Center for Health Policy at BROOKINGS

Promoting Continuous Manufacturing in the Pharmaceutical Sector

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Meeting Summary

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 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.

The Potential Role of Continuous Manufacturing in the Pharmaceutical Sector

Manufacturing a product in traditional batches can 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.[2,3] 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. This type of process offers a number of advantages. For example, continuous processing can permit increased production volumes without the current challenges related to scale-up, 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.[3]

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. [3,4] Hold times between steps in the manufacturing process can potentially be eliminated, and the timelines to produce manufactured products can be significantly shortened.[5] Continuous manufacturing may also facilitate the streamlining of the manufacturing process through the removal of corrective or work-up unit operations. Continuous manufacturing also supports a systematic, scientific, and risk-based approach to pharmaceutical development. As a result, continuous processes can be more efficient, reliable, and cost-effective than traditional batch methods, resulting in significant cost savings.[6]

Despite the fact that the potential benefits of continuous manufacturing have generally been recognized, there are a number of technical, business and operational, regulatory, and workforce challenges that continue to impede the broader adoption of continuous manufacturing.

FDA Efforts in Modernizing Pharmaceutical Manufacturing

The FDA's Center for Drug Evaluation and Research (CDER) oversees several initiatives designed to ensure a continuous supply of quality drugs for patients, including initiatives focused on enhancing product quality through the ongoing modernization of pharmaceutical manufacturing. In 2002, the agency launched the 21st Century Quality Initiative, which was aimed at encouraging the implementation of a modern pharmaceutical quality oversight system.[7] The initiative was designed to achieve several goals, including encouraging the early adoption of new technological advances by the pharmaceutical industry, and ensuring that FDA policies and procedures are based on state-of-the-art pharmaceutical science.[8]

In pursuit of these goals, FDA has taken steps to integrate the concepts of quality by design (QbD), risk management, and robust pharmaceutical quality systems into subsequent regulatory guidances.[9,10] As noted in FDA's guidance on Process Analytical Technologies (PAT) in 2004, quality cannot be tested into products; rather, it should be built-in as part of the product's fundamental design. The FDA has worked closely with other leading regulatory bodies through the International Conference on Harmonization (ICH) to reconcile and standardize the scientific principles of QbD and their pharmaceutical application 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 (such as ICH Q8, Q9, Q10, Q11).[11]

Despite the progress made, recent challenges—including continuing drug shortages and recalls—have prompted FDA to implement additional changes to the way it oversees the pharmaceutical industry.[12] As part of the response to these new challenges, the agency launched the Office for Pharmaceutical Quality (OPQ) in early 2015.[12] OPQ is organized based on discipline and expertise, and integrates review and inspection processes to better leverage expertise and to provide more effective and efficient regulatory decisions. Among other goals, OPQ is working to encourage and facilitate the development and adoption of new technologies by the pharmaceutical industry, including those related to continuous manufacturing.[12]

FDA considers the implementation of emerging technologies as critical for addressing the primary drivers of drug quality issues over the long term. To foster the adoption of these technologies, an emerging technology team (ETT, CDER-ETT@fda.hhs.gov) within OPQ has been formed. In collaboration with OPQ sub-offices, the ETT works to facilitate the implementation of new technologies through a range of strategies (For more information, see Janet Woodcock's presentation from the event.) Furthermore, OPQ supports regulatory science and research, and works to enhance science- and risk-based approaches for quality assessment of emerging technologies through its internal research and scientific collaborations with academia and other government agencies (e.g., Biomedical Advanced Research and Development Authority).

Meeting Objectives

In support of these ongoing efforts, the Center for Health Policy at the Brookings Institution, in partnership with FDA, convened a meeting on October 19, 2015 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 provided 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 day's discussion was divided into four major sessions that focused, respectively, on the current landscape and ideal future direction for continuous manufacturing, priorities for improving scientific and technical knowledge in the field, strategies for addressing the barriers to continuous manufacturing, and approaches to building multi-stakeholder collaborations.

Assessing the Current Landscape and Future Direction for Continuous Manufacturing

Participants began the day by discussing the current state of continuous manufacturing. There was broad agreement among the participants that industry has significant interest in continuous manufacturing, including small-molecule and biologic manufacturers, contract manufacturing organizations, and equipment, instrument, control, and excipient supplier companies. Participants also noted that FDA has been very proactive in the realm of continuous manufacturing and has shown significant leadership in the field.

Participants identified a number of possible steps that stakeholders, including FDA, could take to further the adoption and implementation of continuous manufacturing. For example, it would be beneficial to develop a roadmap focused specifically on the technology that would be needed over the next several years to support continuous manufacturing implementation, and efforts are already underway to develop such a document. Others emphasized the need for investment in a sustainable research funding stream to support training and research activities in academia related to continuous manufacturing. Though the technological needs may vary across manufacturing sectors (i.e. small-molecule innovator, biotechnology, and generic manufacturers), several noted that an important advancement for industry would be the development of a common manufacturing architecture or platform that can serve as a foundation and have the flexibility to suit the needs of the manufacturer.

It was suggested that the FDA consider shifting its current approach to regulatory quality assessment and oversight from a design-based framework to more of a performance-based framework, particularly as industry begins adopting more complex technologies and processes. Focusing on the quality of the end product rather than the design of the manufacturing process itself could help to streamline regulatory quality assessment. Participants noted that this would be similar to how medical devices are currently assessed, as the design of medical devices is generally complex. FDA acknowledged that this approach had been considered, but noted that the agency needs to be able to predict the performance and quality of products once they are produced at commercial scale, which would make it challenging to shift entirely away from the current design-based assessment process. Others pointed out that performance-based assessments require reliable methods for testing products. While some quality attributes are well understood and measurable, such methods do not yet exist for other attributes, and additional understanding is needed to establish clinically relevant specifications. More work is needed to develop rigorous approaches to product characterization and testing from both analytical and sampling perspectives.

Participants also cautioned that continuous manufacturing represents a substantial upfront investment for industry, which presents a risk to companies whose current manufacturing infrastructure relies heavily on batch processes and will continue to be a challenge to broader adoption. FDA noted that industry will be more likely to accept such a potential risk once a few industry pioneers have successfully developed and implemented continuous manufacturing technologies and the benefits have been demonstrated. Others noted that continuous manufacturing may not be appropriate for all contexts and products, and that it will be necessary going forward to determine those contexts most amenable to

such manufacturing technologies. A number of participants suggested that FDA consider developing regulatory incentives that are geared towards encouraging innovation in pharmaceutical manufacturing.

Improving Scientific and Technical Knowledge to Support Continuous Manufacturing

While the basic knowledge is already available to support design and implementation of many continuous pharmaceutical manufacturing processes, participants identified a number of scientific and technical knowledge gaps related to continuous manufacturing that will need to be addressed in order to support broader uptake. Several participants cited the need for further investment by the pharmaceutical industry in the field of process engineering research and development, in order to ensure the successful design and operation of continuous processes. Continuous manufacturing will also benefit from new ways to do rapid real-time testing and data collection during the manufacturing process. Methods (e.g., sensors) for anticipating and handling disturbances, variations, or uncertainties that may occur during continuous manufacturing should also continue to be developed. For the biopharmaceutical sector, participants noted that more technical knowledge regarding stabilization of the cell line may be necessary, along with tools to better understand and characterize the raw materials used in the biotechnology process. The field of synthetic biology may also be an important area for further investment.

Several participants pointed to a gap between the work academics have done to develop continuous manufacturing technologies and the successful translation of that work to the commercial sector. Better translational or knowledge transfer strategies are needed to help address this gap. Others expressed concern that there is currently no easy mechanism to transfer and share knowledge regarding continuous manufacturing amongst stakeholders, not just between academia and industry, but across a range of actors, including equipment vendors. Participants suggested having a centralized database for accruing and storing information on continuous manufacturing, or even having a shared facility where pharmaceutical manufacturers could test out new technologies and learn from one another. Participants also noted that there can be confusion amongst stakeholders regarding the definition of terms related to continuous manufacturing, and having a standard, guideline, or white paper on common languages and universally defined terms would be beneficial for everyone who designs, operates, inspects, or sells continuous manufacturing equipment.

The need for first-principle models and simulation techniques was also cited as an important area for future research and development because of their potential utility in process design and control. Participants suggested that a modeling toolbox could be developed jointly through collaboration among government agencies, academia, and industry and then made available to stakeholders. Others noted that, while modeling is useful, there are other tools that can also be applied for the same purpose, and the decision of how to develop and control continuous processes should be left up to the manufacturer. The need to develop disposable process components was also emphasized, especially for biotechnology processes, as this will allow for much faster breakdown, cleaning, and reassembly of a given process. Participants also reiterated that the innovation surrounding continuous manufacturing should not be focused on individual technologies or steps of the process, but that rather stakeholders should be committed to creating an overarching architectural framework, within which new technologies can be easily adopted as they are developed.

Addressing Barriers to the Adoption of Continuous Manufacturing

Participants outlined a number of obstacles to the implementation of continuous manufacturing. These challenges include the substantial upfront investment in infrastructure that would be required, not only to develop and construct new processes and manufacturing facilities, but also to redesign the process

for products already on the market. Making post-approval changes to manufacturing is already challenging, and it was strongly emphasized that this challenge is magnified exponentially by the global nature of manufacturing and the need to satisfy regulatory requirements in multiple countries. Global regulatory uncertainty was a key challenge emphasized throughout the discussion. Although FDA has shown great interest in and support for continuous manufacturing, regulatory bodies in other countries may not be so forward-thinking, and may not be able or willing to approve a product made via continuous processes.

Participants also cited challenges related to developing an adequately trained workforce, building the internal business case for investment in continuous manufacturing within companies, and encouraging innovation in the equipment vendor industry. In addition to the scientific and technical knowledge gaps noted previously, participants also cited the technical challenges related to managing, analyzing, and interpreting the vast amount of data produced during continuous manufacturing. More work is needed to better understand how a manufacturer can reliably determine when an aberration in the data indicates a problem rather than a random error. For generic manufacturers, intellectual property issues may be a major barrier to the adoption of continuous manufacturing if integrated processes are not designed to be flexible enough to accommodate alternative formulations.

Stakeholders also offered a number of potential solutions to overcoming these barriers, including steps that FDA could take to aid industry in this process. Open, transparent, ongoing communication between industry and FDA during development can foster successful implementation. Transparent communication can include sharing of risk assessments and risk uncertainty, but this openness should not be penalized. Systematic knowledge management approaches should be applied to capture key lessons from early applications, which can help to accelerate the Agency's institutional learning. It may, as noted previously, be worth providing additional incentives to industry that can make the switch from batch to continuous manufacturing more attractive. For example, FDA could establish an accelerated review process, similar to the concept of the breakthrough therapy designation established under FDASIA in 2012. However, those incentives should be tailored to the distinct needs of brand versus generic manufacturers. Others suggested that FDA re-think the role of reviewers and inspectors. Review and inspection, which have historically been separate functions, become less distinct when it comes to continuous processes, and participants encouraged FDA to consider realigning those roles. Many participants agreed that it would be helpful if FDA could develop a standardized approach to making post-approval changes to products that are made via continuous processes. Participants emphasized that leadership from FDA will be an important component in international regulatory harmonization efforts.

FDA noted that they are currently implementing strategies to better align the review and inspection processes, and are also working on regulatory process guidance or procedures on how industry can approach and work with the Emerging Technology Team, which works within OPQ and the Office of Regulatory Affairs to support and encourage the implementation of technologies to modernize pharmaceutical manufacturing, particularly in areas where both FDA and industry have little prior experience. Additionally, the FDA has current programs for interactions with the European Medicines Agency for advanced technologies and regulatory approaches. Stakeholders agreed that additional guidance on interactions with FDA would be very useful, but generally felt that at this moment it was too early for FDA to issue a formal guidance on regulatory considerations for continuous manufacturing applications until more knowledge is gained. Additionally, it was suggested that guidance on continuous manufacturing at the international level, such as through ICH, would be most beneficial.

Building Stakeholder Collaborations to Facilitate the Implementation of Continuous Manufacturing

There was broad agreement that collaboration amongst stakeholders on a number of issues related to continuous manufacturing is necessary and will help to address many of the barriers cited throughout the day. Participants discussed their experiences with a number of collaborations currently underway that have worked well and which may serve as models for future collaborative initiatives. FDA and the Biomedical Advanced Research Development Authority (BARDA) have partnered to support the development of new technologies and to advance the implementation of continuous processes, and it may be advantageous to build off of this existing partnership. The Defense Advanced Research Project Agency has also engaged in research to develop small-scale continuous manufacturing platforms for the US military, and there may be opportunity for additional collaboration with this agency down the road.

The International Institute for Advanced Pharmaceutical Manufacturing is a new collaboration between the UK-based Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallization and the National Science Foundation (NSF) Engineering Research Center for Structured Organic Particulate Systems in the US. This partnership will allow academics to work together internationally to foster innovation in continuous manufacturing, and will engage with both regulators and industry to help accelerate the adoption of continuous manufacturing technologies. Stakeholders also suggested that the current NSF Scholar-in-Residence at FDA program could be expanded to include continuous manufacturing as a field of research and study available to participants in that program. Others proposed using this kind of collaborations to help educate and train the Master's and PhD-level workforce that will be needed to develop and operate continuous processes. Participants also noted that collaborations that include and focus on biologics manufacturers are less common, and lag a bit behind the work done by small-molecule manufacturers.

Participants also proposed that the pharmaceutical industry look to other fields (such as the aviation industry) that have successfully implemented and used new manufacturing technologies, and which may be able to offer lessons learned. Including equipment and instrument suppliers in such collaborative efforts could potentially be useful, as this could help to identify needs and spur innovations in technology.

Some participants envisioned a medicines manufacturing innovation center that could focus specifically on continuous manufacturing. Academics and other innovators could use the center to develop and test new technology, while allowing commercial actors to come in and try them out without the need to invest upfront. Such a center could potentially be housed within the National Network for Manufacturing Innovation, which connects a number of institutes for manufacturing innovation across the country but does not currently have an institute dedicated to pharmaceutical manufacturing.

Others proposed the creation of an institute focused on ways to effectively translate continuous manufacturing from the academic space into the commercial space. This institute could bring stakeholders together for an interactive dialogue to address translational issues and create and refine best practices for implementation of continuous manufacturing. Participants also suggested that staff exchanges between industry, academia, and regulatory agencies could help to facilitate cross-sector learning. There was also general agreement that while current collaborations have typically been comprised of industry and academia, future collaborations should involve academia, industry, and FDA, as this could allow for more effective partnerships moving forward.

Next Steps

Participants agreed on several potential next steps. Increased international harmonization among global regulatory bodies will be essential to making continuous manufacturing a viable option to industry. Leadership from the FDA will be an important element, and it would be helpful for all governmental agencies working on continuous manufacturing to more closely coordinate their related research and development activities. It may be most useful to begin this process within the ICH. The creation and funding of workforce training initiatives will also be necessary for both industry and regulatory staff in order to develop the requisite skills needed for continuous manufacturing. Participants emphasized the need for continued support for collaborative research efforts to develop continuous technologies, and cited the possible creation of a technology roadmap to identify the specific technologies still needed to implement continuous manufacturing as a useful next step. Participants also indicated that increased direction from FDA regarding what industry needs to do to successfully implement and utilize continuous technologies would be beneficial for stakeholders across the board. FDA's proposed guidance on the process for engaging with the Emerging Technology Team will be very helpful in facilitating these interactions.

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