Accelerating adoption of pharmaceutical continuous manufacturing

Policy considerations to ensure a more resilient supply of essential medicines

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Summary

Vulnerabilities in the supply chain for medicines and other critical medical products can lead to shortages during times of emergency or other disruptions. Advanced manufacturing technologies (AMT) have been identified as a promising approach to diversify the supply of medicines and facilitate production of critical medicines in the United States.

Pharmaceutical continuous manufacturing (PCM) is an emerging form of AMT that has the potential to improve manufacturing efficiency, reduce production costs, and diversify the supply chain by advancing domestic production. However, adoption of PCM has been slow overall, especially among companies manufacturing generic medicines, largely due to economic, regulatory, and workforce capacity challenges. This paper presents the relevant background, describes the challenges to adoption of PCM, and proposes policy solutions to help drive the adoption of PCM in the United States. Having policies in place to build a more resilient supply chain, as described in USP's recent public policy position paper, can help ensure the continued availability of safe, quality medicines for patients—even in times of a pandemic or other crisis.

Background

The globalization and specialization of supply chains has led to geographic concentration of manufacturers that produce active pharmaceutical ingredients (APIs), finished dose form (FDF) medicines, and other medical products in locations where labor and raw material costs may be lower, environmental regulations more permissive, and infrastructure subsidized by the public sector. The United States relies on foreign sources for FDFs, raw materials, and APIs. In fact, domestic manufacturing in the United States supplies less than 30% of APIs for branded and generic drugs.[i] Nearly 72% of all API manufacturing facilities and 53% of FDF manufacturing facilities are in other countries;[ii, iii] for example, India is the source for 40% of the U.S. supply of FDFs.[iii] While this dependence on foreign sources for medicines has likely led to lower costs for many products, it poses a risk of unreliable supply in crisis situations.

The COVID-19 pandemic has increased awareness of these risks by creating unprecedented challenges for national public health systems and the modern, global pharmaceutical industry. The first few months of the pandemic exposed long-standing vulnerabilities in the supply chain for medical products, resulting in shortages of critical medicines and other medical products such as hand sanitizer and personal protective equipment (PPE). Difficulties with global manufacture and distribution of medical products resulted from closed national borders, limitations on exports, temporary closures of manufacturing facilities, and unanticipated surges in demand. These challenges, and other crises in recent history, have raised awareness of the urgent need to build a more resilient supply chain for medical products.

To achieve a stronger, more resilient supply chain, countries will need to pursue multiple new approaches, such as diversifying their sources of medical products including APIs, excipients, other raw materials, and FDFs. Diversifying sources of both pharmaceutical ingredients and finished medicines is critical because doing so reduces a country's reliance on a single source that could suddenly be disrupted or cut off. Diversification means relying on a combination of international and domestic manufacturers and establishing redundancies; then, when disruptions occur—whether global like COVID-19 or confined to a specific facility, country, or region—countries are prepared to respond rapidly to mitigate potential shortages of critical medicines and other products. In other words, diverse and redundant supply chains help countries secure an uninterrupted supply of quality medicines and help companies avoid supply disruptions.

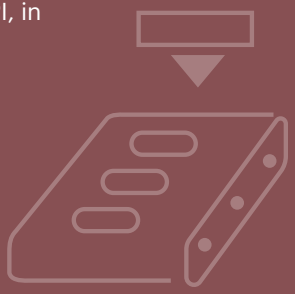
Governments help ensure an adequate supply of the medicines and vaccines needed to address national public health concerns. As such, national governments should facilitate additional manufacturing capacity within their borders. Advanced manufacturing technologies (AMT), and specifically pharmaceutical continuous manufacturing (PCM), could help to accomplish this goal, and many countries have already committed to making these investments (see **Examples of Public Investments in AMT** below). Yet so far, challenges in adopting PCM have limited the uptake of this emerging technology, especially among manufacturers of generic products.

U.S. policymakers and other government leaders could help overcome the potential barriers to AMT adoption, in part, through a combination of public financing and incentives for private investment. These measures could enable more efficient and nimble production of essential medicines, including vaccines, and could also buffer against disruptions in supply. Indeed, whenever possible, all countries should incentivize and accelerate longer-term efforts to help expand the continuous manufacturing infrastructure for production of generic and branded medicines.

Examples of Public Investments in AMT

Several countries and regions have made significant investments in spurring domestic AMT:

- **CHINA** has committed to invest ~$1.2 trillion to transform manufacturing to AMT, with the goal of 50% usage of local products in county-level hospitals.
- **EUROPE** is leaning into AMT with government-led centers and a €1 billion new Sanofi API facility.
- **INDIA** made a $1.3 billion manufacturing investment to reduce its dependence on foreign sources of API, in response to COVID-19.



Batch manufacturing: a traditional approach to pharmaceutical production

Traditional manufacturing processes, otherwise known as "batch" manufacturing, have been used for decades to produce medical products. Some of the most significant advantages of these processes stem from the vast collective experience with the technologies and the clarity on regulatory expectations. Manufacturers have already invested the resources to build production facilities, they have a trained workforce and well-established training materials to prepare new employees as needed, and quality control is integrated throughout the process, between steps.

While well understood, traditional manufacturing approaches have considerable downsides. Batch manufacturing requires sizeable facilities with large equipment, and the consumables used in production, including harmful solvents, must be procured and stored in sufficient quantities to allow for the desired maximum volume of product to be manufactured. Because of this, batch manufacturing can have a significant adverse impact on the environment, which has contributed to the offshoring of pharmaceutical production from the United States to other regions or countries with fewer environmental protection regulations.

Furthermore, traditional manufacturing is labor- and time-intensive: the hold times between steps in the process often add weeks or months to the production time. Between steps, materials are stored in containers or shipped to other facilities for the next step, adding more time and costs for containers and shipping and raising the risk for product degradation. In fact, products manufactured through batch processes have received numerous regulatory citations. Some estimates say that quality issues and other inefficiencies from batch manufacturing cost the pharmaceutical industry approximately $50 billion each year.[iv,v] These added costs may contribute to higher prices for products, impacting government procurement and individual patients, or lead to reduced capacity for industry to develop novel therapeutics, preventatives, or diagnostics. In addition, as demand for products surges, ramping up production with a batch manufacturing process may require additional or larger facilities and equipment, and capital and operating costs tend to scale with volume.

Traditional manufacturing renders the U.S. supply of medicines vulnerable to delays, disruptions, and quality control issues, especially given the reliance on foreign sources.

Definitions

- **Batch manufacturing:** a step-by-step, end-to-end process for manufacturing products; "batch" means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture
- **Continuous manufacturing:** a process in which the input materials are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system

Pharmaceutical continuous manufacturing: an advanced manufacturing technology

AMTs, such as PCM and 3D printing, have the potential to provide more streamlined, consistent, and efficient production of medicines compared with the traditional approach (i.e., batch manufacturing). Advanced technologies also can facilitate the diversification of sources of medical products. PCM offers several advantages to manufacturers, and the technology is widely used outside of the pharmaceutical industry. In fact, many commodity chemicals, including some used as excipients,[1] are manufactured using advanced technologies.

Using PCM, manufacturers can integrate and automate medicine production from start to finish. This achieves better quality control, scale-up, and cost-efficiency of production, allowing manufacturers to respond more nimbly to changes in demand for products. Additionally, manufacturers using PCM technology lower costs by significantly reducing the physical footprint and environmental impact of the production facility. Compared to batch manufacturing, the volume of product generated through PCM is a function of the length of time the system operates and not the size of the facility, allowing for smaller production plants and requiring less materials to be stored. The latter is particularly beneficial when handling highly or potent materials, thereby reducing risks to the people, the facility, and the environment. These advantages may facilitate entry (or re-entry) of certain manufacturers in markets where they currently have no presence, thereby shortening supply chains and enhancing resilience to disruption.

Challenges to adoption of pharmaceutical continuous manufacturing

Traditional manufacturing processes are well established and the risks to return on investment (ROI) are understood, but the same is not true for advanced manufacturing technologies. Although well-established in other industries, continuous manufacturing for medicines is considered a nascent practice and emerging technology. These unknowns present challenges to manufacturers, especially for those producing generic medicines, who already face tough competition, tight profit margins, and uncertain ROI.

Some innovator companies have begun to adopt new technologies; thus far, seven branded products have been approved by the U.S. Food and Drug Administration (FDA) for manufacture using PCM. Yet no generic medicines have been approved to use PCM, and it is unknown if manufacturers of generic medicines have applied for regulatory approval. Regardless, given that 90% of medicines used by U.S. patients are generic, this represents a critical gap in domestic infrastructure and capability.

To make the transition to PCM, companies must commit to significant analytical R&D and build continuous manufacturing lines that are compliant with current good manufacturing practices (cGMP). While these investments offer benefits, challenges remain. For example, when an API production process is converted from traditional, batch manufacturing to PCM, there may be opportunities to streamline the synthesis pathway, thereby making the process more amenable to continuous production or saving time and costs. However, regulatory approval will be required for any process change, and there is uncertainty regarding regulator expectations for drug applications using PCM.

Along with the scientific methods that need to be developed, the capabilities of scientific or technical personnel and enterprise decision makers also need to grow. Because the technology is relatively new for pharmaceuticals, both industry and regulators lack practical experience with PCM, which must be addressed in order to scale adoption. From industry line workers and upper management to regulatory inspectors and U.S. FDA reviewers, the lack of familiarity with advanced manufacturing drives risk-avoiding decisions that can severely slow the adoption of advanced manufacturing.

Overall, efforts to operationalize this technology, especially for manufacturers of generic medicines, have been hampered by challenges in three broad categories: economic, regulatory, and workforce.

[1] Excipients are the materials that, with the API, comprise a finished dose form medicine. Excipients serve many purposes, such as improving the delivery and bioavailability of the API. They are not intended to have a therapeutic effect; however, they are not necessarily inactive.

Challenge 1: Economic

New technology requires upfront investment in new infrastructure, research, and development, while existing market dynamics make realizing a positive ROI uncertain.

Switching from batch to continuous manufacturing requires substantial upfront investment in infrastructure, not only to develop new processes and construct manufacturing facilities, but also to redesign the process for products already on the market. Re-training personnel or hiring and training new employees to operate the new systems also requires advance investment. At the same time, manufacturers already have spent considerable resources to build traditional manufacturing facilities and infrastructure, only some of which may be repurposed in the transition to PCM. To absorb these costs in favor of new technology, manufacturers must be able to reasonably quantify the risks to realizing a favorable ROI. Yet, because of the barriers described below—including regulatory uncertainty and limited workforce with the necessary technical knowledge—positive ROI is uncertain.

Challenge 2: Regulatory

Limited experience with PCM among regulatory reviewers and inspectors, as well as little guidance for industry, leads to regulatory uncertainty among manufacturers, who must seek new regulatory approval for each product using PCM, including for products already approved for manufacture by traditional approaches.

The U.S. FDA encourages the adoption of PCM and has recently expanded its commitment to accelerating adoption of advanced manufacturing technologies:

- In 2019, the agency published draft guidance for industry on quality considerations for continuous manufacturing.[vi] As part of the approval process for currently marketed products made using PCM, the agency has provided one-on-one consultations with the relevant companies.
- In 2020, FDA announced a Center of Excellence for Advanced Manufacturing to generate knowledge, research, and provide training for staff related to advanced manufacturing.[vii] The center, a collaboration between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, is also intended to support standard, policy, and guidance development.
- In 2021, the agency created a new collaboration with the National Institute of Standards and Technology for the purpose of increasing the resilience of the medical supply chain and enabling adoption of advanced domestic manufacturing.[viii]

Though progress has been made, regulatory uncertainty remains because there are few approvals to reference and limited experience among regulatory reviewers with the new technology. As a result, there is a lack of understanding among manufacturers of how FDA will apply regulations to applications seeking approval of products made with PCM, presenting unknown risks to their ROI.

When a company applies for regulatory approval to manufacture a new product, the manufacturing process is described as part of that application. Therefore, companies must complete a time- and resource-intensive undertaking to implement a new continuous manufacturing line or to transition an existing line from batch to PCM for a product originally approved using a batch process. To receive regulatory approval to use the new technology, companies must address the knowledge barriers described below in advance and submit their information to regulators as part of an application for market authorization.

Since there is currently limited knowledge of what regulators expect, this presents a hurdle for companies that operate on razor-thin margins, produce multiple products, or manufacture products for use in multiple countries. Furthermore, a lack of harmonization across national regulators with respect to PCM may mean that each regulator has different requirements. Regulatory bodies in other countries may not be prepared to review and approve applications for medicines produced through continuous manufacturing. Therefore, to effectively transition from traditional to advanced manufacturing technologies, manufacturers need enhanced regulatory clarity and industry-wide understanding of regulatory expectations.

Challenge 3: Workforce

Manufacturers lack staff who are trained with the technical knowledge of the processes, capabilities, and constraints of PCM and must develop new process analytical technologies, chemometric models, and statistical tools while also hiring or re-training their workforce.

Continuous manufacturing represents a paradigm shift in pharmaceutical production, requiring different skills and knowledge to design, implement, and operate the production lines. For example, companies will need staff

with expertise in areas such as process engineering R&D (to ensure the successful design and operation of continuous processes), methods development (to anticipate and handle disturbances, variations, or uncertainties that may occur), and quality control processes (to establish and adhere to relevant cGMP). However, the general pharmaceutical manufacturing workforce was trained on batch manufacturing concepts, resulting in a dearth of the necessary expertise for PCM. Manufacturers cannot incrementally build that expertise; they need a fully developed process before submitting a market authorization application to the regulator. In addition, for biologics and biosimilars—medical products made using living organisms—technical knowledge is further limited regarding the stability of cell lines needed to manufacture these types of products, tools for characterizing raw materials unique to biotechnology processes, or newer scientific approaches such as synthetic biology.

Policy Solutions to Drive Adoption of PCM

These challenges can potentially be overcome with the help of policy solutions that offer a mixture of incentives for manufacturers. The incentives, including direct investments of public resources, can support the development of the scientific, technical, and regulatory knowledge needed to directly bolster the adoption of PCM. Stakeholders have proposed several ways to address these potential barriers to PCM, some of which are presented below. Interested stakeholders should convene to continue discussions around PCM, share their perspectives, discuss the merits of these proposals, introduce new ideas, and develop a call to action for policymakers to support the most promising solutions. Indirectly, such policy solutions may also help to raise awareness among manufacturers about PCM, including its benefits, challenges, and implications for their products and businesses.

Accelerate Scientific and Technical Knowledge

Policy solutions may also require public investments to support the development of "PCM incubators" that could address the barriers described herein. Incubators could offer neutral ground where knowledge gaps, regulatory science, and workforce training could be addressed or developed in a prospective and coordinated manner between industry, academia, and regulators. An incubator concept would allow for the development of a few state-of-the-art facilities, geographically dispersed across the United States, to help overcome the challenges with widespread adoption of PCM in the following ways:

- **Advance regulatory science** by providing regulators with opportunities to observe and interact with a functioning PCM production line. These opportunities will help regulators understand the capabilities, limitations, and potential implications of PCM for the quality of ingredients and finished drug products and facilitate discussion with scientists in industry and academia who are developing the technology and related processes.
- **Adequately resource FDA and other agencies** so they can expand their capabilities and give additional regulatory guidance to industry regarding PCM.
- **Test technological feasibility of producing medicines with PCM** by giving scientists from manufacturers new or additional opportunities to manipulate a PCM line, learn from academic scientists developing the technology, and engage with regulators by raising questions in real time, rather than waiting for formal regulatory submissions.
- **Facilitate technology transfer from academia to industry** by establishing physical test environments where academic researchers can engage with regulators and industry scientists to transform theory into practice, thereby transitioning from research to production settings.
- **Develop a broad talent pool** by creating environments with functioning PCM training lines where manufacturers can send representatives to develop skills and competencies in training programs focused on specific advanced manufacturing techniques and processes.

USP is poised to support more widespread adoption of PCM by leveraging its resources, including its state-of-the-art facilities and scientific expertise, to establish one or more incubators. USP is also ready to collaborate with stakeholders to increase U.S. technological leadership in PCM. The overarching goal is to strengthen the supply of quality, critical medicines in the United States by facilitating at-scale domestic manufacturing.

Establish Incentives for Industry

Manufacturers need time and resources to conduct the process and analytical R&D; to transition their facilities, equipment, and technology; to train their employees; and to prepare and submit their application for approval to regulators for each product they produce. To assist manufacturers with this investment of time and resources,

the following incentives could be made available, particularly to manufacturers of generic medicines, including APIs and FDFs:

- **Establish a standardized approach and accelerated review process** for applications submitted to the U.S. FDA to manufacture products with PCM; the approach should be tailored to the challenges faced by the generics industry (modeled after breakthrough therapy designation established by the Food and Drug Administration Safety and Innovation Act, or FDASIA).
- **Provide low-cost loans** to manufacturers of generic medicines to construct or refurbish plants in the United States, thereby easing entry (or re-entry) to domestic production using PCM.
- **Prioritize public procurement of medicines** by the Departments of Defense, Veterans Affairs, Health and Human Services, and other public entities, so they will purchase medicines produced in the United States using PCM, thereby providing predictable revenue streams to manufacturers who adopt the new approach.

Conclusion

Advanced manufacturing technologies, including PCM, provide an important avenue for diversifying the supply of medicines and other critical medical products. To help drive adoption of PCM in the United States, policy solutions are needed that can overcome key economic, regulatory, and workforce challenges. Along with efforts to increase transparency in the supply chain for medicines as a means to mitigate or prevent drug shortages and other effects of disruptions such as the COVID-19 pandemic, U.S. policymakers must also incentivize and accelerate efforts to expand capacity for domestic manufacturing of critical medicines, including both generic and branded medicines.

About USP

Founded in 1820, USP is an independent, nonprofit, science-based organization that safeguards the public's health globally by developing quality standards for medicines, dietary supplements, food ingredients, and healthcare quality. USP standards describe expectations and tests for identity, strength, quality, and purity; they assist industry in the development, manufacturing, and testing of medicines. USP standards have been used in more than 175 countries and are enforceable by the U.S. Food and Drug Administration (FDA) for medicines and their ingredients imported or marketed in the United States. Standards in the USP compendia are developed by independent experts through a transparent and scientific process, with input from stakeholders and U.S. federal agencies such as FDA and the Centers for Disease Control and Prevention.

USP is implementing a comprehensive program to support the public health response to the COVID-19 pandemic. Our immediate work is focused on facilitating the supply of quality medicines across the global supply chain—especially for those medicines that treat symptoms associated with the virus—by working closely with regulators, manufacturers, and other stakeholders around the world. We are also engaging in middle- and long-term activities to assess vulnerabilities in the global supply chain for medicines, to advocate for greater transparency and more diversity in the sources of medicines and their ingredients, and ultimately to help build a more resilient supply chain.

References

I. U.S. Food and Drug Administration (FDA). 2019 (October). Safeguarding Pharmaceutical Supply Chains in a Global Economy, testimony of Janet Woodcock, Director, Center for Drug Evaluation and Research, to the U.S. House Committee on Energy and Commerce, Subcommittee on Health. Available from: https://www.fda.gov/news-events/congressional-testimony/safeguarding-pharmaceutical-supply-chains-global-economy-10302019.

II. Association for Accessible Medicines (AAM). 2020 (March). A diverse, resilient supply chain for prescription medicine will moderate the risk of drug shortages and ensure patient access during the COVID-19 pandemic and beyond. Accessed from: https://accessiblemeds.org/sites/default/files/2020-03/AAM-Buy-American-One-Pager.pdf.

III. ASH Clinical News. 2019 (May). Quality of Generic Drugs Manufactured Overseas Comes into Question. Accessed from: https://www.ashclinicalnews.org/news/quality-generic-drugs-manufactured-overseas-comes-question.

IV. Neuman, S. 2006. Pharmaceutical industry wastes $50 billion a year due to inefficient manufacturing. The Source. Available from: https://source.wustl.edu/2006/10/pharmaceutical-industry-wastes-50-billion-a-year-due-to-inefficient-manufacturing.

V. Macher, J., and J. Nickerson. 2006. Pharmaceutical Manufacturing Research Project. Georgetown University McDonough School of Business and Washington University in St. Louis Olin School of Business. Available from: http://apps.olin.wustl.edu/faculty/nickerson/results/PMRPFinalReportSept2006.pdf.

VI. FDA. 2019. Draft Guidance for Industry: Quality Considerations for Continuous Manufacturing. Available from: https://www.fda.gov/media/121314/download.

VII. FDA. 2021. Accelerating the Adoption of Advanced Manufacturing Technologies to Strengthen Our Public Health Infrastructure. Available from: https://www.fda.gov/news-events/fda-voices/accelerating-adoption-advanced-manufacturing-technologies-strengthen-our-public-health.

VIII. FDA. 2021. Memorandum of Understanding Between the NIST and FDA. Available at: https://www.fda.gov/about-fda/domestic-mous/mou-225-21-006.

IX. FDA. 2012. FDA Perspective on Continuous Manufacturing. Presentation to the IFPAC Annual Meeting, Baltimore, MD (January 2012). Available from: https://www.fda.gov/media/85366/download.

X. FDA. 2012. Fact Sheet: Breakthrough Therapies. Available from: https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fact-sheet-breakthrough-therapies.