

# TECHNOLOGY SOLUTIONS FOR IMPROVING THE RESILIENCE OF GENERIC PRESCRIPTION DRUG MANUFACTURING

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On March 2, 2023, the authors convened a group of experts from academia, industry, government, and nonprofits to explore technology options for increasing the resilience in the supply of generic prescription drugs. The workshop was convened at the Massachusetts Institute of Technology with the help of the National Network for Critical Technology Assessment and financial support from the Alfred P. Sloan Foundation. This report, authored by the organizers, summarizes the discussion. Because the workshop was organized under Chatham House rules, this summary maintains the anonymity of the speakers and does not attribute comments to individuals.

*The authors would like to thank Rex Reklaitis, Joel Predd, Erika Fuchs, and Anita Kafka for their help with organizing the workshop.*

*Wosińska and Conti's work in this area was supported by a grant from the National Science Foundation. Other than the aforementioned, the authors did not receive financial support from any firm or person for this article or from any firm or person with a financial or political interest in this article. The authors are not currently an officer, director, or board member of any organization with a financial or political interest in this article.*

*The Brookings Institution is financed through the support of a diverse array of foundations, corporations, governments, individuals, as well as an endowment. A list of donors can be found in our annual reports published online. The findings, interpretations, and conclusions in this report are solely those of its author(s) and are not influenced by any donation.*

## Motivation for the workshop

Assured high quality and consistent availability of medicines is a cornerstone of patient care, yet U.S. prescription drug supply chains are highly [vulnerable to disruptions](#). If drug shortages result, they may place patients' health and even their lives at risk through treatment delays, [rationing](#), increased likelihood of [medication errors](#), and the substitution of possibly [inferior alternatives](#).

Drug shortages result when supply chains cannot withstand demand or supply shocks. Recent demand shocks included a post-COVID increase respiratory illnesses driving up demand for amoxicillin or an increase in the off-label use for certain diabetes drugs like Ozempic. But shortages occur more frequently when supply disruptions – whether caused by manufacturing problems, natural disasters, or delays in obtaining ingredients – are significant enough that available inventories or scaling available manufacturing sites does not suffice. Historically, manufacturing quality problems with older generic (off patent) medicines [have been](#) the most common cause of shortages drug shortages.

To ensure that medicines are available when and where they are needed, numerous reports from government, industry, and academia have called for greater supply chain resilience where supply chains can either absorb or recover readily from demand shocks and supply shocks, both unexpected (like natural disasters) and preventable (like manufacturing quality).

Advanced manufacturing technologies (AMTs) such as continuous manufacturing, are among [oft-cited](#) solutions to resolve or mitigate challenges in pharmaceutical manufacturing supply resilience. Proponents of these technologies posit that [AMTs enhance](#) pharmaceutical manufacturing quality, speed, flexibility, and cost-effectiveness. The Food and Drug Administration (FDA) has specifically [called out](#) continuous manufacturing as a technology that can help prevent drug shortages caused by product quality and manufacturing problems.

Despite the promise of AMTs to address drug manufacturing quality and shortages, AMTs have been slow to emerge, especially among generic drugs. To date, [there are](#) a handful of branded drugs approved with continuous manufacturing but no generic drugs. Even conferences and workshops are missing engagement from generic manufacturers.

To explore the application of AMTs in the generics manufacturing context, this workshop convened experts in the fields of material chemistry, manufacturing, economics, and regulatory science. Participants explored the following questions:

- What are the key failure modes for pharmaceutical manufacturing and how do they differ for brands and generics?
- What are the AMT options to overcome those failure modes?
- What are the barriers for generic drug manufacturers to adopt those technologies?
- What are practical next steps that government, industry, or academia could take?

## Main takeaways

The main takeaways from the workshop can be summarized as follows:

- **The cost of AMTs outweighs the return on investment that generic manufacturers might expect relative to other options.** Throughout the workshop, current and former generic business leaders spoke about the economics of the generic drug industry and the constraints they present in adoption of new technologies. Demonstrations using continuous manufacturing for generics suggest that currently any production cost-efficiencies do not suffice when those products compete with low-cost foreign producers.

- **AMTs, continuous manufacturing in particular, do not align with the fast turnover, large portfolio nature of generic drug manufacturing.** The existing evidence on the value of AMT technologies applies to single, continually produced product. This, however, does not translate well to generic drug manufacturing where the unstable nature of demand can lead to 20-30 products run on a single line over a course of a year, leading to frequent switchovers. Developing a platform approach and better documenting the return on investment would be important for driving adoption of AMT technologies among mainstream generic manufacturers.
- **Current direction for reducing regulatory barriers is insufficient.** Business and government leaders acknowledged regulatory constraints and uncertainty that make it costly to change manufacturing technology and processes. On the one hand is the work-in-progress nature of FDA's regulations regarding the use of AMTs, with guidances and pilots in the works. On the other hand is the nature of the generics business, with a large installed base of products and questions about how to address technology adoption for product portfolios, not just individual products. While FDA is making process on the former, the latter remains unaddressed.
- **A full range of technologies, not just AMTs, should be considered when addressing generic prescription drug supply chain resilience.** Although the workshop did not cover the full spectrum of technologies that could help address supply chain resilience for generics, participants argued that basic technologies such as record digitization might provide a better return on investment from a social perspective.
- **The role of technology and its type (AMT vs low-tech) should match the specific vulnerabilities in supply chains.** Workshop participants identified medical countermeasures, antibacterials, and pharmaceuticals with narrow therapeutic index (NTI) as most likely, preliminary use cases for continuous manufacturing. These preliminary use cases should be assessed by the U.S. government as part of a broader effort to evaluate the return on investment on a broad range of interventions, whether technological or not.
- **Given the lack of private incentives, U.S. government must spur AMT innovation and subsidize adoption of AMTs to generic drug supply.** The government can alter the current business case for adopting AMT. To account for the variability in demand that makes continuous manufacturing unattractive for multi-product lines, participants recommended investments in developing a platform approach in such technologies. To address the large upfront costs, participants pointed to semiconductor manufacturing incentives in the CHIPS & Science Act as an example.
- **Government drug supply chain resilience efforts should include prioritization of supply chains.** Given the lack of private incentives, the role of U.S. government is critical. But the size of the generic industry and the chemical industry that supports it is immense. To best identify where and how to engage in support of drug supply chain resilience, U.S. government must take a systematic look on which supply chains are essential and which of these are vulnerable.<sup>1</sup>

The remainder of this document provides a summary of relevant sessions from the workshop.

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<sup>1</sup> Wosińska and Conti subsequently published a framework for how the U.S. government should prioritize drug supply chains for resilience interventions: [A Framework For Prioritizing Pharmaceutical Supply Chain Interventions | Health Affairs](#).

## **Session 1: Failure modes in pharmaceutical manufacturing**

The first session focused on defining the problem: where do things go wrong in manufacturing of small molecule prescription drugs? are there differences in failure rates for generic manufacturing versus branded manufacturing?

### *Key failure modes in prescription drug manufacturing*

A key failure mode, often following improper training, is when personnel does not follow proper processes. Contamination and impurities can result when employees improperly handle raw materials or mix chemicals, when they improperly clean lines between products, or when they enter sterile spaces without properly following procedures. Personnel may also trigger contamination and impurities if they inadequately perform maintenance and calibration of equipment, or improperly set environmental controls such as HVAC systems. Human error can also lead to inaccurate labeling.

Substandard quality of inputs to finished products, be it API, excipients, or parts such as vials with stoppers, can also contribute to product quality issues. Product quality issues also include impurities that may appear during production, with nitrosamines as a prominent example.

Another key failure is lack of assurance of quality. Participants emphasized that proper processes, documentation, and controls are essential to ensuring product quality and meeting patient requirements.

Contributing to all these failures are language barriers and continued reliance on paper-based systems in documentation, which in turn affect data accuracy and collection issues. Workshop participants recognized the need for improvements in the data systems area to ensure better quality control and regulatory compliance within the generic pharmaceutical manufacturing sector. At the same time, participants acknowledged that generics firms are hesitant to invest in IT systems due to cost and the fact that an increase in quality assurance might increase the amount of product needing discarding.

Participants also noted that the concept of 'quality' is varied, and depends on the context in the market, including product quality, process quality, facility quality, and supply chain quality. Having issues with a facility does not necessarily mean the product quality is poor, although there may be a risk associated with it.

### *Differential vulnerability of generic and brand manufacturing*

To contextualize failure modes in manufacturing of generic drugs, one must first appreciate the differences in how branded facilities and generic facilities operate.

Branded product manufacturers benefit from consistent demand, which allows for long-run production with minimal changeovers. This long-term stability incentivizes the manufacturer to improve their processes over time, with high margin making such investments possible.

In contrast, generic manufacturers face unstable demand, which translates to frequent product changeovers that require cleaning between products. Unlike a branded line, which may be dedicated to the same product for several years in a row, generic production lines may switch between 20-30 products in a year. For generic products first to market, batch runs may last a couple of months, but will shorten to three to ten days once the market settles and competitors emerge.

The changeovers are partly due to the broader portfolio of products that generic firms carry and partly due to the frequent contract changes resulting from the competitive nature of the business. The number of manufacturers in individual markets has implications for predictability of demand and the sudden changes in purchasing agreements and prices that result. The threat of entry from non-marketed ANDAs also adds to the unpredictability of demand.

In addition to the economic drivers of how manufacturing lines are utilized, economic pressures on margins also limit investments in a qualified workforce. These factors introduce variability in the production process and can result in subpar quality control that can lead to releasing products not meeting specifications. The low average revenue gained per unit exacerbates pressures on releasing product even if it might not pass quality control.

The global nature of the supply chain creates additional vulnerabilities. Global manufacturing for different markets adds complexity and cultural differences. The availability of API (Active Pharmaceutical Ingredient) and of key starting materials from China and India is crucial for both branded and generic manufacturing. In such countries, external facility infrastructure, such as water, power, and waste management, can also affect manufacturing quality.

For all these reasons, workshop participants emphasized that addressing supply chain resilience challenges among generic drugs require a comprehensive approach beyond technology, including contracting practices, paying for quality, and other avenues of improvement.

## Session 2: Possible AMT solutions

A starting point for the workshop discussion was the work of a National Academies committee that [explored](#) innovation in advanced manufacturing applied to pharmaceuticals and barriers to their adoption. In applying this body of work to generics, four AMTs emerge as having greatest potential to improving supply chain resilience:

- continuous manufacturing
- modular manufacturing
- advanced batch processing, and
- digital twins.

Each technology has its advantages and limitations, with workforce expertise and appropriate implementation crucial to successful adoption.

A reference point for assessing the value of those AMTs is the standard **batch manufacturing** approach, which involves sequential steps with material transfer and testing at each stage. Batch testing can be compared to cooking in the kitchen – it offers flexibility, adaptability, and easy recipe changes. However, it suffers from long cycle times, poor equipment utilization, batch-to-batch variability, and larger footprints due to the idle equipment. Scaling up batch processes also presents challenges.

In contrast, **continuous manufacturing** involves a continuous flow of materials without interruptions. It provides high utilization, smaller footprints, reduced work in progress, and improved control. However, it requires careful design and control to maintain constant rates, and it may be less flexible for accommodating diverse products. Running continuous processes over a longer period is essential to minimize losses associated with start-up and shutdown. Continuous manufacturing significantly reduces cycle time compared to batch systems, potentially reducing it from months to a matter of weeks. This is because continuous manufacturing enables the testing of multiple formulations and process variables in a fraction of the time. It also reduces the amount of expensive active pharmaceutical ingredient (API)

required for formulation. Continuous manufacturing has gained attention in areas such as solid oral dosage, API chemistry, larger biologic molecules, and sterile fill-finish processes.

**Modular manufacturing** involves using prefabricated containers or standardized building blocks that are integrated into existing facilities. The main purpose of modular manufacturing is to enable easy equipment configuration changeovers, allowing for efficient cleaning and uninterrupted production. It also facilitates quick line changes, such as switching between different processes. Modular manufacturing offers benefits such as scale reduction and improved flexibility. The advantages include plug-and-play functionality, standardized data interfaces, and fast implementation. These manufacturing practices have been explored by branded companies like Pfizer, Merck, and Lilly.

**Advanced batch processing** refers to improving traditional batch manufacturing through real-time measurements, predictive models, control strategies, and equipment innovation. Examples include implementing online temperature measurements and controls in lyophilizers, and introducing measurement, control, and reform strategies in crystallization processes. Workforce expertise is crucial for implementing advanced batch processing technologies effectively.

**Digital twins** involve creating virtual replicas of physical processes to optimize performance, monitor real-time data, and predict outcomes. Digital twins can aid in process optimization, control, and troubleshooting.

It is important to note that continuous and batch manufacturing are not mutually exclusive, and a **hybrid approach** may be beneficial in certain processes. By understanding the characteristics and requirements of each technology, the pharmaceutical industry can strive for more efficient and innovative manufacturing practices.

Some participants suggested that early adopters of continuous manufacturing in the development of generic copies of branded products may gain a competitive advantage over others. However, participants did not fully explore the concept at the workshop to yield further insight into those advantages.

Other participants suggested that solutions applied to pharmaceuticals could raise awareness about product quality and potentially change perceptions, allowing customers to differentiate between manufacturers based on quality. Those participants suggested providing this information to patients and other consumers could enable them to make better, informed decisions and choose higher quality, more resiliently supplied products.

Workshop participants also discussed several bridging strategies that can ease transition to AMTs applied to generic prescription drugs. For exposition purposes, we summarize that discussion in section entitled *Next Steps*.

### **Session 3: Barriers to AMT adoption**

Workshop participants described barriers to AMT adoption in pharmaceutical manufacturing as economic, technological and regulatory, and business culture.

#### *Economic barriers*

When making capital investment decisions, each company sets a hurdle rate and payback period. Different companies may set these differently based on the level of risk they are willing to take, which is determined by their business characteristics. Generic and contract manufacturers set lower hurdle rates and shorter payback periods because of their low absolute

margins and the variable nature of their demand beyond the initial entry phase when brands just lose exclusivity.

These hurdle rates and payback periods are then used to assess whether a company should invest in a technology. This is relevant for AMTs as there can be substantial upfront costs. For instance, a continuous manufacturing line for tablets could cost around \$5 million, while the sensors required for a solid dose tablet press may amount to \$200,000 to \$300,000 per line.

When making an investment in equipment or technology, companies also need to consider additional costs. A company looking to use continuous manufacturing methods would have to carefully assess the chemistry of the manufacturing process and the base and active ingredients required for production as not all may be amenable to the application of continuous techniques. Other potential costs may include expenses related to bringing the investment into operation, such as training staff to use it.

Participants explored whether the financial barriers may be lower for contract manufacturers (CMOs) that can make a mix of branded and generic products on their lines. But CMOs also face little incentive to invest in processes dedicated to a sole product without guarantees of continued business – a common characteristic of generic drug markets.

*A case study: Making generic metformin using continuous manufacturing*

To test the benefits and costs of continuous manufacturing, several workshop participants developed demonstration project with a fully integrated continuous system for metformin, a widely used, oral, generic drug used for treatment of Type-2 diabetes. The demonstration showed increased production speed, significant reduction in energy consumption and operational costs, and improved sustainability. However, the benefits did not justify the costs in light of competitive prices from foreign manufacturers.

For future use cases, the metformin project participants proposed developing continuous manufacturing as a platform technology rather than a single-product application, allowing for multiple products to be produced on the same line. This multi-product platform would require substantial investment, which may be more feasible for technology companies rather than generic manufacturers. Workshop participants also highlighted the need for flexibility in meeting changing demands and suggests that continuous manufacturing offers faster response times and increased adaptability. The overarching goal is to shift the paradigm and promote the adoption of multi-product continuous manufacturing as a transformative approach in the pharmaceutical industry.

*Technological and regulatory barriers*

The existing evidence on the value of AMT technologies applies to single, continually produced products. This, however, does not translate well to generic manufacturing where the unstable nature of the demand can lead to 20-30 products be run on a single line over a course of a year, leading to frequent switchovers.

Participants emphasized that flexibility and the potential for redeploying costs to multiple products or technologies are crucial considerations. The fungibility of technologies refers to their

ability to be used for multiple pharmaceuticals or product bundles, which can be a factor in investment decisions. Investing in a line or process dedicated to a sole product pose risks for companies, as there is no guarantee of continuous production.

On the regulatory side, FDA has been issuing guidances, organizing workshops and conferences, and supporting demonstration projects. But as described below, the unsettled nature of the system conflicts with the risk averse approach that generics take. In addition, FDA has been approaching technology adoption not on technology level but product level, which conflicts with the portfolio approach that generic manufacturers take for infrastructure improvements.

### *Business culture barriers*

Setting financial considerations aside, adoption of AMTs requires a significant cultural change in the business model, a higher level of training and education for the workforce (or likely a subset of workforce), and commitment to a long implementation time (over three years).

A company would also need to engage differently with the FDA, working in collaboration with them on adopting the new technology while FDA is still in the process of setting out the requirements. This would be a significant change from the risk averse approach generic manufacturers have in dealing with FDA approvals.

## **Session 4: Next Steps**

Workshop participants highlighted several areas where progress can be made.

### *Demonstrating the economic value of AMTs in generics manufacturing*

Cost considerations were continually raised by industry participants, with participants detailing the expenses associated with different manufacturing approaches and the return on investment on them. For instance, a continuous manufacturing line for tablets could cost around \$5 million, while the sensors required for a solid dose tablet press may amount to \$200 to \$300 thousand per line. Participants noted that the economic benefits must extend beyond batch failure reduction, as the current rate of rejection in generics is small. Better data on the costs of such investments are needed, including relative to other technologies (such as using polymerase chain reaction [PCR] and next-generation sequencing for sterility assurance).

Workshop participants also highlighted the need for studies to determine the point at which continuous manufacturing becomes beneficial compared to batch manufacturing. The flexibility and trade-offs of continuous manufacturing were discussed, particularly regarding the reduction of cleaning time and the ability to switch between products. The question is whether any research has been conducted to find the balance between these factors. There have been numerous published studies on the topic, but they tend to be specific to individual cases and challenging to generalize.

Another need area is demonstrating fully implemented API and excipient manufacturing, showcasing its effectiveness and functionality. The goal is to create a comprehensive package that allows others to learn from and propagate the technology. While this may take about three years with adequate funding, it is considered low-hanging fruit due to the existing scientific foundation.



To advance the development of evidence, participants suggested creating government-funded centers for technology integration, demonstration, transfer, and workforce development to promote knowledge-sharing and support companies lacking experience in innovative technologies.

### *Using bridging strategies*

Workshop participants emphasized the need for easy-to-use, fast, and efficient process development workflow. Without such advancements, generics will struggle to identify the economic benefits of applying these technologies. Moreover, workshop participants emphasized the importance of identifying 'bridging' strategies to start moving generic companies into more advanced manufacturing techniques.

Workshop participants emphasized there are five, general, not mutually exclusive strategies for achieving a faster and more efficient process development workflow, with varied short run applicability to generic prescription drug manufacturing:

- **Process intensification**, which involves making the process itself faster and more efficient. Participants highlighted that continuous manufacturing is one way to achieve this goal.
- **Automated data collection** to reduce costs and enable quick experimentation. Participants highlighted examples of small automated production systems to collect necessary data efficiently.
- **Plug-and-play modules** to simplify the process and make it accessible to a wider range of uses. This approach involves easy physical connections and eliminates the need for complex information flows and structures.
- **Mechanistic models** and **digital twins** to obtain operational information and automate the construction of models for unit operations. The aim is to reuse models instead of beginning from nothing for each new process, including efforts to automate parameter estimation.
- Automating processes with **AI and machine learning**.

Workshop participants highlighted the challenges in hiring specialized data scientists in many of these bridging applications.

Sensors provide many bridging advantages. By integrating sensors, it becomes possible to achieve real-time determination of product quality for a wide range of products. Participants emphasized that sensors can be implemented at about \$200K-300K per line, and the implementation process can be completed within a year. Furthermore, compared to running a continuous manufacturing line, personnel requirements are significantly reduced when sensors are used. Instead of a large team, only one or two individuals with expertise in process analytical technology are needed to operate the equipment effectively.

Workshop participants also emphasized the importance of a transition from batch manufacturing to integrated continuous manufacturing, with a focus on stepwise improvements, the implementation of advanced analytical technologies, and the need to consider compliance and performance as key objectives. A bridging strategy would progress from batch manufacturing to advanced batch manufacturing with process analytical technology (PAT), modular continuous manufacturing, and eventually integrated continuous manufacturing. The focus on stepwise improvements and the implementation of analytical technologies such as Raman and liquid

chromatography-mass spectrometry (LC-MS), would offer significant benefits to generic manufacturers in the short term.

### *Leveraging “first generics”*

The pressure to be first to market and generate revenue for the pipeline and operations plays a significant role in generic firm strategy. As such, some participants argued that first generics – generics that come to market right after the brand loses exclusivity – may be a good early use case for generic manufacturers, because product development using continuous manufacturing can take only six to nine months instead of the typical 16 to 24 months.

Other participants raised two concerns. First, a development timeline matters little when patents prevent earlier entry. Second, with the risk of delays due to the unsettled regulatory nature of AMTs would make manufacturers uneasy about technology investments even if direct costs were lower. There is also the concern that patent settlements may obviate the need for speed.

### *Prioritizing technologies for sterility assurance*

Given the prominence of drug shortages in generic sterile injectables, participants discussed the use of technology in addressing sterility failures and sterility assurance. There, participants identified a need for more rapid and accurate testing for sterility because the current method of sending samples to a lab for testing is time-consuming and with a high rate of false negatives. One suggested technology is PCR next-generation sequencing, which can reduce testing time from a month to about an hour. However, the adoption of such technologies requires clear regulatory guidance and standards, which are currently lacking in the industry.

### *Addressing resilience through non-technological means*

Workshop participants highlighted the importance of API and excipient manufacturing in ensuring the resilience of the U.S. pharmaceutical supply chain. It was noted that even if multiple approved generics exist for a particular product, relying on a single API supplier poses a significant risk. If that supplier experiences issues or disruptions, it can disrupt the entire supply chain. A similar vulnerability may exist among brands. The conversation also touched on the need to consider Key Starting Materials (KSMs) alongside API manufacturing.

Participants also noted that transparency into the pharmaceutical supply chain is an important investment for future resilience efforts. The discussion highlighted the need to map key starting materials to APIs and finished dosage forms, as well as identify the actual manufacturers of pharmaceuticals rather than just those with approved API or finished drug applications.

Participants also touched on the importance of critical components in the supply chain, such as vials, caps, closures, membranes, and single-use bags. Challenges related to backorders and single sourcing of these components were mentioned by participants, emphasizing their significance for ensuring resilience in pharmaceutical manufacturing.

Workshop participants also discussed the role that management of inventory and stockpiles of buffer product to protect against geopolitical risks. The conversation revolved around innovative models and strategies, such as creating a strategic active ingredient reserve. Participants noted that while some finished products, especially sterile ones, have a shelf life of only 12 months, certain active pharmaceutical ingredients (APIs) can last up to ten years or longer.

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Throughout the day, many of the participants kept returning to the premise that economic dynamics creating disincentives for building resilient generic supply chains require solutions other than advanced technology. To the extent that AMT applications create a large enough societal return on investment, participants identified focus areas for the three main stakeholders:

- **Government:** Support development of evidence regarding the business case for AMTs and other technologies for generics; support development of platform approaches for AMT; prioritize supply chains (which includes updating the FDA Essential Medicines list, assessing vulnerability of those drugs, and identified which would benefit most from AMT); provide financial support for AMT in those circumstances.
- **Academia:** Apply economic and statistical methods to assess the potential return on investments to innovations in manufacturing technology; continue identifying ways to lower the cost of AMT; measure the potential impact on patients, payers, innovators, and other stakeholders on improvements to generic pharmaceutical quality and resilience.
- **Industry:** Form a generic pharmaceutical manufacturing industry consortium to facilitate data sharing with academia about baseline manufacturing process, cost structures and supply chains; mirroring similar consortia established in other areas, mechanisms can be put in place to protect confidential or business-sensitive information.