EVOLVING RISKS IN CONTINUOUS DRUG MANUFACTURING

EXPLORING HOW THE CONTINUOUS MANUFACTURING OF PHARMACEUTICAL DRUGS INTRODUCES NEW CHALLENGES WHEN SECURING INSURANCE COVERAGE AND MITIGATING RISKS

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The adoption of continuous manufacturing systems has the potential to transform pharmaceutical drug production by increasing operational capacity and reducing exposure to many traditional vulnerabilities. But the transition from batch to continuous processes not only marks a shift in operations, it also introduces a fundamental shift in risk that must be addressed in a drug maker's risk management analysis and insurance programs, if applicable.

Continuous manufacturing is nothing new to oil refineries, natural gas processing plants and other manufacturers.These processes have led to improved efficiencies, greater processing speed, boosted quality, less manpower and increased safety when compared to batch-production systems. It can enable manufacturers to more nimbly respond to changes in customer demand and more easily scale their businesses.

While the life science industry has been slower to adopt it, continuous manufacturing has the potential to revolutionize how life-saving medicines are developed and delivered. Some pharmaceutical companies have already implemented continuous processes for regular chemical drugs, and it's likely the manufacture of biologics will be transformed by continuous processes in the next several years.

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This industrywide shift is also strongly supported by the FDA, which is pushing for a future of reduced regulatory uncertainties and more consistent quality control. The administration has stated that cost savings experienced by pharmaceutical companies could be passed on to the customer by way of lower drug prices. In fact, the FDA recently awarded three grants[1] worth nearly $6 million in total to universities and nonprofits to study and promote the adoption of continuous manufacturing of drugs and biological products.

> *"Continuous manufacturing utilizes technologies that offer clear benefits for both patients and industry," FDA Commissioner Scott Gottlieb said in an August 2018 statement. "The approach has the potential to shorten production times and improve the efficiency of manufacturing processes. These benefits translate to lower cost of production and thus the cost of medicine."*

Through the lens of risk management, continuous manufacturing represents a fundamental shift. Traditional exposures associated with human error would be significantly reduced and attention would shift to risks associated with the breakdown of processes. As such, many insurance companies are still determining how to underwrite policies in this space.

In order to secure fair and accurate pricing, drug producers must reduce the uncertainty around continuous manufacturing. They must fully understand and clearly convey how continuous manufacturing is reducing their risks in certain areas while opening up new liabilities in others. In this light, there are several shifts drug manufacturers must consider when contemplating making the switch.

1 https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm615431.htm

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Shift in Resources

Continuous manufacturing operations rely heavily on automated machinery and processes that keep the system moving while simultaneously monitoring for quality and specifications in real time. As a result, human intervention is largely removed from the equation. This allows production to continue 24 hours a day and also eliminates human error and the cost associated with employing these workers. Continuous manufacturing equipment also only takes up a fraction of the space of batch-based facilities, thereby reducing the need for giant production facility footprints.

*In total, this significantly reduces operating costs. A 2015 Wall Street Journal article estimated that the time and cost savings gleaned from continuous manufacturing processes could save drug producers up to **30 percent** in annual operating costs.*[2]

While operating costs are significantly lower in a continuous manufacturing system, FM Global Chemical and Pharmaceutical Principal Engineer Pat Mahan told me in an interview the machinery and equipment involved is much more valuable. Repairing and maintaining such complex equipment can be much more expensive, time intensive and labor intensive than fixing the machines used in batch manufacturing. These machines are often custom built or tailored for the production of a specific product, he said.

2 https://www.wsj.com/articles/drug-making-breaks-away-from-its-old-ways-1423444049

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> *"The equipment used in continuous manufacturing is so complex and unique that even a small break can lead to significant bottle necks in the production process and longer-than-expected business interruptions," Mahan said.*

If drug producers are using a truly unique piece of machinery, the risk of these potentially significant business interruptions must be accounted for in their physical property and business interruption coverage. From a risk management perspective, Mahan says it's crucial for manufacturers to "understand where they are introducing these critical potential bottle necks" and address these liabilities in their risk management strategies in batch manufacturing. These machines are often custom built or tailored for the production of a specific product, he said.

PAT MAHAN

Principal Engineer, FM Global Chemical and Pharmaceuitcal

Pat focuses on providing Loss Prevention Engineering services to FM's Chemical and Pharmaceutical clients.

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Shift in Oversight

Perhaps the greatest promise of continuous manufacturing is that quality assurance can occur without interrupting production. Operators can monitor and make adjustments to processes online, without any physical interference on the production line.

For example, in a traditional batch process, a stuck valve could cause a variation in the control conditions, slightly adjusting the temperature of a product. That variation would likely go undetected until the next sample was pulled, at which time the operator would determine how much of the batch was affected and if the variation warranted product disposal.

With continuous processes in place, technology can be continuously monitored and even self-correct any deviations from the control conditions. The risk of a temperature variation would be significantly mitigated, and companies would see far less "out of spec" product. Because continuous processes rely on single-use materials, the risk of product contamination at the manufacturing site is also significantly reduced.

As algorithms become increasingly sophisticated, pharma manufacturers will have the data and devices to prevent production failures. In the future, it may even be possible to leverage machine learning and predictive analytics to conduct preventative maintenance without shutting down the continuous process.

However, these network-connected sensors and monitoring devices create new areas of cyber liability by opening up entry points for cyber criminals to launch an attack.

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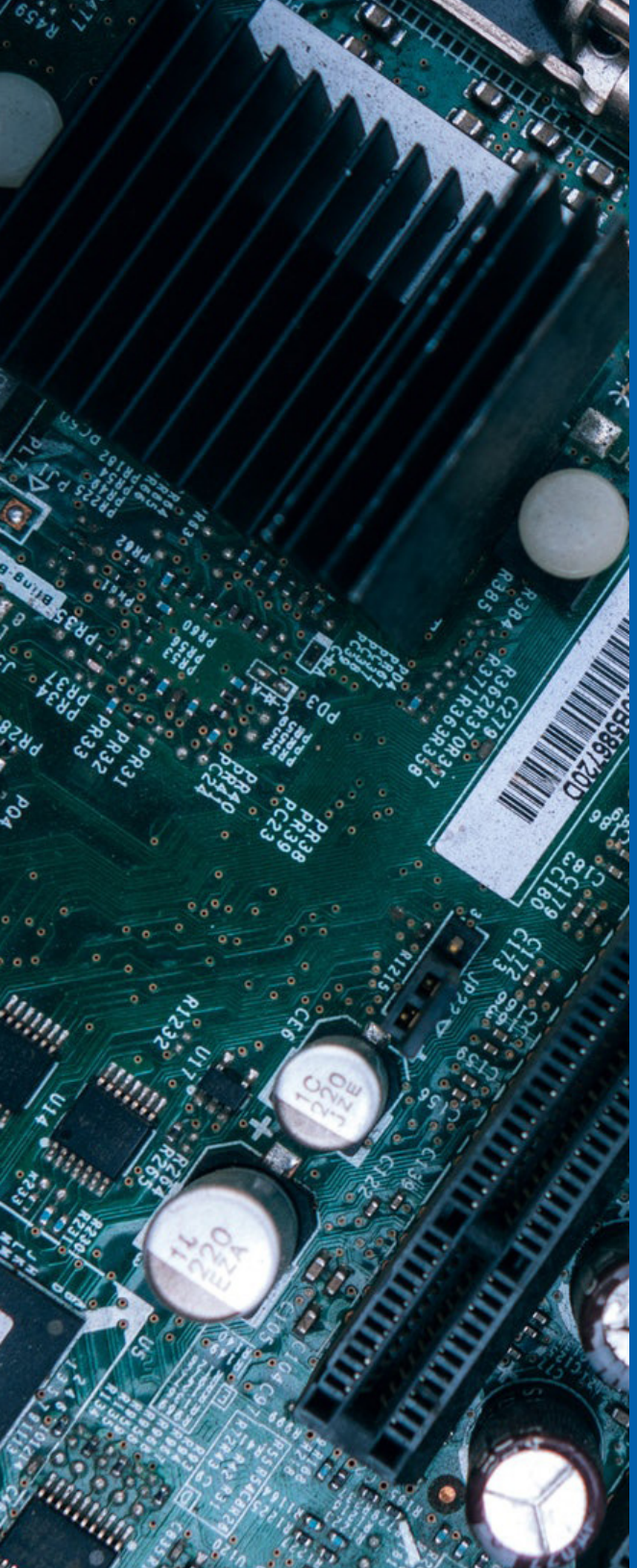

Once inside the network, hackers can gain control of production equipment and make changes to the process that could lead to a litany of costly consequences.

These sophisticated attacks have the potential to go undetected for days at a time, leading to enormous amounts of unusable product.

> "If cyber security isn't appropriately addressed, consequences could include bad product, business interruption, worker injury, and property loss such as fire, explosion or machinery breakdown events," ***Aaron Kalisher,*** Executive Risk Engineering Specialist, Risk Engineering Services at Chubb NA told me in an interview.

These risks must be reflected in physical cyber insurance coverage Kalisher said, adding that there is ample appetite from insurance carriers to take on these risks. Kalisher noted that a comprehensive cyber insurance policy addresses these risks and provides measures and services to help mitigate cyber risk. However, determining the level of coverage and coming to terms on pricing can be difficult given the evolving nature of these liabilities and the potential severity of loss should a drug manufacturer suffer a cyber attack. It is imperative for drug producers to learn the intricacies of these policies as well as their own risks to ensure their risk needs are adequately addressed through a comprehensive cyber insurance policy.

AARON KALISHER
Vice President & Loss Control Executive Specialist, Chubb Insurance
Aaron focuses on cyber security risk management for Chubb's Life Sciences practice.

Shift in Regulatory Footing

The switch from batch to continuous production of pharmaceutical drugs is not only a massive change for manufacturers; it's a big change for regulators as well. While the FDA has been widely supportive of the transition so far, it will take time for regulators to adjust their guidance, approvals, and oversight of this new means of production.

For instance, ***Frank Goudsmit***, CPCU, Senior Vice President, Life Sciences Industry Practice at Chubb NA told me in an interview that the speed in which regulators are able to validate manufacturing lines may slow given the complexity and automation of continuous manufacturing operations. Initially, regulators' lack of familiarity with these facilities and the high-tech equipment involved will likely present some roadblocks to getting these production lines moving in the near future, he said. Also, when the equipment breaks down, the revalidation process will also require more time on behalf of regulators as they continue to familiarize themselves with new processes.

Looking further out, Goudsmit said continuous manufacturing will present new challenges for faulty product entering the stream of commerce and subsequent recalls. In theory, continuous manufacturing facilities contain state-of the-art sensor technology that should catch an excursion that is trending out of specifications. This real-time control would minimize the frequency of product recalls.

But when these sensors fail to recognize and self-correct an issue, does the severity of the impact increase? Cyber-related events can also impede the integrity of the manufacturing process when an out-of-specification condition is not properly recognized.

FRANK GOUDSMIT
Senior Vice President, Life Science Industry Practice,
Chubb Insurance
Frank is the home office underwriter responsible for the profitability and development of Chubb's Life Sciences practice.

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A New Frontier

The adoption of continuous manufacturing will certainly mitigate some of the traditional production risks surrounding oversight and deployment of resources. It has the potential to significantly cut operating costs and revolutionize the way drugs are produced for the better. But any shift in processes this large innately introduces new areas of liability. Making a switch to continuous manufacturing necessitates a ground up review of these risk exposures and pharmaceutical manufacturers must take proactive steps to address them.

Vulnerable network-connected devices, expensive and highly-customized equipment, and new regulatory setbacks redefine risks such as potential physical equipment breakdowns, cyber security events, business interruptions, and potentially lengthy and costly product recalls. Fully understanding these risks, where they come from, and how to address them must be considered by manufacturers, risk managers, and underwriters.

Considering the novelty of this technology in the pharmaceutical space, many insurance carriers are still discovering how to properly price and underwrite these continually evolving risks.

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Pharmaceutical manufacturers looking to implement continuous processes should engage knowledgeable insurance brokers who truly understand the benefits of this approach and how those should be reflected in pricing.

These professionals can work with manufacturers to explain to insurers how risks are transferring from certain areas to others and how that will need to influence the insurer's response.

It is only a matter of time before continuous manufacturing takes hold of the pharmaceutical industry. Manufactures are wise to begin looking at these processes and identifying the risks associated with them today to ensure they are prepared when the time inevitably comes to make a change.

For more information on how the adoption of continuous manufacturing will impact insurance coverage and risk management in the pharmaceutical industry, or any questions on the services we provide the life sciences companies, **call us at 1 (877) 861-3220.**

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