Policy considerations to help harness pharmaceutical continuous manufacturing

for a more resilient medicine supply chain

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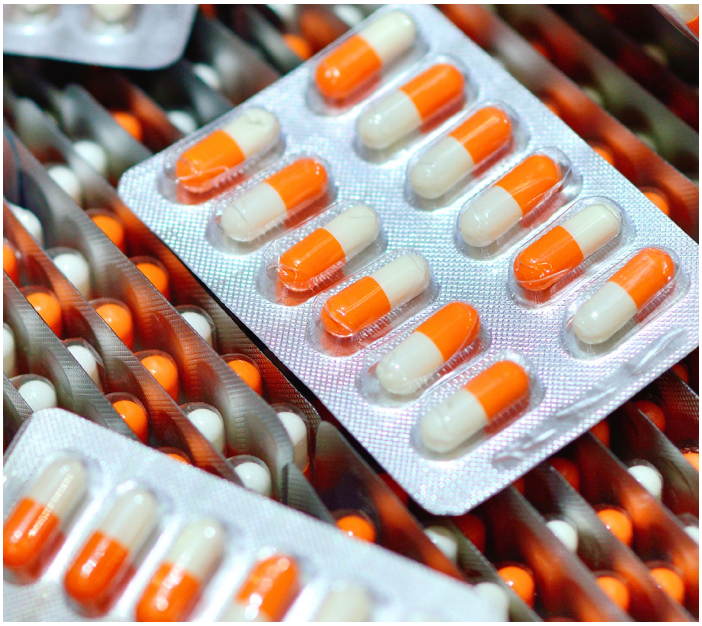
Summary

Vulnerabilities in the supply chain for medicines can lead to shortages during times of emergency or other disruptions. Several advanced manufacturing technologies (AMT) have been identified as promising approaches to diversify the supply of medicines and facilitate production within the United States for the medicines relied upon by Americans, which are sometimes referred to as "essential medicines".

Pharmaceutical continuous manufacturing (PCM) is an emerging form of AMT that has the potential to improve manufacturing efficiency and reduce production costs. Deploying PCM is a promising way to diversify the supply chain through additional domestic production. However, adoption of PCM by industry has been measured overall, 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 concepts to foster 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 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 some medicines and other medical products such as hand sanitizer and personal protective equipment (PPE). Difficulties with the 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 to producing medicines, 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 important 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 key 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.

The COVID-19 pandemic has focused governments everywhere on prioritizing an adequate supply of the medicines and vaccines needed to care for their population. Fostering additional manufacturing capacity within their borders is one way to increase local supply, which is important in times of global need. Advanced manufacturing technologies, and specifically pharmaceutical continuous manufacturing, could help to accomplish this goal, and many countries have already committed to making these investments (see examples below). Yet so far, challenges in adopting PCMhave hindered the uptake of this emerging technology.

U.S. policymakers and other government leaders could help overcome barriers to PCM 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.

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 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. 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 or preventatives. 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.

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.

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 an emerging technology.

To make the transition to PCM, manufacturers 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

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

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 increase. 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 slow the adoption of advanced manufacturing.

To date, seven branded products have been approved by the U.S. FDA through the use of PCM processes. This is an encouraging development that can help inform solutions to the economic, regulatory, and workforce challenges affecting broader adoption of PCM.

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 advanced 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 the limited workforce with the necessary technical knowledge—positive ROI is uncertain.

Challenge 2: Regulatory

Limited experience with PCM across regulatory reviewers, as well as limited 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.

In recent years, the U.S. FDA has offered resources for manufacturers interested in pursuing PCM, such as issuing guidance on quality considerations for continuous manufacturing[iv] and creating the Emerging Technology Program to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing.[v] More recently, the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research partnered to create the Center of Excellence for Advanced Manufacturing to generate knowledge and research.[vi] Early in 2021, the agency also announced a collaboration with the National Institute of Standards and Technology to facilitate information sharing.[vii] However, regulatory uncertainty remains because there are few approvals to reference and limited experience among regulatory reviewers with the new technology.[viii] 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.

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 regulator expectations, this presents a hurdle for many 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 regulatory agencies 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 need more staff who are trained with the technical knowledge of the processes, capabilities, and constraints of PCM to enable them to 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, because the general pharmaceutical manufacturing workforce was trained on batch manufacturing approaches, training is needed to develop the necessary expertise for PCM. In addition, for 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 concepts to foster adoption of PCM

These challenges can potentially be reduced with policy reforms 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 encourage adoption of PCM. Stakeholders have proposed several ways to address the challenges to PCM adoption, 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 concepts. 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

One concept to help address these adoption barriers is the establishment and public funding of “PCM incubators”. 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** 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 providing industry with 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.

Establish Incentives for Industry

Manufacturers need time and resources to conduct 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:

- **Establish a standardized approach and accelerated review process** for applications submitted to the U.S. FDA to manufacture products with PCM.
- **Provide low-cost loans** to manufacturers of generic medicines to construct, alter, or refurbish plants in the United States, thereby easing entry (or re-entry) to domestic production using PCM.
- **Prioritize public procurement of medicines** produced with PCM by the Departments of Defense, Veterans Affairs, Health and Human Services, and other public entities, thereby providing predictable revenue streams to manufacturers who adopt the new approach.

In addition, other market incentives should be considered as "pull" mechanisms that help make the deployment of PCM economically feasible, especially for medicines that are likely to be lower margin relative to the investment that may be required to build PCM lines.

Conclusion

Pharmaceutical continuous manufacturing provides an important avenue for diversifying the supply of medicines, improving manufacturing efficiency, and enhancing supply chain resilience. To help drive adoption of PCM in the United States, policy reforms are needed to address key economic, regulatory, and workforce challenges. Moreover, it is essential for stakeholders to share perspectives and work together to harness the benefits of advanced manufacturing technologies in the interests of patients. USP is committed to working with stakeholders to share perspectives and implement initiatives that help harness PCM for a more resilient medicine supply chain.

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.

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