United States Government Accountability Office

Report to Congressional Committees

March 2023

DRUG MANUFACTURING

FDA Should Fully Assess Its Efforts to Encourage Innovation

GAO-23-105650

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GAO Highlights

Highlights of GAO-23-105650, a report to congressional committees

Why GAO Did This Study

FDA, a component agency within the Department of Health and Human Services' (HHS), is responsible for ensuring that drugs marketed in the U.S. are safe and effective. The agency also plays a role in supporting manufacturing innovation. GAO has previously reported on challenges FDA has faced in its oversight of the drug supply chain and deficiencies in FDA and other HHS entities' preparation for and response to public health emergencies. As such, GAO has designated both as high-risk areas.

The CARES Act includes a provision for GAO to report on the federal pandemic response. This report (1) examines FDA's efforts to support advanced manufacturing, including in response to the COVID-19 pandemic. In addition, it (2) describes stakeholders' perspectives on the regulatory challenges to increasing the use of advanced manufacturing for drugs and (3) describes FDA actions to address challenges to increasing the use of advanced manufacturing. For this work, GAO reviewed FDA documents, national supply chain resiliency strategies, and interviewed FDA and 15 drug industry stakeholders, including companies with approved drugs and those seeking approval.

What GAO Recommends

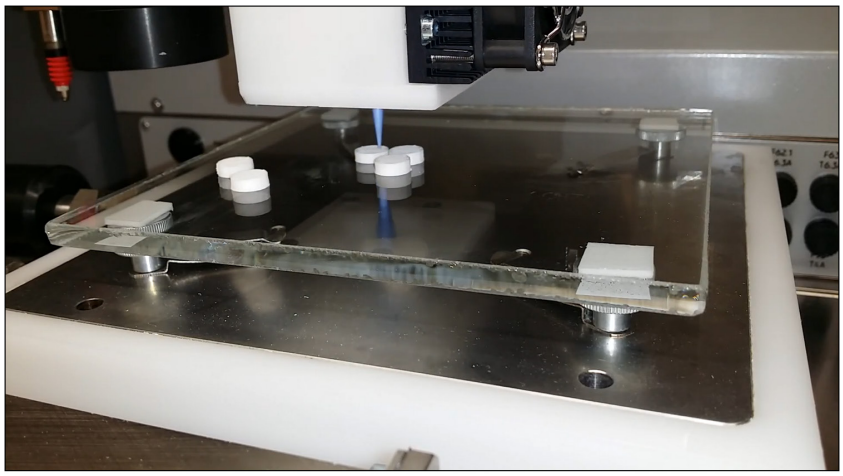
GAO is recommending that FDA document and finalize performance goals and measures related to its advanced manufacturing program efforts and regularly assess program progress. HHS concurred with this recommendation.

View GAO-23-105650. For more information, contact Mary Denigan-Macauley at (202) 512-7114 or deniganmacauleym@gao.gov.

What GAO Found

The COVID-19 pandemic revealed vulnerabilities in the medical supply chain that led to drug shortages. The Food and Drug Administration (FDA) has highlighted advanced manufacturing—innovative technologies that improve product quality and process performance—as a way to enhance supply chain resiliency. However, at the time of this report, few drugs had been made using advanced manufacturing (see figure).

3D printing of drugs, an example of advanced manufacturing



Source: Food and Drug Administration. | GAO-23-105650

FDA has three efforts focused on increasing advanced manufacturing for drugs related to (1) industry engagement, (2) policy and guidance, and (3) research. During the COVID-19 pandemic, FDA leveraged its industry engagement effort to approve two drugs for the treatment of a COVID-19 complication, which are made using advanced manufacturing technology. GAO found, however, that FDA lacks information on the extent to which its industry engagement and policy and guidance efforts encourage adoption of advanced manufacturing. This is because FDA has not documented and finalized performance goals—defining what it expects these efforts to achieve and performance measures—to regularly assess progress the agency is making in achieving these goals. Taking these steps would help FDA make informed program management decisions, including the allocation of finite resources.

The 15 industry stakeholders GAO interviewed reported that regulatory challenges contributed to uncertainty about when and whether a drug manufactured using advanced manufacturing will be approved. This uncertainty weakens the business case for, and contributes to slow adoption of, advanced manufacturing. For example, according to stakeholders, the unfamiliarly of FDA application review staff with advanced manufacturing may lead to delays in approval. FDA has taken steps to address regulatory challenges, including using its industry engagement program to provide opportunities for companies to discuss new technologies with FDA and its research program to familiarize staff with advanced technologies, such as through a yearly training on 3D printing.

Contents

Abbreviations

ASPR	Administration for Strategic Preparedness and Response
CDER	Center for Drug Evaluation and Research
ETP	Emerging Technology Program
FDA	Food and Drug Administration
FRAME	Framework for Regulatory Advanced Manufacturing Evaluation
HHS	Department of Health and Human Services
NIST	National Institute of Standards and Technology

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U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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March 10, 2023

Congressional Committees

The COVID-19 pandemic revealed vulnerabilities in the medical product supply chain that led to shortages of medical products, including drugs.[1] The use of advanced manufacturing for drugs—including technologies such as 3D printing—has been increasingly highlighted by the Food and Drug Administration (FDA) as a way to enhance the resiliency of the drug supply chain by increasing domestic manufacturing capabilities, improving drug quality, and enabling a faster response to (or even avoiding) drug shortages.

FDA is responsible for ensuring that drugs marketed in the United States are high quality, safe, and effective. The agency plays a role in supporting manufacturing innovations to improve product quality and prevent drug shortages. However, despite its potential benefits, challenges and limitations to the adoption of advanced manufacturing have been identified in a report commissioned by FDA.[2] We have previously reported on issues FDA has faced in its oversight of the increasingly global supply chain for drugs marketed in the United States and in its efforts to ensure drug availability, which led us to designate the agency's oversight of medical products as a high-risk area in 2009.[3] Further, in 2022 we identified the Department of Health and Human Services' (HHS)—of which FDA is a component agency—leadership and coordination of public health emergencies as a high-risk area due to persistent deficiencies in FDA and other HHS entities' preparation for and

[1]Drugs are defined to include, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and include components of those articles. See 21 U.S.C. § 321(g)(1)(B), (D).

[2]See National Academies of Sciences, Engineering, and Medicine, *Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations* (Washington, D.C.: 2021).

[3]See GAO, *High-Risk Series: Dedicated Leadership Needed to Address Limited Progress in Most High-Risk Areas*, GAO-21-119SP (Washington, D.C.: Mar. 2, 2021).

response to public health emergencies, including COVID-19 medical supply chain challenges.[4]

The CARES Act includes a provision for us to report on the federal response to the COVID-19 pandemic.[5] In this report, we:

1. examine FDA's efforts to support advanced manufacturing, including in response to the COVID-19 pandemic;
2. describe stakeholders' perspectives on regulatory challenges to increasing the use of advanced manufacturing for drugs and the actions FDA can take to address them; and
3. describe FDA actions to address challenges to increasing the use of advanced manufacturing.

To examine FDA's efforts to support advanced manufacturing, we reviewed agency documents outlining the agency's advanced manufacturing activities and interviewed FDA officials about these activities. Where available, we also reviewed the information the agency uses to track its activities. We focused on FDA's advanced manufacturing efforts related to drugs regulated by FDA's Center for Drug Evaluation and Research (CDER), including CDER-regulated drugs that are biological products.[6] We additionally focused on efforts initiated between

[4]See New High-Risk Designation: HHS and Public Health Emergencies appendix in GAO, *COVID-19: Significant Improvements Are Needed for Overseeing Relief Funds and Leading Responses to Public Health Emergencies*, GAO-22-105291 (Washington, D.C.: Jan. 27, 2022).

[5]Specifically, the act requires us to monitor and oversee the federal government's efforts to prepare for, respond to, and recover from the pandemic. Pub. L. No. 116-136, § 19010(b), 134 Stat. 281, 580 (2020). The American Rescue Plan Act of 2021 also includes a provision for us to conduct oversight of the COVID-19 response. Pub. L. No. 117-2, § 4002, 135 Stat. 4, 78. All of GAO's reports related to the COVID-19 pandemic are available on GAO's website at https://www.gao.gov/coronavirus.

[6]Biological products are a diverse category of products that includes vaccines and allergenic products, blood and blood components, and proteins applicable to the prevention, treatment, or cure of a disease or condition. See 42 U.S.C. § 262(i)(1). Biological products are generally derived from living material, such as the human body or a microorganism. While CDER regulates some biological products—such as monoclonal antibodies, a therapeutic protein—most biological products are regulated by FDA's Center for Biologics Evaluation and Research.

2012—when the first national advanced manufacturing strategy was issued—and the present.[7]

We reviewed relevant national strategies that support federal supply chain resiliency efforts, including the 2018 *Strategy for American Leadership in Advanced Manufacturing* (which was the most recently issued advanced manufacturing national strategy at the time that we initiated our review) and the 2021 *National Strategy for a Resilient Public Health Supply Chain*, and interviewed FDA officials about their role in developing these strategies.[8] In addition, we reviewed documents and interviewed officials from another federal agency within HHS—the Administration for Strategic Preparedness and Response (ASPR)—as well as other agencies with which FDA coordinates on advanced manufacturing efforts, including the Defense Advanced Research Projects Agency and the Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense within the Department of Defense; the National Institute of Standards and Technology (NIST), an agency of the Department of Commerce; and the White House Office of Science and Technology Policy.

In these interviews, we discussed how FDA coordinates with these agencies on efforts related to the advanced manufacturing of drugs and also discussed the extent to which such coordination was used during the COVID-19 response. Finally, we examined the extent to which CDER's advanced manufacturing program efforts incorporate key practices that are part of a performance assessment system identified in our prior work: clear program goals (including long-term strategic goals and near-term performance goals), performance measures linked to program goals, and regular use of performance information to assess progress toward

[7]In response to the America COMPETES Reauthorization Act of 2010, every 4 years the federal government develops a national strategic plan to guide federal programs with activities supporting advanced manufacturing. Pub. L. No. 111-358, § 102, 124 Stat. 3982, 3985 (2011) (codified as amended at 42 U.S.C. § 6622(b)(7) and (c)).

[8]National Science and Technology Council, Committee on Technology, Subcommittee on Advanced Manufacturing, *Strategy for American Leadership in Advanced Manufacturing* (October 2018) and Department of Health and Human Services, Department of Defense, Department of Homeland Security, and Department of Veterans Affairs, *National Strategy for a Resilient Public Health Supply Chain* (July 2021).

achieving these goals.[9] We further examined the extent to which CDER's performance measures aligned with certain key characteristics of successful performance measures identified in our past work.[10]

To describe stakeholders' perspectives on the challenges to increasing the use of advanced manufacturing for drugs and actions FDA can take to address them, we reviewed the 2021 National Academies of Sciences, Engineering, and Medicine report *Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations* (2021 National Academies report).[11] This report highlighted the challenges to increasing the use of advanced manufacturing for drugs. We focused on regulatory challenges, excluding challenges that were economic or technological in nature. We then reviewed documents from and interviewed 15 industry stakeholders—10 individual drug companies and five organizations that represented or worked closely with drug companies on issues related to manufacturing innovation—about the extent to which they agreed that the challenges identified in the National Academies report influenced the use of advanced manufacturing in the drug industry.

We also reviewed documents from, and interviewed, these industry stakeholders to determine what current or future FDA efforts could address the identified challenges. The 10 companies included both those identified by FDA as having an FDA-approved product manufactured using an advanced manufacturing technology and those identified through our outreach to industry organizations as currently seeking or that may soon seek approval for such a product. The 10 companies include representation from brand drug companies, generic drug companies, and companies under contract with brand or generic drug companies to

[9]See GAO, V*eterans Justice Outreach Program: VA Could Improve Management by Establishing Performance Measures and Fully Assessing Risks*, GAO-16-393, (Washington, D.C. Apr. 28, 2016), 7-8 and *Coast Guard: Additional Actions Needed to Improve Commercial Fishing Vessel Safety Efforts*, GAO-23-105289, (Washington, D.C.: Nov. 2, 2022), 26.

[10]GAO, *Tax Administration: IRS Needs to Further Refine Its Tax Filing Season Performance Measures*, GAO-03-143 (Washington, D.C.: Nov. 22, 2002), 3.

[11]National Academies, *Innovations in Pharmaceutical Manufacturing on the Horizon*. The National Academies committee was tasked by FDA with identifying emerging technologies and the challenges that might prevent their adoption and to recommend ways of overcoming any regulatory challenges. As the task was focused on the role of FDA in preparing for and facilitating innovation, the report did not make recommendations to other drug industry stakeholders.

manufacture products for them.[12] The five organizations included those that could provide the views of both large and small drug companies as well as brand and generic drug companies.[13] The perspectives from these drug companies and organizations are not generalizable to all drug companies and organizations that represent drug companies.

To describe FDA actions to address the challenges to increasing the use of advanced manufacturing, we reviewed agency documents and interviewed FDA officials. Through these reviews and interviews, we identified FDA perspectives on the challenges identified in the National Academies report and steps the agency has taken, or plans to take, in response to these challenges, as applicable.

We conducted this performance audit from January 2022 to March 2023 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

FDA Responsibilities in the Drug Approval Process

FDA's approval is generally required before brand-name prescription drugs and generic prescription drugs can be marketed for sale in the United States.[14] To obtain approval to market a drug, companies must generally submit a drug application containing information on the drug

[12]We interviewed representatives of the following 10 companies: Aprecia; Catalent Pharma Solutions; Dr. Reddy's Laboratories, Inc.; Eli Lilly and Company; GlaxoSmithKline; The Janssen Pharmaceutical Companies of Johnson & Johnson; Merck & Co.; Pfizer Inc.; Teva Pharmaceuticals; and Thermo Fisher Scientific.

[13]We interviewed representatives of the following five organizations: Association for Accessible Medicines, Biotechnology Innovation Organization, National Institute for Innovation in Manufacturing Biopharmaceuticals, Pharma & Biopharma Outsourcing Association, and Pharmaceutical Research and Manufacturers of America.

[14]For biological products, FDA generally licenses them for marketing in the United States through approval of a biologics license application. According to FDA, as part of each application review, it assesses manufacturing processes, establishments involved in manufacturing, and the quality and consistency of the biological product. When a brand-name product's patents expire and exclusivity periods end, a "biosimilar" product may enter the market. A biosimilar must be demonstrated to be highly similar to an already licensed biological product and to have no clinically meaningful differences in terms of safety, purity, and potency from the brand-name product.

components and composition, manufacturing process, and location of manufacturing facilities. For a brand-name drug, the drug company must also present data on the drug's safety and effectiveness. For generic drugs, companies must submit data demonstrating therapeutic equivalence to a brand-name drug, which includes showing that the two products have the same active ingredient and other key characteristics. A team of FDA reviewers evaluates whether the brand-name or generic drug meets manufacturing quality standards and is safe and effective for its proposed use. As part of the application process, FDA reviews the drug's manufacturing process, including the use of any advanced manufacturing technology. Due to identified deficiencies or the need for additional data, certain application reviews may take multiple rounds as FDA seeks additional information from the company.

Once a drug is approved for marketing in the United States, FDA shifts to monitoring the drug's safety, quality, and promotion. After obtaining FDA's approval, drug companies may make post-approval changes, for example to the product manufacturing location or process, or to the type or source of inactive ingredients. Companies must generally submit an application supplement to notify FDA of the change and, if the change has a substantial potential to have an adverse effect on the product, obtain FDA's approval.[15]

In addition to its oversight of drugs marketed in the United States, FDA plays a role in global pharmaceutical regulatory oversight. Drug companies that market their products globally, need approval from multiple international regulators to market their drug outside of the United States.[16] FDA engages with regulators from different countries to respond to the complex and global nature of pharmaceutical industry operations and related regulatory oversight.

[15]21 C.F.R §§ 314.70 (new drugs), 314.97 (generic drugs), and 601.12 (biological products) (2021). Specifically, any change that has a substantial potential to adversely affect factors such as the identity, strength, quality, purity, or potency of a drug product requires FDA review and approval of a "prior approval" supplement before a drug manufactured using this change can be distributed.

[16]Drugs manufactured overseas, but marketed in the United States, are still subject to FDA oversight. See GAO, *Drug Safety: FDA Should Take Additional Steps to Improve Its Foreign Inspection Program*, GAO-22-103611 (Washington, D.C.: Jan. 7, 2022).

Federal Focus on Advanced Manufacturing for Drugs

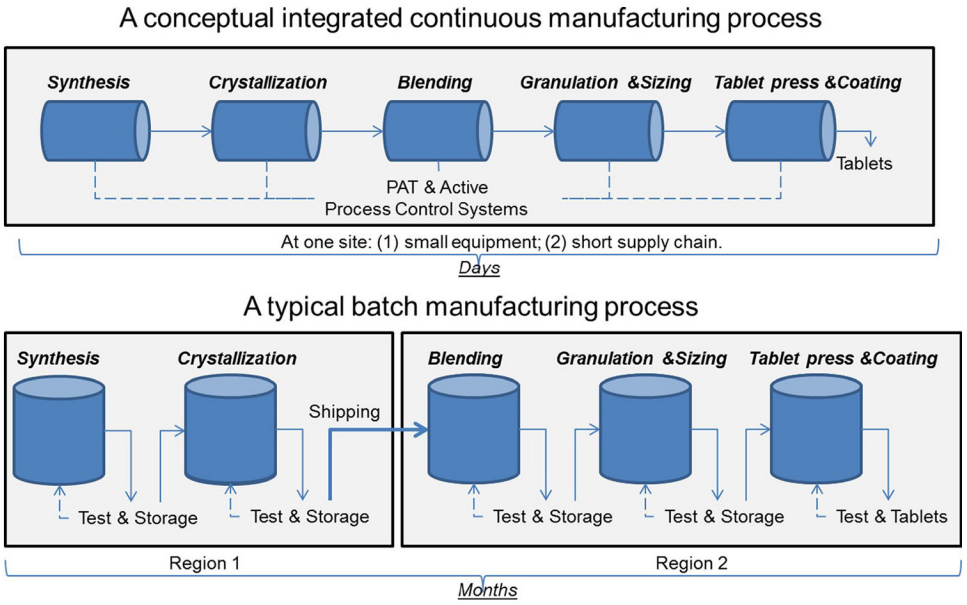
The term “advanced manufacturing” covers a large range of technologies that are applicable to multiple sectors of the U.S. economy, including drug manufacturing. According to the 2021 National Academies report, advanced manufacturing is defined as manufacturing developments in which innovative technologies are used to upgrade or replace existing manufacturing systems to improve product quality and process performance.[17]

Advanced manufacturing for drugs includes technology such as continuous manufacturing, which, according to FDA, offers manufacturing advantages compared to traditional batch manufacturing. For example, as outlined in figure 1, in a fully continuous process, the finished drug product is produced in a continuous stream, as opposed to traditional batch manufacturing where breaks, or stops, exist between different manufacturing processing steps. Thus, using continuous manufacturing can produce finished drug products in days as opposed to traditional batch manufacturing that can take months. Further, according to FDA, the use of automated monitoring that occurs in continuous manufacturing may help avoid supply disruptions, because such monitoring can detect manufacturing equipment failures before they occur. Such monitoring can also enable product quality to be precisely controlled, thereby reducing the quality issues that may trigger drug shortages.[18] In addition, in the event of increased demand for a product, a continuous manufacturing process can be run for a longer period of time, which may also reduce the likelihood of shortages, according to FDA.

[17]National Academies, *Innovations in Pharmaceutical Manufacturing on the Horizon.*

[18]See Statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, *Safeguarding Pharmaceutical Supply Chains in a Global Economy*, testimony before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, 116th Cong., 1st sess., October 30, 2019. We and others have found that shortages are often caused by manufacturing quality problems. See GAO, *Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge*, GAO-16-595 (Washington, D.C.: July 7, 2016); Food and Drug Administration, *Drug Shortages: Root Causes and Potential Solutions*, (2019); and National Academies of Sciences, Engineering, and Medicine, *Building Resilience into the Nation’s Medical Product Supply Chains*, (Washington, D.C.: 2022).

Figure 1: Example of Continuous Manufacturing Process Compared to Batch Manufacturing Process for a Drug

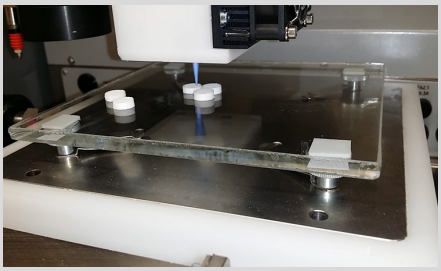


Source: Food and Drug Administration. | GAO-23-105650

Note: According to Food and Drug Administration guidance, conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality at various stages of the manufacturing process. In contrast, Process Analytical Technology (PAT) is a system for designing, analyzing, and controlling manufacturing through measurements of critical quality and performance attributes during processing.

In traditional batch manufacturing there may be hold times between steps and the material may be stored in containers or shipped to other facilities in different regions around the world to complete the manufacturing process. This can add weeks or months to processing time.

An Example of Advanced Manufacturing for Drugs: 3D printing



3D printing, or additive manufacturing, is used to manufacture drugs by repeatedly layering material in a particular 3D shape. This method of manufacturing drugs can be advantageous for special populations because of the ability of 3D printing to tailor tablet size and dosage form (such as instantly dissolving tablets). In addition to personalizing medicine, 3D printing may offer the ability to manufacture a drug on demand at the point-of-care.

Source: Food and Drug Administration (FDA) information (text); FDA (image). | GAO-23-105650

Another example of advanced manufacturing technology is additive manufacturing, or 3D printing.

Federal focus on increasing the use of advanced manufacturing spans multiple sectors of the U.S. economy including health care. Under the America COMPETES Reauthorization Act of 2010, the Committee on Technology within the National Science and Technology Council is responsible for developing and updating a strategic plan to guide federal programs and activities in support of advanced manufacturing research and development.[19] The 2018 *Strategy for American Leadership in Advanced Manufacturing* (2018 Advanced Manufacturing National Strategy) outlines goals and objectives intended to promote American leadership in advanced manufacturing across industrial sectors to ensure national security and economic prosperity.[20]

In addition to the federal programs focusing on advanced manufacturing, FDA has emphasized the importance of adopting advanced manufacturing, and has taken steps to identify barriers to implementation. CDER commissioned the 2021 National Academies report, which identified multiple types of challenges, including regulatory challenges, to implementing advanced manufacturing for drugs. The regulatory challenges include, among others,

- lack of consistent expectations across international health authorities,
- the need for more guidance related to advanced manufacturing technologies,
- FDA's approval process for changes to the manufacturing process after a product has been approved, and
- lack of expertise with innovative technologies, organizational culture issues, and capacity constraints within FDA.

[19]Pub. L. No. 111-358, § 102, 124 Stat. 3982, 3985 (2011) (codified as amended at 42 U.S.C. § 6622(b)(7) and (c)). The strategic plan is required to be updated every 4 years.

[20]In October 2022, the Committee on Technology within the National Science and Technology Council published an update to the 2018 Advanced Manufacturing National Strategy that will guide efforts moving forward and which we plan to examine in future work. National Science and Technology Council, Committee on Technology, Subcommittee on Advanced Manufacturing, *National Strategy for Advanced Manufacturing* (October 2022). The updated strategy is available at https://www.whitehouse.gov/wp-content/uploads/2022/10/National-Strategy-for-Advanced-Manufacturing-10072022.pdf.

While the National Academies report was focused on the role of FDA, the report also noted the critical need for other drug industry stakeholders to undertake actions in support of shared advanced manufacturing goals.[21]

FDA Efforts Support Adoption of Advanced Manufacturing, but FDA Has Not Fully Assessed All of Its Efforts

FDA Has Three Efforts to Increase the Adoption of Advanced Manufacturing for Drugs

FDA's CDER leads three efforts specifically focused on increasing the adoption of advanced manufacturing for drugs:

- **Emerging Technology Program (ETP).** CDER created ETP in 2014 to enable early engagement between FDA and drug companies seeking to use an advanced manufacturing technology. Through ETP, drug company representatives can meet with staff from FDA's application review and inspection components before the company submits an application to market a drug. According to FDA officials, such interactions can happen even before the company identifies the drug associated with the proposed new technology and may continue throughout product development as ETP staff participate in the review of the application. Companies can also host site visits to demonstrate the novel technology to FDA staff. According to FDA's website and guidance, these interactions are intended to identify and resolve technical and regulatory issues early, and to provide information on what to include in the drug application before it is submitted.
- **Development of policy and guidance.** CDER develops policy and guidance documents related to advanced manufacturing for drugs. For example, CDER's 2019 draft guidance on continuous manufacturing is intended to help drug companies implement this

[21]In March 2022, the National Academies published a follow-up report that included FDA perspectives on the challenges identified in 2021 National Academies report and clarifications to industry. See National Academies of Sciences, Engineering, and Medicine, *Innovations in Pharmaceutical Manufacturing on the Horizon: Proceedings of a Workshop in Brief* (Washington, D.C.: 2022).

advanced manufacturing technology.[22] Specifically, the draft guidance describes several key quality considerations, such as potential differences in how a company may need to take samples of a drug to demonstrate a drug's stability over its shelf life. It also provides recommendations for how companies should address these considerations in their drug applications. CDER also took a leadership role in the development of guidance documents harmonized with other international regulators.

To further its policy and guidance development, in 2021 CDER began implementing its Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) Initiative. Through FRAME, CDER is examining its statutory authorities, regulations, and guidance to identify changes that may need to be made to facilitate its review of applications that use advanced manufacturing technologies. As part of this initiative, CDER plans to seek stakeholder input by issuing discussion papers and holding workshops on advanced manufacturing technologies; may issue new or updated advanced manufacturing guidance; and plans to work to harmonize international guidelines to ensure global regulatory practice is clear to stakeholders implementing advanced manufacturing.

- **Internal and external CDER-led research.** CDER also conducts its own research and awards grants and contracts to drug companies and universities to conduct research on a range of advanced drug manufacturing topics. For example, CDER conducted research on how different 3D geometric designs affect the performance of 3D printed drugs. CDER also provided grants to academic institutions focused on researching advanced manufacturing topics, such as the use of real-time quality assurance testing for continuous manufacturing.

[22]See U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, *Quality Considerations for Continuous Manufacturing: Guidance for Industry (Draft)* (Silver Spring, MD: February 2019).

According to FDA officials, this internal and external research helps inform CDER's feedback to, and guidance development for, drug companies seeking to use advanced manufacturing technologies. FDA officials told us that the agency also uses the results of advanced manufacturing research to develop and deliver training to FDA staff on these advanced manufacturing technologies. According to FDA officials, as more application reviewers are trained on technologies like continuous manufacturing, FDA can expeditiously review more applications for drugs that use such technology.

Despite these efforts, FDA data show that relatively few drugs manufactured using an advanced manufacturing technology are currently approved for marketing in the United States. Between 2015 (when CDER first approved a drug that used advanced manufacturing technology) and October 2022 (the most recent data available), CDER had approved 16 applications or supplemental applications that used an advanced manufacturing technology.[23] FDA reported that from calendar year 2015 through the end of October 2022, CDER had accepted 112 proposals for participation in ETP.[24] If these proposals result in applications submitted to the agency, there could be additional approvals of drugs produced using advanced manufacturing in the coming years.

However, FDA officials told us that an individual drug company's decision to adopt advanced manufacturing is based on multiple factors, most of which are outside the scope and control of FDA. FDA officials cited instances in which companies had worked with ETP on the early stages of developing an application for a drug that used an advanced manufacturing technology, but the application was ultimately not submitted to FDA for reasons unrelated to the manufacturing technology. Further, FDA officials noted that establishing the business case for its use is the dominant factor for industry when determining whether to adopt an advanced manufacturing technology.

Examples of Broader Advanced Manufacturing Efforts

In addition to its efforts focused specifically on the advanced manufacturing of drugs, the Food and Drug Administration (FDA) also engages in broader research and a range of partnerships with public and private stakeholders that aim to increase the adoption of advanced manufacturing for all medical products, including drugs.

- **Research.** FDA conducts research on the advanced manufacturing technology of 3D printing at its Additive Manufacturing of Medical Products Lab, which focuses on 3D printing for a range of products, including drugs.
- **Partnerships.** According to agency officials, FDA helped to draft, and provided feedback on, the development of the National Science and Technology Council's 2018 *Strategy for American Leadership in Advanced Manufacturing*. While this National Strategy applied to multiple industries, it identified specific action items for the government to focus on related to certain advanced manufacturing technologies for medical products, including drugs. According to agency officials, FDA also contributed to the development of the 2021 *National Strategy for a Resilient Public Health Supply Chain* that seeks to develop U.S. capability for manufacturing drugs and other medical products for future pandemics and biological threats. To do so, the 2021 Strategy highlights the potential of advanced manufacturing technologies that enable manufacturers to quickly transition production from one medical product to another in response to demand, among other things.

Source: GAO analysis of FDA information. | GAO-23-105650

[23]For context, in 2021 CDER approved more than 800 applications for brand or generic drugs, as well as thousands of supplemental applications using traditional manufacturing methods. The 16 approved applications that use an advanced manufacturing technology relate to drugs used to treat cystic fibrosis, HIV/AIDS, cancer, and epilepsy, among other conditions. Twelve of the 16 applications use the advanced manufacturing technology of continuous manufacturing.

[24]Drug companies (and other organizations developing advanced manufacturing technology) submit proposals to participate in ETP and, if accepted, can then interact with an ETP team of FDA staff from across the agency.

FDA Took Steps to Support Advanced Manufacturing during the COVID-19 Pandemic

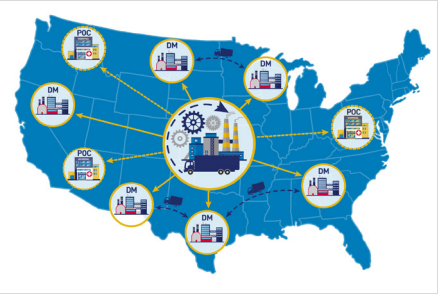
According to officials, FDA leveraged existing advanced manufacturing partnership efforts to address COVID-19 medical product supply chain gaps. For example:

- According to ASPR officials, ASPR coordinated with FDA regarding two applications for drugs that would be made using advanced manufacturing technology.[25] FDA officials further told us that ASPR coordinated with industry on these submissions and that the approval of these applications—which were part of ETP— helped avoid a potential shortage of a drug used to treat a complication of COVID-19. The manufacture of the two drugs used equipment that automated the entire filling line for the drug and thus minimized the need for human intervention and interaction, a key concept during an infectious disease outbreak. According to FDA officials, this type of automation could be critical during a future pandemic when human on-site presence may be limited.
- FDA also sought to facilitate applications for products that could help address medical product supply chain gaps. FDA and ASPR offered technical expertise to companies developing medical products needed during the pandemic that were made using advanced manufacturing. FDA officials told us based on the information that companies shared in meetings with the agencies, officials also provided advance notice to relevant FDA staff that an application for a product using an advanced manufacturing technology would soon be submitted.
- On a more limited basis, FDA and NIST collaborated to answer questions from, and provide direction to, companies seeking to address domestic medical product supply chain gaps, including for drugs used in the COVID-19 response. They did this through an existing public-private partnership through which NIST interfaces with small and medium manufacturers across the country, according to agency officials.

FDA officials told us the agency has modified one existing partnership and is modifying some of its other advanced manufacturing efforts in response to the COVID-19 pandemic.

[25]Advanced manufacturing was also used to produce other medical products as part of the COVID-19 response, such as medical devices. See U.S. Department of Commerce, National Institute of Standards and Technology, Office of Advanced Manufacturing and Department of Defense Manufacturing Technology Program Office, *Manufacturing USA: Rapid Response to COVID-19 – Advanced Manufacturing Leadership to Support National Resiliency* (2021).

An example of Advanced Manufacturing for Drugs: Distributed Manufacturing



Distributed manufacturing is a decentralized manufacturing strategy in which portable manufacturing units may be deployed to multiple locations. Distributed manufacturing has the potential to enhance domestic supply resiliency by enabling on-demand production of drugs across the United States. For example, distributed manufacturing could be deployed to a location following a public health emergency to meet local demand for certain drugs.

Point-of-Care manufacturing is a type of distributed manufacturing in which manufacturing units are deployed to places close to where patients may receive care, such as a health care facility. Point-of-care manufacturing could thus be used by health care facilities to meet the specific needs of its patients.

Source: Food and Drug Administration (FDA) (text); FDA (image). | GAO-23-105650

- While the agencies had worked together prior to the pandemic, in 2021 FDA entered into a memorandum of understanding with NIST specifically focused on using advanced manufacturing to increase supply chain resiliency and domestic manufacturing.
- Further, the agency has also prioritized its efforts to develop policy and fund research on the advanced manufacturing technologies of distributed manufacturing and point-of-care manufacturing. To the extent they are adopted, these technologies could help address some of the supply chain issues seen during the COVID-19 pandemic and with future pandemics, because they have the potential to provide flexibility and agility for a rapid and localized response to patient demand, according to FDA officials.[26] FDA officials told us the COVID-19 pandemic showed the problems associated with long, tangled, international supply chains and the need for agile responses to local and rapidly changing patient demand, such as that following an outbreak. However, according to FDA officials, given the nuances of specific drug manufacturing circumstances, and the range of scenarios that distributed manufacturing could be comprised of, this technology may not be able to address supply chain resiliency concerns in all instances.

[26]We previously reported on supply chain concerns seen during the COVID-19 pandemic. For example, see GAO, *COVID-19: Opportunities to Improve Federal Response and Recovery Efforts*, GAO-20-625, (Washington, D.C.: June 25, 2020); *COVID-19: Federal Efforts Could Be Strengthened by Timely and Concerted Actions*, GAO-20-701, (Washington, D.C.: Sept. 21, 2020); *COVID-19: Urgent Actions Needed to Better Ensure an Effective Federal Response*, GAO-21-191, (Washington, D.C.: Nov. 30, 2020); *COVID-19: Critical Vaccine Distribution, Supply Chain, Program Integrity, and Other Challenges Require Focused Federal Attention*, GAO-21-265 (Washington, D.C.: Jan. 28, 2021); *COVID-19: Sustained Federal Action Is Crucial as Pandemic Enters Its Second Year*, GAO-21-387, (Washington, D.C.: Mar. 31, 2021) and *COVID-19: Current and Future Federal Preparedness Requires Fixes to Improve Health Data and Address Improper Payments*, GAO-22-105397, (Washington, D.C.: Apr. 27, 2022).

FDA Has Not Fully Utilized Key Practices to Assess Its Efforts to Support Advanced Manufacturing

FDA has stated that advanced manufacturing is a high priority because the agency believes it will help address supply chain and drug quality concerns, and provide flexibility to respond to public health emergencies like the COVID-19 pandemic. However, FDA's CDER does not fully utilize important performance assessment practices that could help it determine whether and how its advanced manufacturing efforts are supporting this high priority.

In our prior work, we have identified key practices that help agencies achieve results and improve performance.[27] These practices are an important component of effective program management and include the following:

1. **Establish program goals**, which communicate what the agency proposes to accomplish and allow agencies to assess or demonstrate the degree to which those desired results were achieved. Program goals comprise
   - **Strategic goals and objectives**, which are long-term goals that set a general direction for a program's efforts; and
   - **Performance goals**, which are the specific results an agency expects its program to achieve in the near term. Our prior work has found that it can be beneficial for performance goals to have specific targets and time frames that reflect strategic goals.
2. **Establish performance measures**, which are concrete, objective, observable conditions that permit the assessment of progress made toward the agency's goals. Performance measures show the progress the agency is making in achieving performance goals. Our past work has also identified key characteristics of successful performance measures including that they are clearly stated and have quantifiable, numerical targets or other measurable values that allow for easier comparison with actual performance.[28]
3. **Regularly assess progress**, by using performance information to assess progress toward program goals and inform management decisions.

These practices provide decision makers with useful information to help determine whether and why a program is working well or not.

[27]GAO-16-393 and GAO-23-105289.

[28]GAO-03-143.

In support of FDA's designation of advanced manufacturing as a high priority, CDER has developed long-term strategic objectives that set a general direction for its advanced manufacturing efforts, as listed in Table 1.

Table 1. Long-Term Strategic Objectives for the Center for Drug Evaluation and Research's Advanced Manufacturing Efforts

Strategic Objective 1: Establishing a regulatory program and framework to accelerate the development and implementation of advanced manufacturing of pharmaceuticals.
Strategic Objective 2: Advancing drug development science to support technology implementation, science- and risk-based regulatory evaluation, and workforce development in advanced manufacturing.
Strategic Objective 3: Engaging with stakeholders through strategic partnerships and proactive communication to promote the implementation of advanced manufacturing, perform technology forecasting activities, and reduce barriers to entry.
Strategic Objective 4: Leading the global effort to encourage international regulatory convergence for development, implementation, operation, and lifecycle management of advanced manufacturing.

Source: Food and Drug Administration. | GAO-23-105650

However, CDER lacks information on the extent to which two of its three efforts help it achieve these long-term strategic objectives. CDER cannot do so because it has not formalized performance goals that define the specific results it expects its efforts to achieve in the near term. It also has not formalized performance measures to collect the information it needs to regularly assess progress the agency is making in achieving these goals.

Specifically, CDER has performance goals with specific targets and time frames for what its research program effort is expected to achieve in the near term and performance measures that link to its strategic objective two. However, it has not formally documented this performance information for ETP or finalized it for its FRAME Initiative. Further, it has not formally documented or finalized plans for conducting a regular assessment of its progress toward achieving its goals for ETP or its FRAME Initiative. (See text box for further descriptions of these efforts.)

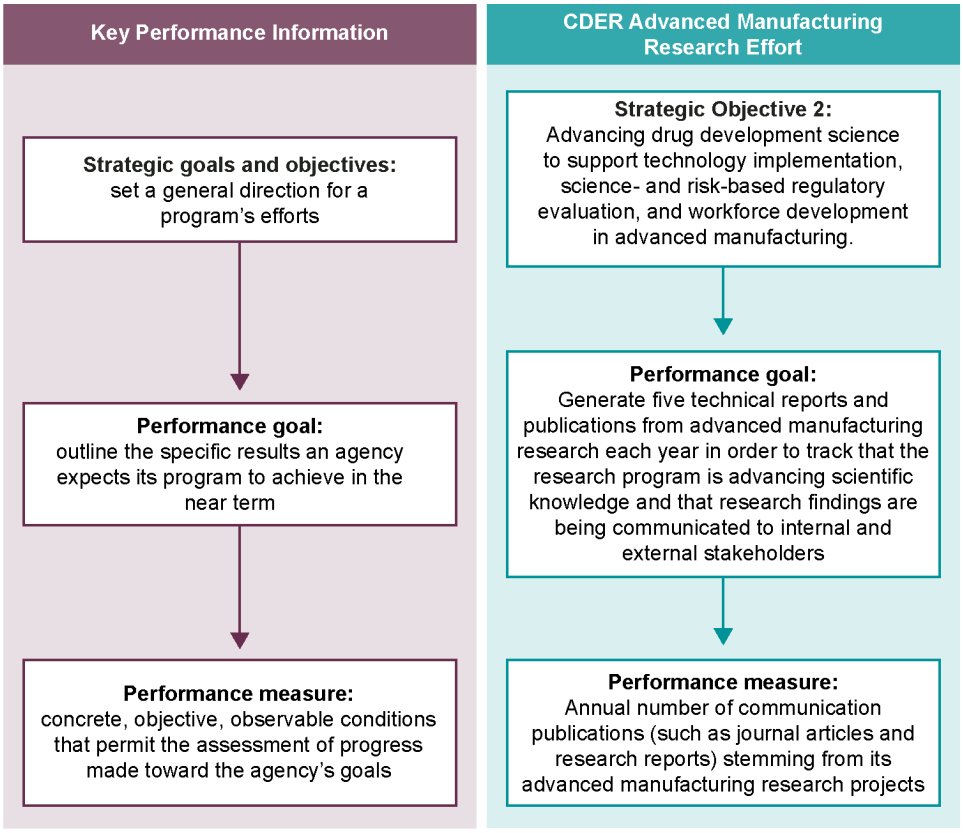
Center for Drug Evaluation and Research's (CDER) Advanced Manufacturing Program Efforts

- **Internal and external CDER-led research.** CDER conducts its own research and awards grants to drug companies and universities to conduct research on a range of advanced drug manufacturing topics.
- **Emerging Technology Program (ETP).** Through ETP, drug company representatives can meet with staff from the Food and Drug Administration's application review and inspection components before the company submits an application to market a drug.
- **Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) Initiative.** Through its FRAME Initiative, CDER is examining its statutory authorities, regulations, and guidance to identify changes that it may need to make to facilitate the review of applications for drugs that use advanced manufacturing technologies. As part of this initiative, CDER plans to seek stakeholder input through discussion papers and workshops; may issue new or updated guidance; and plans to work to harmonize international guidelines.

Source: GAO analysis of Food and Drug Administration information. | GAO-23-105650

- **Research.** CDER has developed and documented three performance goals and related performance measures for its advanced manufacturing research program effort, which support its second strategic objective of advancing drug development science (see fig. 2). CDER researchers also annually report the outcomes of each internal research project, and, according to FDA officials, CDER reviews research outcomes every year and establishes annual targets.

Figure 2: Example of Linkages between Strategic Objective, Performance Goal, and Performance Measure for the Center for Drug Evaluation and Research's (CDER) Advanced Manufacturing Research Program Effort



Source: GAO analysis of Food and Drug Administration information. | GAO-23-105650

Note: Other performance goals relate to the number of advanced manufacturing research projects initiated and the number of trainings as a result of these research projects. CDER officials told us they also monitor the number of regulatory actions taken—e.g., the number of application approvals—that were influenced by CDER advanced manufacturing research. However, since such activity depends on regulatory submissions, no target or time frame are set for this performance indicator.

- **ETP.** CDER has not explicitly documented a performance goal or measure for ETP, but conducted a limited assessment of this program effort. According to CDER officials, ETP supports its first, third, and fourth strategic objectives. CDER officials said the overall performance goal for ETP is to ensure that, once an ETP drug application is received, the advanced manufacturing technology element should not delay review of the application. CDER officials told us they also set a secondary performance goal related to ETP external engagement, focused on the number of presentations given

and the number of international engagements undertaken annually.[29] However, neither the overall goal nor the secondary goal have been formally documented as performance goals with specific targets for what CDER expects ETP to achieve in the near term.

To measure progress toward achieving ETP's overall performance goal of not having the advanced manufacturing technology element delay the review of a drug application, CDER uses a dashboard to track the review status of applications associated with ETP. Specifically, as each application is subject to review time frame goals under FDA's user fee programs, FDA tracks whether the application is reviewed within the applicable user fee time frame goal.[30] Similarly, related to its secondary performance goal, CDER maintains a database of presentations given. However, CDER has not documented an explicit performance measure related to its review times for applications involving advanced manufacturing technology against applicable user fee review time goals or related to external engagement in clear terms with a measurable target.

Instead, CDER officials told us that they wrote a recent journal article that analyzed data on the amount of time taken to approve applications for products that use the advanced manufacturing technology of continuous manufacturing.[31] The analysis found that the mean and median approval time frames were faster for the applications using continuous manufacturing than for the comparison applications using traditional batch manufacturing. CDER officials told us that this article demonstrates that ETP's overall goal is being met,

[29]According to officials, CDER has temporarily paused its international engagements related to emerging technologies due to COVID-19 travel restrictions. Thus, CDER does not have a written performance goal for this activity, although officials said they plan to establish one when travel is more feasible.

[30]FDA receives user fees from the drug industry under congressionally authorized user fee programs to supplement agency resources available for review of drug applications and related activities. In exchange for receiving user fees, FDA commits to meeting certain performance goals, such as reviewing applications within a specified time frame. For example, one such performance goal for fiscal years 2023 through 2027 is to review and act on 90 percent of certain drug applications within 10 months of receipt. See FDA, *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027*. CDER's ETP application review dashboard shows that for the 16 approved applications for products that use an advanced manufacturing technology, all 16 were approved on time.

[31]A.C. Fisher et al. "An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US," *International Journal of Pharmaceutics,* vol. 622 (2022): 121778. FDA focused this article on the applications for immediate release solid oral dosage form drugs that were approved at the start of 2022.

and that CDER would continue to internally track such review time frames.

However, due to study design, this analysis only focused on five of the 16 approved applications that use an advanced manufacturing technology.[32] The analysis also did not include data on applications currently under review. CDER officials further told us that in response to recommendations in a January 2020 ETP Program Enhancement Strategy, they also developed and are tracking a number of key performance indicators, such as the number of proposals accepted into ETP and the number of ETP meetings held with drug companies. These indicators provide useful information, but lack measureable targets and a clear linkage to its program goals. Thus, these indicators do not allow CDER to demonstrate progress toward achieving ETP's overall goal of no delays in advanced manufacturing application review.

Finally, CDER officials told us there is no need to formally document performance goals and measures for ETP, because the leadership across various advanced manufacturing efforts is the same. Thus, staff understand the program's goals and linkages to its strategic objectives. They further noted that all CDER staff are trained on the application review time frame goals negotiated under various user fee agreements, that meeting review time goals is an expectation in every application reviewer's performance plan, and that such user fee goals are tracked. However, they also said they were open to feedback about how best to document their ETP performance information.

- **FRAME Initiative.** CDER has not finalized performance goals or measures for FRAME, but according to a draft document, it is planning to track its activities related to achieving its draft goals. According to CDER officials, they are currently implementing the FRAME Initiative, which will also support CDER's first, third, and fourth strategic objectives. CDER officials told us they have developed a draft roadmap with four performance goals under consideration. For example, according to CDER officials, one performance goal is to undertake public engagement to receive stakeholder input on the regulatory framework for four prioritized advanced manufacturing technologies. CDER is also considering associated performance measures. For example, for its proposed performance goal on public

[32]FDA officials explained that the analysis focused on a subset of advanced manufacturing applications in order to allow for the inclusion of a comparison group (which was only possible for certain continuous manufacturing applications) and to allow for the assessment of post-approval activities (which was only possible for applications approved long enough ago for certain post-approval activities to have taken place).

engagement, CDER is considering the following performance measure: “Beginning in 2021 and until complete, increase the number of prioritized advanced manufacturing technologies that have undergone public engagement every year by greater than 25 percent.” According to draft documents, CDER plans to track its activities related to achieving this goal. The draft FRAME roadmap includes a time line for seeking public engagement on specific technologies—such as its plan for issuing a discussion paper on distributed manufacturing—and the current status of its public engagement efforts. However, CDER officials told us that the draft roadmap is highly speculative, as it describes potential, future goals that will change based on additional information and analysis. They said they are currently refining the draft roadmap into a public action plan that will include formal performance goals with specific targets and time frames. The action plan does not yet have a target date for public release.

We have previously reported that fundamental to an organization’s efforts to manage for results is its ability to set near-term performance goals with specific targets and time frames that reflect strategic goals and objectives.[33] An organization also should regularly assess progress toward its goals using performance measures. As CDER continues its efforts to encourage advanced manufacturing, taking these steps for ETP and FRAME will help CDER make informed decisions about which efforts should be continued or expanded or whether corrective actions are warranted. This in turn will contribute to the larger federal focus on increasing the use of advanced manufacturing for drugs and the best allocation of finite resources.

Stakeholders Largely Agreed That Regulatory Challenges Contribute to Slow Adoption of Advanced Manufacturing

[33]GAO-16-393 and GAO-23-105289.

Multiple Regulatory Challenges Create Uncertainty about Product Approval and Affect Adoption of Advanced Manufacturing Technology, According to Stakeholders

Of the 15 industry stakeholders that we interviewed, all of them described concerns related to at least one of the selected regulatory challenges identified in the 2021 National Academies report, and most described concerns with more than one. According to stakeholders, these challenges create uncertainty about FDA approval of products manufactured using advanced technology and can contribute to the slow adoption of such technology.

- **Regulatory definitions.** Eleven stakeholders stated that regulatory definitions were a challenge to adopting advanced manufacturing technologies. When discussing this challenge, stakeholders focused on uncertainty regarding how certain regulatory terms would be applied to advanced manufacturing technology. For example, one stakeholder said FDA's manufacturing quality regulations are not designed for some types of advanced manufacturing, such as distributed manufacturing where manufacturing units deployed to multiple locations may not fit the regulatory definition of a manufacturing establishment.
- **Global harmonization.** Fourteen stakeholders stated that global harmonization was a challenge to adopting advanced manufacturing technologies. Even if a company is relatively certain it can receive an approval from FDA, the company may still be hesitant to use advanced manufacturing technology if there is uncertainty about how other global regulators will react. For example, one stakeholder said that, in addition to FDA, it interacts globally with 15 major and 50 minor regulatory authorities, and using a new manufacturing platform could create delays when seeking approvals from all of these authorities.
- **Product and technology review process.** Thirteen of the stakeholders stated that the product and technology review process was a challenge to adopting advanced manufacturing technologies. Specifically, stakeholders expressed concerns about the potential for increased application review times and uncertainty about product approval when using a new manufacturing technology, because FDA does not approve manufacturing technology independent of a product application. Rather, as agency officials stated, during the drug approval process, FDA reviews the manufacturing technology in the context of the product it is being used to produce. Thus, even if a technology has been used before, it is unclear whether FDA will approve an application that uses the technology for a different product.

These concerns applied both to the use of a new technology to produce a previously approved product, and even more to the use of new technology to produce a new product. For example, one stakeholder was hesitant to use an advanced manufacturing technology when seeking approval for a new product, because the stakeholder did not want to risk having a product stalled in regulatory review solely due to the use of the technology. To mitigate risk, this stakeholder has transitioned to continuous manufacturing on a product-by-product basis, using already-approved products. This "bridging" strategy is less risky, according to the stakeholder, because FDA does not have to review a new drug and new technology in the same application.

- **Post-approval changes.** Eleven stakeholders stated that challenges related to post-approval changes may limit companies from transitioning a currently marketed product to advanced manufacturing. FDA must approve certain manufacturing process changes for an approved drug.[34] Two stakeholders reported hesitancy to switch to an advanced manufacturing process for a drug already on the market due to the resource and time commitment for such approvals. Three stakeholders had concerns about unpredictable timelines. One of these stakeholders expressed concerns about additional questions from FDA reviewers about the manufacturing process that the stakeholder said would not be asked if the company was using traditional manufacturing methods, among others.
- **Guidance.** Ten stakeholders stated there are challenges with existing FDA guidance related to advanced manufacturing. Four stakeholders expressed the need for more clarity to avoid confusion and different interpretations, while two requested more timely guidance. For example, one stakeholder noted that guidelines are purposefully broad to allow flexibility. However, such flexibility could result in different interpretations across the regulatory agency. Another stakeholder referenced the lack of guidance about post-approval changes when moving from one manufacturing technology to another. This stakeholder noted that there are multiple ways to move from one technology to another. Without guidance, companies are uncertain about the expectations and boundaries for post-approval changes. In

[34]If a drug company wants to change any part of its original new drug application or abbreviated new drug application after its approval—such as changes to manufacturing location or process—it must generally submit an application supplement to notify FDA of the change. If the change has a substantial potential to adversely affect factors such as the identity, strength, quality, purity, or potency of the drug, the sponsor must obtain FDA approval. See 21 C.F.R. §§ 314.70, 314.97 (2021).

addition, two stakeholders stated that guidance can come too late to be beneficial. One of these stakeholders said that guidance has been published several years after it would have been beneficial to the company.

- **Expertise, capacity, and culture.** Fourteen stakeholders stated that issues related to expertise, capacity, or organizational culture at FDA were challenges to adopting advanced manufacturing technologies. Regarding expertise and capacity, according to seven stakeholders, FDA reviewers can lack knowledge about advanced manufacturing technology. Some stakeholders further noted that this may lead to the reviews of applications with such technology taking longer than reviews of applications with traditional manufacturing technology. Specifically, three stakeholders stated that having less knowledgeable reviewers can increase the time it takes to approve a product, because reviewers may ask questions that are not relevant to the technology used in the manufacturing process, among other things.

  Regarding organizational culture, one stakeholder stated that while FDA leadership encourages the use of advanced manufacturing, this has not always been reflected in interactions with FDA review staff. According to this stakeholder, because of FDA reviewers' possible lack of expertise with advanced manufacturing, reviewers may be more risk averse, which may lead to more questions for the company. Another organizational culture challenge cited by two stakeholders was a lack of communication between FDA teams or centers, which stakeholders say can hinder FDA understanding of new technologies.

All stakeholders we spoke to agreed that these challenges cause uncertainty about when and whether a product manufactured using an advanced manufacturing technology will be approved. According to stakeholders, this uncertainty can weaken the business case for adopting such technology, since delays in regulatory approval can be costly. Advanced manufacturing technologies are expensive to implement, and additional regulatory scrutiny could slow the product's speed to market, costing the company additional resources. This sentiment is consistent with findings from the 2021 National Academies report, and also with the findings of a 2019 active listening session with representatives of 11 large

biopharmaceutical companies.[35] Eleven of the 15 stakeholders we spoke with agreed that without a strong business case, companies will be slow to adopt new technology. This may especially be the case when the same product can be made using traditional manufacturing methods. According to the stakeholders, this could be more pronounced for smaller companies with fewer resources. To counteract the uncertainty these challenges create, three industry stakeholders we interviewed said they would like more transparency from FDA about its experiences in approving products that use advanced manufacturing technologies.

Generic Drug Stakeholders Reported Facing Additional Challenges to Adopting Advanced Manufacturing Technology

While generic drug companies face the same challenges as brand companies, generic companies may experience them more intensely, according to the three generic stakeholders we interviewed.[36]

According to the White House 100-Day Review *Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth, 9*0 percent of drugs prescribed in the United States are generics, and 67 percent of drugs that were in shortage between 2013 and 2017

[35]The National Academies report noted that satisfying all regulatory requirements for approving a product might lead to unanticipated activities, costs, and time for a company, which could affect the financial viability of the product. Thus, the report stated that unless regulatory challenges are addressed, industry will continue its risk avoidance with respect to innovation, unless innovation is necessary to bring a new product to market.

The 2019 active listening session was facilitated by the National Institute for Innovation in Manufacturing Biopharmaceuticals. The session found that the participating biopharmaceutical companies rarely saw a business case for implementing new manufacturing technologies and, similarly, it was not an uncommon business decision to revert back to traditional technologies for a large scale manufacturing process and for formal submission based on a company's perception of regulatory risk. J.L. Mantle and K.H. Lee, "NIIMBL-Facilitated Active Listening Meeting between Industry and FDA Identifies Common Challenges for Adoption of New Biopharmaceutical Manufacturing Technologies," *PDA Journal of Pharmaceutical Science and Technology*, vol. 74, no. 5 (2020): 497-508. The National Institute for Innovation in Manufacturing Biopharmaceuticals is a Manufacturing USA public-private partnership sponsored by the Department of Commerce. The Departments of Commerce, Defense, and Energy have established a network of innovation institutes—known as Manufacturing USA institutes—to promote research, development, and commercialization of advanced manufacturing technologies. We are mandated to regularly assess the operation of this network. See, for example, GAO, *Advanced Manufacturing: Innovation Institutes Report Technology Progress and Members Report Satisfaction with Their Involvement*, GAO-22-103979 (Washington, D.C.: Dec. 16, 2021).

[36]These three generic stakeholders are included in the 15 total stakeholders we interviewed.

had an approved generic.[37] Generic companies' adoption of advanced manufacturing could potentially have a large effect on drug manufacturing and ease shortages. However, shorter exclusivity periods and smaller profit margins, among other reasons, make it harder for generic companies to make the business case for adopting advanced manufacturing technologies.

The three generic drug company stakeholders told us that generic companies operate in a more competitive environment with narrower profit margins and do not have the same lengthy exclusivity periods as brand-name companies. For example, the first generic drug company to submit a complete application to FDA may be eligible for a 180-day exclusivity period, as compared to 5 years for brand-name drugs that use new chemical entities. One stakeholder noted that it can be particularly challenging for generic companies to adopt new technology, because they would have to make large investments to adopt the technology for a product that would lose value relatively quickly with the 180-day generic exclusivity period.

An additional distinction between brand and generic companies is the number of products manufactured on one production line, which creates greater challenges in switching manufacturing methods. For example, as one generic stakeholder stated, while brand companies may only make one product per production line, generic companies may make multiple products per production line. If the generic company modifies the technology used on that production line, it would require them to re-formulate and seek regulatory approval for all products produced on that line.

Further, two generic drug company stakeholders described concerns about future regulatory expectations related to advanced manufacturing. Although FDA has communicated to companies otherwise, one stakeholder raised concerns that FDA may require generic companies to manufacture a drug using the same advanced manufacturing technology as the brand-name company, which could impact drug availability and costs.

[37]The White House. *Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth*. 100-Day Reviews under Executive Order 14017. (Washington, D.C.: 2021).

Agency Actions to Address Stakeholder Concerns about Regulatory Challenges

FDA has taken, or plans to take, steps to address concerns about the regulatory challenges to increasing the use of advanced manufacturing raised by the 2021 National Academies report and stakeholders we spoke with, according to agency documentation and interviews. These steps include increasing communication and outreach through ETP and other venues; developing and contributing to guidance; and conducting internal training.

Increasing communication and outreach. According to FDA officials, the agency will continue to proactively communicate with industry, which may address challenges such as product and technology review; and expertise, capacity, and culture. These communication efforts include sponsoring workshops, publishing information to address stakeholder concerns about challenges, and identifying additional opportunities for the agency to provide information to, and receive input from, its stakeholders. For example,

- In 2021, FDA presented about the FRAME Initiative at virtual workshops with industry and academia. This initiative was established to prepare a regulatory framework to support the adoption and implementation of manufacturing innovations for drugs.
- In November 2022, as part of the FRAME Initiative, FDA hosted a joint workshop with the Product Quality Research Institute—a nonprofit consortium including academia, regulatory agencies, and industry. This workshop focused on the regulatory framework for two types of advanced manufacturing—distributed manufacturing and point-of-care manufacturing. Through this workshop and other initiative activities, FDA obtained input from industry stakeholders on areas of policy consideration—such as guidance and global harmonization—to find ways to address them, thus facilitating the development and review of products that use advanced manufacturing technologies. In advance of this workshop, FDA also released a discussion paper and solicited formal comments from stakeholders on distributed manufacturing.[38]
- As part of FDA's commitments under the most recent reauthorization of the Prescription Drug User Fee Act, the agency stated that it would convene a public workshop with industry stakeholders before the end

[38]See https://www.fda.gov/drugs/distributed-manufacturing-and-point-care-manufacturing-drugs-discussion-paper, accessed February 22, 2023.

of fiscal year 2023.[39] As part of this workshop, FDA plans to discuss barriers to the adoption of advanced manufacturing technologies and will present case studies from previously approved technologies, among other topics.

- In addition to these more formal methods of communication, FDA officials told us they keep abreast of industry advancements by attending conferences, where they receive feedback on industry challenges regarding new technology.

FDA officials told us that some of the challenges identified in the 2021 National Academies report were stakeholder-perceived challenges, such as product and technology review, rather than actual challenges. These officials stated the agency is working to inform industry about how some of FDA's existing activities address these challenges. For example, in response to perceptions that applications for products that use advanced manufacturing technologies have longer review times, CDER analyzed data on approvals for five applications using continuous manufacturing. CDER examined whether time to market and regulatory approval time frames were longer for these types of applications compared to traditional batch manufacturing applications. CDER found that the continuous manufacturing applications were approved in a shorter amount of time than the comparable batch applications, and published the findings in April 2022.[40]

FDA officials also told us the agency is working to clarify and address other perceived challenges related to both product and technology review; and expertise, capacity, and culture. For example, the FDA website has a list of technologies that have been accepted into ETP, thus informing industry stakeholders about the type of technologies FDA has experience reviewing. Further, in response to perceptions that a technology cannot be reviewed without the context of a specific product, agency officials told us ETP members have emphasized that ETP can give, and has given, feedback on a technology independent of a product. Feedback may occur through multiple venues such as public forums, conferences, and workshops, in addition to meeting directly with

[39]See Food and Drug Administration, *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027*, accessed November 14, 2022, https://www.fda.gov/media/151712/download. PDUFA VII was enacted as part of the FDA User Fee Reauthorization Act of 2022. See Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023, Pub. L. No. 117-180, div. F, tit. I, 136 Stat. 2114, 2139-47 (2022).

[40]Fisher et al. "An audit of pharmaceutical continuous manufacturing."

companies. However, FDA officials acknowledged that in such instances, the feedback given is less specific than feedback that would be given to a company in the context of an application. For example, a company may not be able to provide background information that is related to product-specific risks and their relation to the proposed manufacturing process and controls.

FDA officials told us the agency is continuing to consider additional opportunities to improve communication with stakeholders. The agency hired a consulting company to inform FDA leadership about the scope of its advanced manufacturing activities across all FDA-regulated products, including drugs, and support future planning and decision-making. The consultant's report, which was issued in March 2022, found a need for FDA to communicate the agency's expertise to industry.[41] The report recommended that the agency consider ways to proactively engage in external communication to reduce regulatory uncertainty and foster industry confidence in bringing innovative technology into the regulatory space. FDA officials told us the agency has not yet initiated actions in response to the report's findings, but plans to do so in the future.

Increase guidance. FDA officials told us they will continue to issue guidance on advanced manufacturing innovations that may address challenges regarding regulatory definitions and stakeholders' need for additional guidance. For example,

- In 2021, FDA issued guidance for an advanced manufacturing technology used domestically to identify and test drug products using near infrared light.[42]
- Through the FRAME Initiative, CDER may issue new or updated guidance to explain the agency's thinking about different regulatory issues related to advanced manufacturing, according to agency officials.

In addition to providing guidance domestically, the agency will continue to address global harmonization challenges by collaborating across different international regulatory agencies, including those in Europe, Japan, and

[41]Booz, Allen, Hamilton, (March 2022).

[42]FDA published "Development and Submission of Near Infrared Analytical Procedures" in August 2021, which provides recommendations to aid the development, validation, and use of near infrared based analytical procedures in evaluating the identity, strength, quality, purity, and potency of drug substances and drug products.

Brazil. For example, FDA has taken a leading role in creating internationally harmonized guidelines in conjunction with other international regulators such as "Continuous Manufacturing of Drug Substances and Drug Products," which was finalized and adopted in November 2022.[43]

Provide internal training. FDA officials told us about several internal trainings that may address concerns about expertise, capacity, and culture raised in the National Academies report and by stakeholders we interviewed. For example,

- FDA is conducting internal training on advanced manufacturing technology across the agency, including with drug application reviewers, to build their knowledge base. FDA officials believe training may ease industry stakeholder concerns about FDA having enough expertise when reviewing a new technology. For example, according to agency officials, FDA research programs are being used to familiarize staff with new technologies, so that as additional applications with advanced manufacturing technology are submitted, the agency will have staff with the necessary expertise to review these applications. Specifically, FDA officials told us the agency conducts a yearly training for FDA inspection staff on 3D printing, based on research conducted at its Additive Manufacturing of Medical Products Center.
- FDA also engages in public-private partnerships, such as FDA's Centers of Excellence in Regulatory Science and Innovation (a collaboration between FDA and scientific experts that aims to advance regulatory science), the National Institute for Innovation in Manufacturing Biopharmaceuticals, and other Manufacturing USA institutes. These partnerships encourage innovation in regulatory science, and help FDA keep abreast of industry advancements. FDA officials told us that as the agency learns more about advanced manufacturing technologies, it can be more effective in encouraging their adoption to manufacturers. Members of ETP provide training to other FDA reviewers on advanced manufacturing technologies once ETP has had significant experience evaluating a technology. This technology may then "graduate" from ETP. Graduation indicates that FDA has received a minimum number of applications from multiple

[43]International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, *Q13 Continuous Manufacturing of Drug Substances and Drug Products,* (Nov. 16, 2022).

companies (reflecting industry readiness to adopt a new technology) and that FDA reviewers have the necessary expertise to review applications using similar technology with little guidance from members of ETP.[44] According to agency officials, it is not currently necessary to train the entire FDA workforce on advanced manufacturing technologies due to the small number of proposals accepted into the program. Specifically, from 2015 through 2022, ETP received a yearly average of approximately 19 proposals to participate in the program.

As FDA has multiple activities that have recently been completed, are in progress, or are planned for future implementation, it is too early to assess how, if at all, these efforts will address the challenges identified in the 2021 National Academies report. Further, the National Academies report noted that while regulatory and technical challenges may be hurdles to increasing the use of advanced manufacturing, insufficient, conflicting, or countervailing incentives to innovation for regulators and drug companies may be an even larger barrier. Nevertheless, FDA officials told us the agency is constantly evaluating and evolving to address the challenges to increasing the use of advanced manufacturing.

Conclusions

FDA and multiple federal strategies highlight the importance of advanced manufacturing for addressing supply chain concerns and providing resiliency in the face of public health emergencies like the COVID-19 pandemic. However, relatively few drugs on the market today are produced using advanced manufacturing. While there are many factors—including those outside of FDA's control—that contribute to this, work by the National Academies of Sciences, Engineering, and Medicine and interviews with industry stakeholders show that regulatory challenges contribute to uncertainty for industry stakeholders, weakening the business cases for adoption of such technology.

Given these challenges, FDA's efforts to encourage advanced manufacturing of drugs are important. CDER continues to enhance ETP in response to its January 2020 report and is in the process of developing an action plan for its FRAME Initiative. As it continues its efforts to encourage advanced manufacturing, CDER needs information on the extent to which its ETP and FRAME efforts are successful. This requires documenting goals, formalizing means to measure progress, and conducting regular assessment of progress toward these goals. This information will help CDER make informed decisions about which efforts

[44]In October 2021, ETP graduated its first technology, continuous direct compression.

should be continued or expanded or whether corrective actions are warranted, thus contributing to the larger federal focus on increasing the use of advanced manufacturing for drugs. Going forward, this information could also give FDA insight into whether its actions are helping to address stakeholder concerns, and thus facilitating stakeholders' adoption of advanced manufacturing technology.

Recommendation for Executive Action

The Commissioner of FDA should ensure that, for its ETP and FRAME program efforts, CDER documents and finalizes (1) performance goals with specific targets and time frames, and (2) associated clear performance measures with measurable results, both of which are linked to its long-term strategic objectives. CDER also should regularly assess progress toward achieving program goals. (Recommendation 1)

Agency Comments

We provided a draft of this report to HHS, the Department of Defense, the Department of Commerce, and the White House Office of Science and Technology Policy for review and comment. We also provided excerpts of this report to the National Academies of Sciences, Engineering, and Medicine and the 15 industry stakeholders that we interviewed for their review and comment. The Department of Defense told us it had no comments on the draft report. HHS, NIST (an agency of the Department of Commerce), the White House Office of Science and Technology Policy, the National Academies of Sciences, Engineering, and Medicine, and 4 of the 15 industry stakeholders provided technical comments, which we incorporated as appropriate.

We also received written comments from HHS that are reprinted in appendix I and summarized below. In its comments, HHS concurred with our recommendation. HHS noted that FDA understands the importance of performance goals and measures and agrees there are additional opportunities to utilize them for its advanced manufacturing program. HHS described the challenges to developing explicit goals for ETP, but noted that it will be valuable to provide additional documentation of its goal of taking timely action for drug applications using advanced manufacturing technology. In response to HHS comments, we clarified our discussion of FDA's performance assessment practices and our recommendation to acknowledge the information that FDA already tracks or is planning to track related to ETP and FRAME that should be formalized.

We are sending copies of this report to the appropriate congressional committees, the Secretary of Health and Human Services, the Secretary of Commerce, the Secretary of Defense, the Director of the Office of

Science and Technology Policy, and other interested parties. In addition, the report is available at no charge on the GAO website at https://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or DeniganMacauleyM@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix II.

Mary Denigan-Macauley
Director, Health Care

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Appendix I: Comments from the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

February 17, 2023

Mary Denigan-Macauley
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Denigan-Macauley:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "***DRUG MANUFACTURING: FDA Should Fully Assess Its Efforts to Encourage Innovation***" **(GAO-23-105650).**

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Melanie Anne Egorin

Melanie Anne Egorin, PhD
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT ENTITLED -- DRUG MANUFACTURING: FDA SHOULD FULLY ASSESS ITS EFFORTS TO ENCOURAGE INNOVATION (GAO-23-105650)

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

GAO Recommendation 1
The Commissioner of FDA should ensure that, for its ETP and FRAME program efforts, CDER develop and document (1) performance goals with specific targets and time frames, and (2) associated clear performance measures with measurable results, both of which are linked to its long-term strategic objectives. CDER also should regularly assess progress toward achieving program goals.

HHS Response
HHS concurs with GAO's recommendation.

FDA understands the importance of performance goals and measures and agrees there are additional opportunities to utilize them for its advanced manufacturing program, specifically FRAME and ETP.

As noted in the report, CDER has shared specific performance goals for its FRAME initiative that are part of an internal FRAME Roadmap, a living document that is updated based on stakeholder and collaborator engagement. The report also notes that CDER plans to release a public Action Plan for advanced manufacturing technologies that describes planned actions based on recent stakeholder engagement and feedback and can be used to track initiative progress.

The report focuses on "regulatory challenges, excluding challenges that were economic or technological in nature." The additional complexity of these excluded factors challenges the establishment of explicit goals, for example as related to a specific number of approvals for ETP, a specific number of applications submitted, or a specific number of graduated technologies per year. Such goals depend heavily on factors (e.g., business case, overall economy) outside of FDA control, an observation also reflected in a recent NASEM report[1]. It will be valuable to provide additional documentation of the most critical performance measure: timely action for drug applications using advanced manufacturing technology and its connection to strategic objective(s) for advanced manufacturing. As the COVID-19 public health emergency under section 319 of the Public Health Service Act draws to a close, CDER may be more capable of international engagement activities related to advanced manufacturing, and may be able to set additional performance goals, such as a number of international engagements on advanced manufacturing issues.

[1] https://nap.nationalacademies.org/catalog/26539/innovations-in-pharmaceutical-manufacturing-on-the-horizon-proceedings-of-a

1

Appendix II: GAO Contact and Staff Acknowledgments

GAO Contact

Mary Denigan-Macauley, (202) 512-7114 or DeniganMacauleyM@gao.gov

Staff Acknowledgments

In addition to the contact named above, Jennel Lockley (Assistant Director), Katherine L. Amoroso (Analyst in Charge), Jack Knauer, Meg McAloon, and Ashley Nurhussein made key contributions to this report. Also contributing were Sam Amrhein, Cheryl Andrew, Kaitlin Farquharson, Ben Licht, Christopher Murray, Ravi Sharma, Aaron Shiffrin, and Roxanna Sun.

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