjusted, patches were not downloaded, or because an operator failed to change passwords regularly. If you have inadequate security procedures, the best application in the world is not going to produce the desired result. Unintentional or unanticipated inputs can lead to unexpected results.

Much can be learned from the aerospace industry about post risk investigation and systemic risk analysis. The FAA evaluates and learns from every plane crash. Was the crash caused by equipment failure, environmental factors, pilot error or a combination of the three? The aerospace industry has developed its systemic risk analysis with the help of thorough post failure analysis, which has demonstrated that failures are usually not due to a single event but rather are caused by a combination of weaknesses that culminate in an adverse event.

## C. Risk Tolerance – Perception is Reality

The most difficult element of systemic risk to measure is the public's understanding, perception and tolerance for risk – particularly what physicians, scientists and engineers call "acceptable risk."

When it comes to pharmaceuticals, the public has a very high expectation of safety and a very low tolerance for risk. Except in the most extreme cases, such as "life and death" decisions, the public is largely unwilling to entertain the notion of acceptable risk.

Industry and FDA scientists know that if pharmaceutical companies were to wait until they could produce completely risk-free drugs, there would be no drug products and the public would suffer. Physicians and scientists continually wrestle with how to explain "acceptable risk" to the public. Differing perceptions about acceptable risk are a principal cause of litigation.

When it comes to the public's perception, balancing the risk/benefit equation is never going to be an exact science. Perfect manufacturing quality is never going to be achieved. It is statistically certain, for example, that in extremely large batches there will always be some variance in a drug's contents, which is why such variance is considered an acceptable risk. Moreover, even perfectly made prescription drugs are risky because they do not act on all people in the same way.

The FDA, industry and physicians have a lot of work to do when it comes to educating the public about the nature of risk. One thing seems certain, however: the public's tolerance for risks they believe were created by poorly made drugs will always be extremely low. As a result, the impact of an adverse event on a company that is caused by a preventable manufacturing error will continue to be extremely high.