FDA's Strategy Document on Innovative Manufacturing Technologies

I. Executive Summary

As part of the *Prescription Drug User Fee Act (PDUFA) Reauthorization Performance Goals and Procedures Fiscal Years 2023-2027 (PDFUA VII)*, the U.S. Food and Drug Administration (FDA) committed to advancing the use and implementation of innovative manufacturing. In connection with this effort, FDA committed (1) to conduct a public workshop on the use of innovative manufacturing technologies for products regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), including barriers to their adoption and submission strategies, and (2) to issue a draft strategy document for public comment that outlines the specific actions the agency will take over the course of PDUFA VII to facilitate the use of innovative manufacturing technologies, including addressing barriers to their adoption. The actions described in the draft strategy document are to be based on lessons learned from the Agency's experiences with submissions involving advanced manufacturing technologies, as well as feedback from the workshop and other public input. This document meets the commitment to issue a draft strategy document.

On June 8, 2023, FDA cosponsored a public workshop hosted by the Duke-Margolis Center for Health Policy on "Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches." The workshop convened FDA officials, pharmaceutical industry representatives, and researchers to discuss the current state of innovative manufacturing technologies and the incentives for widespread adoption. Key summaries of the stakeholder feedback include:

- The CDER Emerging Technology Program (ETP)[1] and CBER Advanced Technologies Team (CATT)[2] provide an avenue for companies considering the adoption of innovative manufacturing to engage early with FDA and solicit feedback on the potential acceptability of their approach in a less formal setting. ETP's efforts have helped companies develop submissions that received FDA approval, especially with continuous manufacturing. Faster feedback in earlier stages of development can be valuable, especially for smaller companies with less experience or fewer resources to invest in navigating the regulatory process.

- While there are some areas for potential improvement in the work of ETP and CATT, a major regulatory barrier to further adoption of innovative manufacturing is a lack of international harmonization in regulatory requirements. Even with a clear set of FDA regulatory expectations, manufacturers remain uncertain regarding regulatory acceptability

[1] See the FDA web page about the Emerging Technology Program, available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program-etp.

[2] See the FDA web page about the CBER Advanced Technologies Program, available at https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-program.

in foreign markets, which may discourage adoption. Speakers recommended FDA continue engaging with its international counterparts to ensure alignment where possible.[3]

- Other key barriers to the adoption of innovative manufacturing may lie outside FDA's purview — most notably, financial and commercial considerations. Adopting innovative manufacturing methods entails a significant upfront investment and manufacturers may have limited resources to invest, may not expect a sufficient long-term return on that investment, or may decline to adopt innovative manufacturing methods regardless of the regulatory landscape. These considerations are particularly important for generic manufacturers, which operate on smaller profit margins.

II. Background

Innovative manufacturing technologies — including but not limited to continuous manufacturing, distributed manufacturing, modern aseptic manufacturing equipment, and novel analytical methods — can increase product development speed, bolster supply chains, and prevent drug shortages. On June 8, 2023, FDA supported a public workshop hosted by the Duke-Margolis Center for Health Policy on "Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches." At this workshop, industry stakeholders shared feedback on their interactions with the FDA's CDER ETP and CATT to guide submissions using innovative manufacturing technologies. Regulators, academic researchers, and industry representatives discussed the current barriers to using these technologies and shared ideas on how initiatives such as the newly created Advanced Manufacturing Technologies Designation Program (AMTDP) could alleviate these barriers.

This workshop fulfilled a PDUFA VII commitment related to advancing the use and implementation of innovative manufacturing, as well as section 506L(e)(1) of the Federal Food, Drug, and Cosmetic Act, as amended by section 3213 of the Food and Drug Omnibus Reform Act of 2022[4] regarding the AMTDP.

The following sections describe perspectives and recommendations from the workshop.

A. Reflections on ETP and CATT

The workshop began with presentations from FDA on current opportunities for the support of innovative manufacturing technologies through the CDER ETP and CBER's CATT. Industry representatives also presented case studies of their interactions with ETP and CATT to support applications using innovative manufacturing approaches. Presenters

[3] International collaborations that resulted in harmonized guidance finalized since the PDUFA VII commitment include ICH guidance for industry *Q13 Continuous Manufacturing of Drug Substances and Drug Products* (March 2023) and ICH guidance for industry *Q5A(R2) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* (January 2024). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] Signed into law as part of the Consolidated Appropriations Act, 2023, Pub. L. No. 117-328 (2022).

agreed that early interaction with FDA while developing applications was integral to understanding the data and specifications required or recommended for the review process. Manufacturers used CATT meetings to discuss how their innovative technology could be applied across various products and appreciated CATT's inclusion of multiple product review offices during meetings. ETP also provided vital feedback to industry sponsors through site visits, sustained guidance on specific technology applications, and advice on how other innovative manufacturing technology applications could be approached in the future.

However, multiple speakers cited longer-than-desired review times for their products as an area of potential concern. Presenters also raised concerns that differing regulatory requirements across countries delay the adoption of innovative manufacturing technologies in foreign markets, and they agreed that global harmonization of regulatory expectations for submissions using innovative manufacturing should be prioritized. The panel recognized and appreciated FDA working with its international counterparts, such as the European Medicines Agency (EMA), on the regulatory framework for emerging technologies and suggested the addition of regulators from more jurisdictions. One panelist expressed that formalized and public communication between regulatory agencies could reduce barriers to global market acceptance and incentivize manufacturers to pursue innovative manufacturing techniques.

B. Other Considerations and Regulatory Challenges

This session began with a presentation from FDA highlighting previously identified regulatory challenges and the work FDA has already undertaken to address those challenges. Through interactions with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), FDA has worked to address regulatory barriers related to international harmonization, particularly regarding continuous manufacturing — though panelists later noted some aspects remain a challenge for industry. It was also noted how other efforts such as FDA-funded research and the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) initiative have supported addressing challenges to adoption.[5] It was noted FDA has solicited interested parties' input regarding several innovative manufacturing technologies, including distributed manufacturing (DM) and artificial intelligence (AI), and published discussion papers to support a cohesive regulatory framework for those technologies and others.

A subsequent discussion focused specifically on regulatory challenges to adoption, and panelists noted that manufacturers' hesitancy to adopt innovative manufacturing methods is due in large part to concerns of commercial viability. Decisionmakers within industry face uncertainty regarding the profitability of the research, adoption, and implementation of innovative manufacturing. Panelists again raised concerns about inconsistency in the global regulatory landscape for emerging manufacturing technologies. While they generally agreed that the FDA's efforts have been helpful, they noted that international barriers may still discourage adoption.

[5] See the FDA web page about the FRAME initiative, available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cders-framework-regulatory-advanced-manufacturing-evaluation-frame-initiative.

Panelists also discussed how industry can collectively work to reduce uncertainty and hesitancy regarding innovative manufacturing methods. They supported the idea of finding opportunities to share important learnings related to innovative manufacturing in pre-competitive spaces to promote collaboration. Others noted that specific legislation, guidance, and financial incentives offered to facilitate the adoption of innovative manufacturing could be particularly valuable for generic drugs that often experience supply chain disruptions and drug shortages. They noted that manufacturers of generics operate on slimmer profit margins than those of branded drugs and therefore may find it more difficult to invest the time and money needed to develop an application for a product using innovative manufacturing.

C. Advanced Manufacturing Technologies Designation Program

To begin the next session, FDA presented the key provisions of the AMTDP, an FDA program created by the Food and Drug Omnibus Reform Act of 2022. Panelists generally felt that the approach laid out in the AMTDP, in which FDA considers a technology rather than a technology and application together, could be quite valuable, especially as the legislation does not limit AMTDP applications to sponsors (e.g., contract development and manufacturing organizations are eligible to apply). Still, they acknowledged the difficulties regulators might encounter with such an approach and acknowledged that to implement the program effectively, FDA may need to strike a careful balance, providing applicants with the right degree of both flexibility and certainty.

Some speakers suggested that the "data and information" provided in requests to participate in the AMTDP should include evidence that the innovative technology is applicable to commercial products and would be scalable, even if it is still in an early development phase. They also noted that innovative manufacturing technologies for diverse uses and product types will necessitate different data to demonstrate their suitability compared to product-specific technologies. When possible, they recommended FDA specify the data requirements for these scenarios.

Panelists emphasized the importance of setting appropriate expectations when defining key elements of the program, such as the "substantial improvement" the technologies must provide or any "expedited development and review" designation benefits holders may receive for future submissions.

III. Action Plan Summary

As a result of the workshop and the feedback received, FDA will undertake the following activities:

1. *Continue to Enhance the Emerging Technology Program and CBER Advanced Technologies Team as Mechanisms to Support Innovation*

The current 2017 guidance ETP document,[6] will be updated by the end of 2026. This guidance update will address specific recommendations from the workshop where possible, including additional details on communicating the type of products and stages of development for which a requestor can approach the ETP for acceptance.

Additionally, by December 2026, FDA will issue a report summarizing the activities performed by the Emerging Technology Team (ETT), including meetings convened with representatives of industry, academia, other Federal agencies, workgroups established to support international harmonization, and trainings developed for regulatory staff.

Finally, the ETT will establish program goals and performance measures of the program including, but not limited to:

- Routine monitoring of the readiness of technologies in the ETP for graduation. No annual target is established as it is conditional on application submission and approval.

- Participating in at least five relevant public industry engagements (e.g., conferences, workshops). The target will be reassessed annually.

- Holding at least one engagement annually with international health authorities. The target will be reassessed annually.

- Monitoring and Ensuring User Fee Goals[7] are met for applications with ETP support. Targets for meeting goal dates are established to be consistent with User Fee program goals.

- Overseeing training opportunities for ETP team members and assessors (e.g., seminars, lab training). At least two trainings will be considered annually for assessors.

- Identifying intramural topics for Office of Pharmaceutical Quality Research (OPQR) consideration. At least two topics will be identified annually.

The CATT will continue to evolve to provide a valuable pre-submission engagement opportunity for technology developers, or prospective sponsors, to address potential scientific and regulatory issues associated with the implementation of advanced manufacturing technologies. CBER is currently revising internal procedures, internally referred to as CATT 2.0, with the goal of providing a better service to stakeholders interested in early engagement with CBER. The specific actions under this effort are the following:

[6] See the guidance for industry *Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization* (September 2017).

[7] For more information on user fees, see the FDA web page explaining user fees, available at https://www.fda.gov/industry/fda-user-fee-programs/fda-user-fees-explained.

- Develop a revised process for the CATT program to streamline the process and provide efficiencies in terms of tracking and timely review of meeting requests, and communication with requesters by providing periodic updates. This action will be completed by November 2024.

- The public-facing CATT website will be revised to provide additional clarity about the CATT meeting process, eligibility, meeting request content, general timelines, and potential outcomes of CATT engagements. This action will be completed by November 2024.

Like ETP, CATT will continue to participate in public industry engagements, discuss with international health authorities' potential areas of collaboration and harmonization, and work closely with CDER on the FRAME initiative to develop the regulatory framework necessary to evaluate advanced manufacturing technologies.

2. Support and Utilize Ongoing Initiatives for Advanced Manufacturing to Address Potential Barriers

FDA will continue to explore existing mechanisms for harmonization, including guidances such as those developed by ICH, and available pilot programs such as those created by the International Coalition of Medicines Regulatory Authorities (ICMRA). In addition, existing tools such as Parallel Scientific Advice will be used to facilitate joint interactions with groups such as the EMA Quality Innovation Group (QIG)[8] where applicable and appropriate. In collaboration with ICH working groups, FDA will develop training on:

- *ICH Q13*, by August 2024. This guidance applies to continuous manufacturing of drug substances and drug products for chemical entities and therapeutic proteins.

- *ICH Q5A(R2)*, by December 2024. This guidance includes specific viral safety considerations for continuous manufacturing for biological product manufacturing.

FDA will continue to support ongoing initiatives, such as the FRAME initiative, for prioritized advanced manufacturing technologies. Specific steps include:

- Develop guidance, as appropriate, to clarify areas of regulatory uncertainty, including the following proposed draft guidances: Considerations for Complying with 21 CFR 211.110, Approaches to Meeting CGMP Requirements for Distributed Manufacturing, by December 2024.

- Engage participants in the CDER ETP and the CBER CATT who are developing DM technologies and visit development sites.

[8] See EMA's webpage about the Quality Innovation Group, available at https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/quality-innovation-group.

3. Implement the Advanced Manufacturing Technology Designation Program

In 2023, FDA established a mailbox for the submission of Advanced Manufacturing Technology Designation Program Requests. Consistent with feedback received at the public workshop, FDA has published the draft guidance *Advanced Manufacturing Technology Designation Program* (February 2024),[9] which includes discussion of the data and information needed to support and obtain a designation, the benefits a designation provides, and several and answers intended to further describe key elements of the program. FDA intends to finalize the guidance no later than 2 years after December 29, 2022, incorporating feedback obtained including during public comment period.

[9] When final, this guidance will represent the FDA's current thinking on this topic.