

Promoting Continuous Manufacturing in the Pharmaceutical Sector

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Discussion Guide

Introduction

Over the past decade, drug shortages and product recalls in the US have occurred at unprecedented rates, limiting patient access to critical medicines and undermining health care. A majority of these shortages and recalls have been due to manufacturing quality issues. Recent scientific policy discussions have centered around methods for confronting these new and increasingly complex challenges in ensuring a consistent supply of high quality drugs, including the implementation of innovative manufacturing technologies. Pharmaceutical manufacturing processes are still largely accomplished using traditional “batch” methods, which in many cases may lack the agility, flexibility, and reliability needed to combat failures in drug product quality. As part of the ongoing efforts to ensure a continuous supply of high-quality pharmaceuticals in the US, the Food and Drug Administration (FDA) is pursuing a range of strategies designed to improve the flexibility, reliability, and quality of pharmaceutical manufacturing. Among these strategies is the promotion of continuous manufacturing, which can address some of the challenges associated with batch manufacturing, as well as mitigate the risks of quality failures.¹ At present, however, continuous manufacturing processes are not widely used by the pharmaceutical industry, and there remain a number of barriers to their broader adoption.

In collaboration with a range of industry, academic, and government partners, FDA is currently exploring ways in which it can help to address these barriers and facilitate the uptake of new manufacturing technologies. In support of these efforts, and under a cooperative agreement with FDA, the Center for Health Policy at Brookings is convening this workshop in order to: 1) identify the major scientific/technological, operational, and regulatory barriers to the adoption of continuous manufacturing in the pharmaceutical industry, 2) discuss regulatory policies and strategies that could help to address those barriers, and 3) explore approaches to improving public and private sector alignment and collaboration to promote the adoption of continuous manufacturing.

The Potential Role of Continuous Manufacturing in the Pharmaceutical Sector

The vast majority of pharmaceutical manufacturing is currently accomplished using traditional “batch” methods. Broadly speaking, batch processes allow for raw materials to be input into the system at the beginning of the process and then discharged all at once as a finished product sometime afterwards. The finished batch needs to have uniform characteristics throughout and to meet set quality standards.^{2,3} These processes involve a number of separate steps (blending, granulation, drying, etc.), with the intermediate product being collected, stored, and often transported to another facility between each stage of production. Manufacturing a product in batches can therefore be a long, disconnected process, and one that typically lacks the agility, flexibility, and reliability needed to respond to sudden changes in supply and demand for the final product or its ingredients.^{4,5}

Continuous manufacturing processes, by contrast, allow for raw materials to be input into the system and the finished product to be discharged from the system in a continuous fashion. In a recent publication, FDA outlined a future vision for continuous processes where, ideally, the individual steps

found in batch manufacturing would be transformed to a single, integrated continuous manufacturing process. As part of this, PAT systems would be utilized to produce real-time data that allow for monitoring and control of the process, and engineering process control systems would be used to mitigate the risk of process variability on finished product quality.⁶

This type of process offers a number of advantages over batch manufacturing. First, continuous processing is more agile and flexible, and can therefore respond more rapidly to changes in supply or demand. This is particularly advantageous in emergency situations, such as critical drug shortages or pandemics.⁷ For example, continuous manufacturing can potentially allow for more rapid increases in production volume by operating the process for longer periods of time, utilizing parallel processing lines, or increasing the flow rate through the process. Reducing or eliminating scale-up bottlenecks could also help to accelerate the path to market for breakthrough pharmaceuticals.⁸

The equipment used by continuous processes is typically much smaller than that used by batch processes, and requires a smaller volume of materials to operate.^{9,10} Hold times between steps in the manufacturing process can potentially be eliminated, and the supply chain necessary to manufacture products can be significantly shortened.¹¹ Continuous manufacturing may also facilitate the streamlining of the manufacturing process through the removal of corrective or work-up unit operations. As a result, continuous processes can be more efficient, reliable and cost-effective than traditional batch methods, resulting in significant cost savings down the line.¹² One estimate pegs the yearly operational expense of a small-scale continuous manufacturing plant at 30% less than a traditional batch manufacturing plant, and that switching from batch to continuous manufacturing could save the pharmaceutical industry billions of dollars per year.¹³ Continuous systems may also produce a smaller environmental footprint and reduce the risk of product quality failures compared to batch systems.^{14,15}

Continuous manufacturing also supports a systematic, scientific and risk-based approach to pharmaceutical development. Development of a robust process relies on utilizing the acquired product and process understanding to identify sources of variation to product quality and to design appropriate control strategies to address these risk areas. Continuous manufacturing provides an opportunity to utilize this enhanced product and process understanding to adopt advanced manufacturing controls and to produce uniformly high quality products with reduced waste resulting from the generation of out-of-specification material.

Barriers to the Adoption of Continuous Manufacturing

Although there is general agreement that continuous manufacturing offers substantial benefits over batch manufacturing, the pharmaceutical industry has been much slower to adopt it than other industries.¹⁶ This is due to a number of technical, operational, and economic challenges that have slowed progress, which are described briefly in the section below. (For a fuller exploration of these challenges, see the recently released [white papers](#) from the International Symposium on Continuous Manufacturing of Pharmaceuticals.)

Technical Challenges

There are currently a number of technical challenges associated with continuous manufacturing, which vary depending on the specifics of the product under development. For example, major issues include (though are by no means limited to) drug substance characterization and handling, the development of accurate process operations models, and optimal approaches to start-up and shutdown.¹⁷ Integrated pharmaceutical processes often involve the handling and transportation of materials. As such, monitoring the flow of materials and being able to trace these materials individually throughout the

integrated processes can be challenging. It is also challenging to develop small-scale continuous manufacturing lines that can be used during clinical development (i.e. before approval), due to lack of commercially available equipment. Currently, processes conducted in the lab at the clinical development phase are largely batch in nature, and are not easily switched over to a continuous process for commercial manufacturing.¹⁸ Additionally, although continuous manufacturing has a number of safety advantages compared to batch manufacturing, it presents its own set of safety concerns that designers and operators will need to anticipate, including, for example, how to prevent overfilling, over-pressurization, material spills, backflow of material into other parts of the equipment, and other potential hazards not normally present in batch manufacturing.¹⁹ In continuous processes, material is constantly flowing through the system so product quality needs to be measured in real-time. To achieve widespread adoption of continuous manufacturing technologies, new generations of equipment, sensors and automation will need to be developed that monitor and control the process in real-time. Developing or adapting continuous manufacturing processes for the generics market will present additional challenges, as manufacturing strategies differ substantially between the two sectors.

Business and Operational Challenges

These various technical challenges are compounded by business and operational factors at play in the pharmaceutical industry. In order to be as effective and efficient as possible, continuous manufacturing processes should be adopted in the early stages of product development.²⁰ However, aligning the design and development of manufacturing processes with clinical development timelines is challenging, and will likely require changes to current organizational structures within companies. The uptake of continuous manufacturing processes will also depend on the development of innovative enabling technologies, which take time to evaluate, validate, and implement widely.²¹ The pharmaceutical industry has historically been slow to adopt new technologies—owing in part to its significant existing capital investments in batch processing facilities—which may slow the pace of innovation among equipment vendors.²²

The pharmaceutical industry's conservative business culture is also perceived as being a barrier. New manufacturing approaches must often be proven superior from both a technological and financial standpoint, as well as tied to the development of a specific product, before they are implemented more widely.²³

Regulatory Challenges

The pharmaceutical sector is highly regulated, and many companies fear that any significant changes to existing manufacturing processes could create regulatory delays.^{24,25} This perceived uncertainty has further contributed to a “business as usual” mindset that leads to slow adoption of continuous processes.²⁶ Furthermore, while continuous manufacturing aligns strongly with both FDA and ICH guidelines, pharmaceutical manufacturing is a global enterprise, and companies must gain approval for their products in multiple countries with their own regulatory bodies. Although FDA has been promoting continuous manufacturing for several years, not all global regulatory agencies may be similarly willing or able to review and approve a continuous process for use. More work is likely required to resolve issues related to regulatory harmonization.²⁷

Workforce Challenges

Designing, implementing, and adequately regulating these new approaches to manufacturing will require a highly skilled and well-trained workforce, both within industry and regulatory bodies. For example, continuous manufacturing is more engineering intensive than traditional batch methods, and will require industry personnel to gain expertise in new technologies related to process control,

measurement techniques, and other aspects of continuous systems.²⁸ Regulators will also be required to learn about these new processes, their potential failure points, and how to assess if they are being implemented and run properly.²⁹ There is concern within the pharmaceutical industry that the understanding of and enthusiasm for continuous manufacturing shown by agency leadership will not be disseminated evenly down to the ranks of the inspectors and other regulators working with companies to implement continuous processes.³⁰ Continuous systems also produce a substantial amount of data compared to batch systems, which will likely require greater statistical training for engineers, scientists, and regulators alike.

At present, there is a mismatch between these necessary skills and those currently being developed and recruited.³¹ Addressing this gap will likely require sustained institutional commitment and direct financial investments from a broad range of stakeholders, including academic institutions, government agencies, and industry.

FDA Efforts in Modernizing Pharmaceutical Manufacturing

The Center for Drug Evaluation and Research (CDER) oversees several initiatives designed to ensure a continuous supply of high quality drugs for patients as well as facilitate the ongoing modernization of pharmaceutical manufacturing. This includes the maintenance and enforcement of certain manufacturing regulations collectively known as current Good Manufacturing Practices (cGMPs). cGMPs represent the standard that manufacturers must meet regarding the manufacturing, processing, packaging, or holding of a drug.³² FDA conducts regular inspections of pharmaceutical manufacturing facilities to certify that manufacturers are in compliance with cGMP regulations, both before a drug is approved and at regular intervals following approval.³³ Failure to comply with cGMP standards can result in regulatory action, including seizure of drugs, requests for recall, and fines.³⁴ In 2002 the agency launched the Pharmaceutical cGMPs for the 21st Century initiative to encourage the implementation of a modern, science- and risk-based pharmaceutical quality assessment system. The initiative was designed to achieve several goals, including encouraging the early adoption of new technological advances by the pharmaceutical industry, and ensuring that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science.³⁵

In pursuit of these goals, FDA has taken steps to integrate the concepts of quality by design (QbD) into subsequent regulatory guidances. First introduced in FDA's guidance for industry on Process Analytical Technologies (PAT) in 2004, QbD is a systematic science- and risk-based approach to pharmaceutical development.^{36,37} QbD holds that quality cannot be tested into products; rather, it should be built-in as part of the product's fundamental design. This is achieved through a comprehensive understanding of the intended use, characteristics, design, and manufacturing process of the product using principles of engineering, material science, and quality assurance. The FDA has worked closely with other leading regulatory bodies through the International Conference on Harmonization (ICH), to reconcile and standardize its scientific and technical principles, including QbD, with the regulatory agencies of the European Union and Japan. To ensure that those principles are implemented uniformly among its member nations, ICH has issued a number of quality guidelines and supporting documents, including: ICH Q8 (R2) (Pharmaceutical Development), ICH Q9 (Quality Risk Management), ICH Q10 (Pharmaceutical Quality System), the ICH Q1WG on Q8, Q9, Q10 Question and Answers, the ICH Q8/Q9/Q10 Points to Consider document, and the ICH Q11 (Development and Manufacture of Drug Substances).³⁸

However, despite the progress made towards the goals of the 21st Century initiative, recent challenges—including increases in the number of drug shortages and recalls—have prompted FDA to implement

additional changes to the way it oversees the pharmaceutical industry.³⁹ As part of the response to these new challenges, the agency launched the Office for Pharmaceutical Quality (OPQ) in early 2015. By integrating FDA’s review, inspection, surveillance, policy, and research operations, OPQ will strive to promote “One Quality Voice” for FDA and increase the agency’s oversight of quality during all stages of a drug’s lifecycle.⁴⁰ OPQ is organized based on discipline and expertise, and utilizes team-based Integrated Quality Assessment (IQA)—which integrates review and inspection processes—to leverage the relevant expertise within OPQ to provide patient-focused and risk-based quality recommendations. This will ultimately lead to more effective and efficient regulatory decisions.

Among other goals, OPQ is working to encourage the development and adoption of new technologies by the pharmaceutical industry, including those related to continuous manufacturing.⁴¹ FDA considers the implementation of emerging technologies as critical for addressing the primary drivers of drug quality issues such as shortages over the long term. To foster the adoption of these technologies, an emerging technology team (ETT) within OPQ has been formed. In collaboration with other OPQ offices, the ETT will facilitate implementation of new technologies through: 1) enhanced communication with sponsors, 2) ensuring consistency, continuity and predictability in review and inspection; 3) identification and evaluation of regulatory roadblocks; and 4) the establishment of review and inspection standards and policy, as needed.

Workshop Objectives

In support of these ongoing efforts, the Center for Health Policy at the Brookings Institution is convening this workshop in order to explore methods by which FDA and other key stakeholders can facilitate the more widespread adoption of continuous manufacturing within the pharmaceutical industry. This workshop will provide an opportunity for pharmaceutical manufacturers, regulators, academics, and government agency representatives to discuss the major barriers to the adoption of continuous manufacturing in the pharmaceutical industry, identify regulatory policies and strategies that could help to address those barriers, and explore approaches to improving public and private sector alignment and collaboration to promote the adoption of continuous manufacturing. The structure of the day’s discussion and the questions to address are described below.

Session I: Assessing the Current Landscape and Future Direction for Continuous Manufacturing

Objective: This session will allow for a discussion of the current state of continuous manufacturing in the pharmaceutical industry, and identify high-level goals for both FDA and industry to pursue in both the short and long term (5-10 years). This session will help to frame the rest of the day’s discussion, which will focus on how FDA can pursue these goals. Questions to address include:

- The current status of CM in the pharmaceutical industry
 - For brand companies
 - For generic companies
 - For small-molecule drugs
 - For biologics
- Feasible and measurable near- and long-term goals that the different stakeholders can set for itself as part of its effort to encourage uptake of CM

Session II: Improving Scientific and Technical Knowledge to Support Continuous Manufacturing

Objective: Identify any major knowledge gaps in scientific/technical understanding in the field of continuous manufacturing, and prioritize for action those research activities that FDA, in collaboration

with other federal and international agencies, can support to address those gaps. Questions to address include:

- What are the major gaps in scientific/technical knowledge regarding CM processes, and to what extent do these gaps impact their broader uptake?
- From a regulatory science perspective, what research activities are needed to help address those knowledge gaps?

Session III: Addressing Barriers to the Adoption of Continuous Manufacturing

Objective: Discuss the major barriers to the broader implementation of CM processes, and explore potential approaches that FDA might consider to help address those barriers. Questions to address include:

- What barriers exist to implementing continuous manufacturing in the pharmaceutical sector?
 - At the operational level?
 - At the regulatory review level?
 - At the facility readiness level?
- Acceptance by international health authorities
- What additional standards, policies, or strategies could FDA consider to encourage implementation of continuous manufacturing?

Session IV: Building Stakeholder Collaborations to Facilitate the Implementation of Continuous Manufacturing

Objective: Identify strategies that can help to facilitate collaboration and alignment between key stakeholders to encourage the adoption of CM, and discuss how FDA can best support these collaborations. Questions to address include:

- What major efforts are currently underway (in industry, academia, government) to promote the uptake of CM processes?
- What opportunities exist to improve alignment and collaboration between these stakeholder groups?
 - In terms of global regulatory harmonization?
 - In terms of scientific research support?
 - In terms of policy and regulatory guidance development?
- How best can FDA facilitate this collaboration, and what role should the agency play? (Participant, Leader, etc.)

¹ Lee, S. L., et. al. (2015). Modernizing pharmaceutical manufacturing: from batch to continuous production. *Journal of Pharmaceutical Innovation*, 10(3), 191-199. doi: 10.1007/s12247-012-9215-8.

² Ibid.

³ Chatterjee, S. (2012). FDA perspective on continuous manufacturing. Accessed October 8th, 2015 from <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM341197.pdf>.

⁴ Trout, B., Bisson, W. (2009). Continuous manufacturing of small-molecule pharmaceuticals. Accessed October 8th, 2015 from <http://www.qbd-dtc.com/wp-content/uploads/continuous-manufacturing.pdf>.

⁵ Lee, S. L., et. al. (2015). Modernizing pharmaceutical manufacturing: from batch to continuous production. *Journal of Pharmaceutical Innovation*, 10(3), 191-199. doi: 10.1007/s12247-012-9215-8.

⁶ Ibid.

⁷ Ibid.

⁸ Ibid.

⁹ Ibid.

¹⁰ Jacoby, R., et. al. (2015). Advanced biopharmaceutical manufacturing: an evolution underway. Accessed October 8th, 2015 from <http://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-advanced-biopharmaceutical-manufacturing-white-paper-051515.pdf>.

¹¹ Lee, S. L., et. al. (2015). Modernizing pharmaceutical manufacturing: from batch to continuous production. *Journal of Pharmaceutical Innovation*, 10(3), 191-199. doi: 10.1007/s12247-012-9215-8.

¹² Jacoby, R., et. al. (2015). Advanced biopharmaceutical manufacturing: an evolution underway. Accessed October 8th, 2015 from <http://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-advanced-biopharmaceutical-manufacturing-white-paper-051515.pdf>.

¹³ Mascia, S., Trout, B. (2015). Integrated continuous manufacturing. *Pharmaceutical Manufacturing*. Accessed October 8th, 2015 from <http://www.pharmamanufacturing.com/articles/2014/integrated-continuous-manufacturing/>.

¹⁴ Jacoby, R., et. al. (2015). Advanced biopharmaceutical manufacturing: an evolution underway. Accessed October 8th, 2015 from <http://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-advanced-biopharmaceutical-manufacturing-white-paper-051515.pdf>.

¹⁵ Myerson, M.S., et. al. (2014). Control systems engineering in continuous pharmaceutical manufacturing. *Journal of Pharmaceutical Science*, 104(3), 832-9. doi: 10.1002/jps.24311.

¹⁶ Baxendale, I. R., et. al. (2015) Achieving continuous manufacturing: Technologies and approaches for synthesis, work-up and isolation of drug substance. *Journal of Pharmaceutical Sciences*, 104(3), 781-91. doi: 10.1002/jps.24252.

¹⁷ Byrn, S., et. al. (2014). Achieving continuous manufacturing for final dosage formation: challenges and how to meet them. Accessed October 8th, 2015 from <https://iscmp.mit.edu/sites/default/files/documents/%28NEW%29%20ISCMP%202014%20White%20Paper%2020-%20Achieving%20Continuous%20Manufacturing%20for%20Final%20Dosage%20Formation.pdf>.

¹⁸ Baxendale, I. R., et. al. (2015) Achieving continuous manufacturing: Technologies and approaches for synthesis, work-up and isolation of drug substance. *Journal of Pharmaceutical Sciences*, 104(3), 781-91. doi: 10.1002/jps.24252.

¹⁹ Ibid..

²⁰ Byrn, S., et. al. (2014). Achieving continuous manufacturing for final dosage formation: challenges and how to meet them. Accessed October 8th, 2015 from <https://iscmp.mit.edu/sites/default/files/documents/%28NEW%29%20ISCMP%202014%20White%20Paper%2020-%20Achieving%20Continuous%20Manufacturing%20for%20Final%20Dosage%20Formation.pdf>.

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²² Jacoby, R., et. al. (2015). Advanced biopharmaceutical manufacturing: an evolution underway. Accessed October 8th, 2015 from <http://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-advanced-biopharmaceutical-manufacturing-white-paper-051515.pdf>.

²³ Byrn, S., et. al. (2014). Achieving continuous manufacturing for final dosage formation: challenges and how to meet them. Accessed October 8th, 2015 from <https://iscmp.mit.edu/sites/default/files/documents/%28NEW%29%20ISCMP%202014%20White%20Paper%2020-%20Achieving%20Continuous%20Manufacturing%20for%20Final%20Dosage%20Formation.pdf>.

²⁴ Ibid.

²⁵ Ibid.

²⁶ Ibid.

²⁷ Ibid.

²⁸ Baxendale, I. R., et. al. (2015) Achieving continuous manufacturing: Technologies and approaches for synthesis, work-up and isolation of drug substance. *Journal of Pharmaceutical Sciences*, 104(3), 781-91. doi: 10.1002/jps.24252.

²⁹ Ibid.

³⁰ Byrn, S., et. al. (2014). Achieving continuous manufacturing for final dosage formation: challenges and how to meet them. Accessed October 8th, 2015 from <https://iscmp.mit.edu/sites/default/files/documents/%28NEW%29%20ISCMP%202014%20White%20Paper%2020-%20Achieving%20Continuous%20Manufacturing%20for%20Final%20Dosage%20Formation.pdf>.

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- ³⁵ US Food and Drug Administration. Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach: Second Progress Report and Implementation Plan. Accessed October 14th, 2015 from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/UCM071836>.
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- ³⁹ Yu, L., Woodcock, J. (2015). FDA pharmaceutical quality oversight. Accessed October 14th, 2015 from <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM442666.pdf>.
- ⁴⁰ Ibid.
- ⁴¹ Ibid.