



Navigating the Adoption of Continuous Pharma Manufacturing Amid Unprecedented Global Challenges

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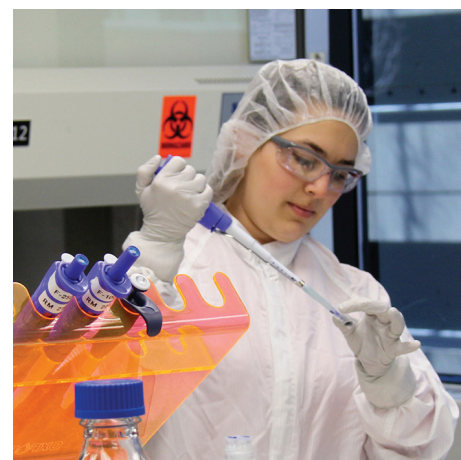


In addition to the devastating impact the COVID-19 global pandemic has had on public health, the economy, and the overall quality of our day-to-day lives, it has also exposed significant risks in today's pharmaceutical supply chain. Improvements in speed to market and quality assurance, among other factors, need to be made to ensure not only the timely delivery of safe and efficacious drugs but also the stability necessary to manage future risks and disruptions.

Among many other benefits, continuous manufacturing can predictably shorten processing times, reduce the risk of human error, deliver better consistency and yield, and provide higher assurance of quality. It has long been considered a viable solution to speed and quality challenges posed by legacy methods. However, while there has been an increase in continuous manufacturing across the pharmaceutical industry over the last several years, many speed bumps prevent its widespread adoption. Driving a path forward for continuous manufacturing calls for a closer look at the current global challenges, existing barriers to implementing it, and each stakeholder's responsibility in pioneering the ideas and initiatives necessary to fulfill its potential.

Lack of advanced manufacturing methods in U.S. impacting market dominance

When the FDA introduced its Process Analytical Technology (PAT) framework in 2004, the intent was to promote the adoption of technologies that would allow for better process understanding and control while also alleviating concerns about regulatory uncertainty that have historically hindered innovation in pharma.¹ The foundation of PAT was that quality cannot be tested into a product but rather built into it. To do so requires a more comprehensive focus on measuring critical material attributes and process parameters and their effect on product quality and performance over its shelf life and real-world utility. PAT encompasses the integrated application of appropriate tools necessary to measure, analyze, and predict manufacturing's chemical and physical aspects. For example, for OSD products, this includes in-process measurement and control of blend homogeneity, the granulation process' endpoint, and real-time release of the final product. The PAT initiative ultimately led to several new technologies, such as real-time material attribute measurements using Raman, Infrared, and near-infrared spectroscopy techniques. These techniques are fast, non-contact, and non-destructive and can provide chemical and physical information about pharmaceutical substances and products during processing.



The industry is shifting to explore additional manufacturing methods.

PAT encompasses the integrated application of appropriate tools necessary to measure, analyze, and predict manufacturing's chemical and physical aspects.

Forging a path toward more efficient and effective process control strategies via the PAT guideline was crucial to expand awareness of the need and opportunity to overcome traditional batch manufacturing with limited laboratory testing as well as usher in more advanced methods. Despite encouragement by the FDA, PAT's uptake lagged, in part, due to the "low-hanging" opportunities for offshore manufacturing to countries with low labor costs. In 2019, Dr. Janet Woodcock, then director of the Center for Drug Evaluation and Research, testified in front of the House Committee on Energy and Commerce about the pharma industry's transition to a global enterprise and how this has led to the U.S.' growing reliance on foreign manufacturers for the supply of raw materials.²

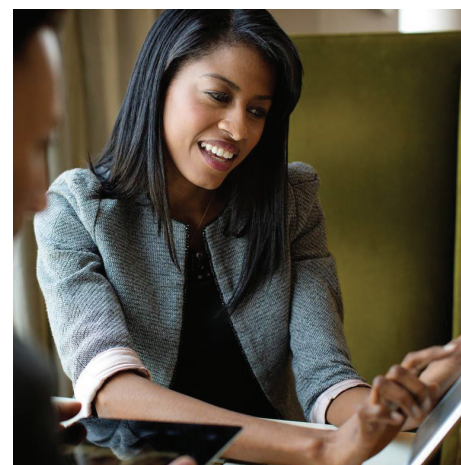
Dr. Woodcock described how cost pressures had driven many U.S. companies to establish more facilities overseas, such as China and India, where savings can be achieved from lower labor costs and environmental regulations. Resolving these issues and bringing manufacturing back to the U.S. requires a twofold effort. First, the industry must invest in maturing its quality management systems. The FDA believes these efforts should be incentivized using a quality management maturity system that “enables purchasers to compare differences in quality and choose whether to reward more reliable manufacturers financially and with increased market share.”² The second recommendation is for the agency to continue encouraging manufacturers to invest in advanced manufacturing technologies, such as continuous manufacturing. The scientific rigor of continuous manufacturing provides a higher level of predictability and quality assurance by using risk assessments based on real-time data rather than opinions. And in an evidence-based system, data and its integrity are at the foundation of every critical decision.

With vulnerabilities of the pharma supply chain in the public eye due to the COVID crisis, the FDA once again called for investing in advanced manufacturing to support public health preparedness.³ So, what can we do to help forge a path to widespread adoption?

Existing barriers to widespread adoption of continuous manufacturing

One of the biggest barriers manufacturers point to when it comes to the lack of widespread adoption of continuous manufacturing is uncertainty. Uncertainty of time to FDA approval relates to regulatory expectations about process validation and therapeutic equivalence when switching from batch to continuous, or developing and launching a product using continuous manufacturing and how that transition could impact their path to market. Many of their questions seem to focus on the FDA’s *Quality Considerations for Continuous Manufacturing* guidance.⁴ This guidance offers insight into how drug manufacturers can align their applications with the FDA’s current thinking. However, overcoming legacy practices and mindsets can still pose significant challenges.

While continuous manufacturing does offer many attractive benefits in an increasingly challenging and complex market, it is important to determine whether continuous or batch manufacturing is the best fit for your product. Small-scale studies using data collected during Phase II trials - such as characterization - to understand the materials and how they interact with the process, should drive this decision.⁷ Manufacturers who want to move from batch to continuous need to determine if the economic benefits are significant enough to make the switch, which will require considerable time and investment in terms of regulatory filing work. The FDA recognizes it can be challenging to adopt innovative methods, so the agency established its Emerging Technology Program to “discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of a novel technology before filing a regulatory submission.”⁵ This group is available for any early dialogue companies need or want before submitting their drug application. Utilizing resources such as this to engage early with the FDA can help manufacturers avoid the delays and issues frequently associated with adopting continuous manufacturing.



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Many of the regulatory review and inspection inquiries relate to failure modes, the rigor of risk-assessment, and control strategy validity. Legacy practices, such as the small sample size of conventional compendia testing and rudimentary assessment of critical physical attributes, can be difficult to resolve in the context of real-time measurements and multivariate statistical process control capabilities being introduced in a continuous manufacturing process. Furthermore, challenges in international harmonization of compendial or market standards add to business uncertainty^{6,7}.

The role of CDMOs in change

Regulatory questions about continuous manufacturing and, filling the knowledge gap needed to execute it, successfully are certainly high on the list of challenges. However, making a cultural shift to continuous manufacturing may be the biggest challenge of all. The pharmaceutical industry and its stakeholders are often averse to change for several reasons. Manufacturing is often treated like the stepsister of pharma's R&D. CDMOs play a unique role in this transition, as manufacturing is the core of their business, making them a crucial component of driving new and innovative platforms.



CDMOs continue to play a unique role in the progression of continuous manufacturing.

And with small pharma companies responsible for 63% of all new prescription drug approvals in the past five years, CDMOs will play a major role in the future of patient health and delivering new drugs to the market.⁹

Over the last couple of decades, the evolution of the drug development and manufacturing landscape, motivated by factors such as the patent cliff and highly complex drug substances, has led to the substantial growth of the CDMO market. In 2018, its worth was over \$130 billion; by 2026, this number is expected to grow to nearly \$279 billion due to the value much of the industry sees in strategic partnerships.⁸ CDMOs can offer specialized services and expertise and, most importantly, make investments in capacity and technology that smaller and/or less experienced companies do not have the capital to invest (or the willingness to take the risk). And with small pharma companies responsible for 63% of all new prescription drug approvals in the past five years, CDMOs will play a major role in the future of patient health and delivering new drugs to the market.⁹ If they implement methods that offer faster and more cost-effective ways to provide high-quality medicines, such as continuous manufacturing, they can catapult the industry into the modernized manufacturing evolution it needs.

For example, Thermo Fisher Scientific is scaling its business in several ways to meet its customers' changing needs by looking at how their teams can evolve the technology they currently offer, such as equipment or PAT tools, and leverage it with their existing offerings. As a CDMO in a growing market, Thermo Fisher Scientific knows it must also expand its capacity to accommodate demand. In 2019, the company announced an investment to expand its solutions, capacity, and talent globally, including creating an expanded API network in Florence and Greenville, SC; Linz, Austria; Regensburg, Germany; and Cork, Ireland. Thermo Fisher Scientific trains existing personnel and adds new talent to support the oncoming capacity and services for continuous manufacturing. These efforts highlight the type of commitment CDMOs need to make in a rapidly changing environment. Thermo Fisher Scientific continues to become key players in providing and advancing more efficient drug development routes and manufacturing.

Taking the first step

Moving today's network of drug developers and manufacturers toward a future with continuous manufacturing will not be easy; however, disruptive – but necessary – change never is. The first step is acknowledging the need to do so. In 2019, 60% of drug shortages were caused by supply chain interruptions due to manufacturing and/or quality issues, with the potential for some shortages to last up to eight years.¹⁰ As COVID-19 wreaks havoc across the globe, it is intensifying the devastating impact of drug shortages, as the supply of medications for the treatment of malaria, rheumatoid arthritis, and lupus have been used as potential therapies for treating COVID-19.¹¹ Dr. Woodcock's warnings about the risks the U.S. faces by relying heavily on China became a reality when research found that 57 drugs, including cancer and HIV treatments, may face shortages because of issues with manufacturing in China during the pandemic.¹²

The year 2020, although challenging, has forced the hand of many industries to adopt new technologies to continue business amid COVID-19 restrictions. While these approaches may have initially been viewed as temporary solutions, the benefits and cost efficiencies that resulted from implementing them will likely not be forgotten once decisions need to be made about moving forward in a post-COVID-19 world. Yet, the pharmaceutical industry should not need to learn any more lessons to make the right decision. The responsibility we have to the patients who depend on us is too great not to change when it is so desperately needed. Continuous manufacturing is just one way to get started.



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