

Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches

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National Press Club, Washington D.C.

Workshop Summary

The Duke-Margolis Center for Health Policy, with support from the U.S. Food and Drug Administration (FDA), hosted a public workshop on “Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches.” The June 8, 2023 workshop convened FDA officials, pharmaceutical industry representatives, and researchers to discuss the current state of innovative manufacturing technologies and the incentives for widespread adoption.

This workshop fulfilled the commitments described in the FDA User Fee Reauthorization Act of 2022, and in accordance with commitments described in the Prescription Drug User Fee Act (PDUFA) VII commitment letter “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027,” related to advancing utilization 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 (FDORA) regarding the Advanced Manufacturing Technologies Designation Program.

Innovative manufacturing technologies— continuous manufacturing, point of care or distributed manufacturing, and other novel analytical methods — can improve product quality, increase manufacturing speed, bolster supply chains, and prevent drug shortages. Industry stakeholders shared feedback on their interactions with the FDA’s [Center for Drug Evaluation and Research \(CDER\) Emerging Technology Program \(ETP\)](#) and [Center for Biologics Evaluation and Research \(CBER\) Advanced Technologies Team \(CATT\)](#) to guide submissions using innovative manufacturing technologies. Regulators, academic researchers, and industry representatives discussed the current barriers to utilizing these technologies and shared ideas on how initiatives such as the newly created Advanced Manufacturing Technologies Designation Program (AMTDP) could alleviate these barriers.

Key takeaways from the day included:

- ETP and CATT provide an avenue for companies considering 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, the major regulatory barrier to further adoption of innovative manufacturing is variation in the international regulatory environment. Even with a clear set of FDA regulatory expectations, manufacturers remain uncertain regarding regulatory acceptability in global markets, which may discourage adoption. Speakers recommended FDA continue working with its international counterparts to ensure alignment.
- 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 up-front 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.
- Under the AMTDP, FDA will create a process to request a technology used in the manufacture of drugs, biologics, or active pharmaceutical ingredients (API) be designated an Advanced Manufacturing Technology (AMT). A request for an AMT designation must demonstrate that the technology is novel and that it will substantially improve the manufacturing process. If FDA grants an AMT designation, the person or organization that submits an application that uses a designated technology will receive expedited development and review of applications using that technology within a certain context of use. Panelists discussed a number of key considerations left open to interpretation in the legislation creating the AMTDP, including:
 - How “novelty” and “substantial improvement” will be construed by FDA, ensuring that the definition is not so broad as to be unmanageable for the Agency but not so narrow as to discourage potential applicants;
 - What documentation (i.e., data and information) applicants should provide to FDA when requesting a designation to effectively demonstrate the value of a technology without placing undue burden on the applicant;
 - How and to what extent applications using a designated AMT may be expedited, and whether certain types of applications or technologies will be prioritized; and
 - What constitutes a reasonable definition of “context of use.”

Current Regulatory Frameworks and Tools

The workshop began with presentations from FDA on current pathways for the approval of innovative manufacturing technologies through the CDER ETP and the CATT. CDER's presentation highlighted the collaborative approach taken between manufacturers and the ETP through early and repeated engagement, including pre-approval inspections, quality assessments, and site visits. Since July 2015, ETP has facilitated 19 approved applications, 14 of which used continuous manufacturing approaches. ETP's aim, beyond facilitating submissions that incorporate innovative manufacturing technologies, is to “graduate” those manufacturing

technologies – in other words, to develop FDA’s expertise to the point that future applications can proceed through the standard assessment process without ETP support. Once a technology is “graduated,” manufacturers can have greater confidence in the technology’s regulatory acceptability, and ETP members will have bandwidth to dedicate to newer innovative approaches. Graduating a technology requires ensuring communication, training and continuity of regulatory requirements and quality assessment between ETP staff and standard FDA review staff. [CDER’s Framework for Regulatory Advanced Manufacturing Evaluation \(FRAME\)](#) Initiative contributes to the development of these regulatory standards for emerging technologies and assists some CBER technology assessments as well.

CBER’s presentation highlighted CATT’s role of providing early engagement and non-binding regulatory advice to developers of innovative manufacturing technology for biologics. Established in 2019, the CATT is newer than ETP, and differs in some ways. Some manufacturing technologies, such as continuous manufacturing, are well-established in the small-molecule space or are even “graduated” through ETT, but are still newer and less established in the manufacture of large molecule products under the purview of CBER. CATT has recently held discussions with stakeholders on continuous manufacturing for vaccines, the use of AI and advanced imaging technologies for real-time quality assessment, and more. While ETP engages primarily with prospective sponsors early on and maintains engagement throughout the regulatory process, CATT focuses more on early-stage engagement, particularly aiming to provide a venue for technology developers to receive feedback even if they have not identified a specific product yet. Both presentations underscored ETP and CATT’s shared goal of streamlining the process of developing innovative manufacturing technologies and working toward greater clarity on how those technologies may be incorporated into an application, both for regulators and industry stakeholders.

Case Studies and Lessons Learned

In the next session of the workshop, industry representatives presented case studies of their interactions with ETP and CATT to support applications using innovative manufacturing approaches. Speakers then participated in a panel discussion on best practices for submitting applications and areas of improvement. Presenters agreed that early interaction with FDA teams in preparing their application was integral to understanding the data and specifications required 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 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 presenters cited longer-than-desired review times for their products. Presenters also raised concerns that differing regulatory requirements across countries delay the global adoption of innovative manufacturing technologies, 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 thought formalized and public communication between regulatory agencies could reduce barriers to global market acceptance and incentivize manufacturers to pursue innovative manufacturing techniques.

Regulatory Challenges to Adoption

This session began with a presentation from FDA highlighting previously identified regulatory challenges and work FDA has undertaken to address them. Through interactions with the International Council for Harmonization 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 that this remains a challenge for industry. The speaker discussed how FDA-funded research has supported the development of innovations in manufacturing, as well as FDA’s efforts to circulate knowledge and develop its assessor workforce internally to create more continuity and standardization during the review process. Finally, through the FRAME Initiative, FDA has solicited stakeholder input regarding a number of 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.

Following the presentation, regulators, manufacturing experts, and industry representatives participated in a panel discussion on current challenges to the adoption of innovative manufacturing and potential approaches to alleviate those challenges. While the discussion was focused specifically on regulatory challenges to adoption, panelists noted that manufacturers’ hesitancy to adopt innovative manufacturing methods is due in large part to commercial viability. Decision-makers within industry face uncertainty regarding the profitability of the research, adoption, and implementation of innovative manufacturing.

Panelists again raised concerns about variability 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. Panelists suggested greater information sharing and collaborative regulatory training across countries to produce more cohesive guidance and possibly create joint processes of application review and approval.

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, in order to promote collaboration and progress while avoiding concerns about sharing

confidential or proprietary information. They also emphasized that the case for adopting innovative manufacturing methods may look quite different for manufacturers of different product types. For example, one panelist recommended there be specific legislation, guidance, and financial incentives offered to facilitate the adoption of innovative manufacturing for generics that often experience supply chain disruptions and drug shortages. 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 using innovative manufacturing. Though these generic drugs are less profitable to produce, they are integral to patient health and account for the majority of prescriptions in the U.S., so greater adoption of innovative manufacturing in this sector would have a significant impact and merits particular attention.

Advanced Manufacturing Technologies Designation Program

To begin the next session, FDA presented the key provisions of the Advanced Manufacturing Technologies Designation Program (AMTDP), an FDA program created by the Consolidated Appropriations Act of 2023. The legislation directs FDA to establish a pathway for people or organizations to apply for a designation of a technology used in the manufacture of drugs, biologics, or API as an Advanced Manufacturing Technology (AMT). Applicants will submit data and information detailing the technology's use and benefits, which FDA will review and use to decide whether or not to grant a designation. Applications that use a designated technology will receive expedited development and review. To be eligible for designation, a manufacturing method must:

1. Incorporate novel technology or use existing technology in a novel way;
2. Substantially improve the manufacturing process by reducing product development time and/or improving the supply of critical drugs; and
3. Yield equivalent or better-quality products compared to conventional methods.

The speaker explained that FDA is seeking stakeholder input for its upcoming guidance document on the program's application process, required metrics for enrollment, and the implementation of expedited review. The presentation segued into a panel discussion on these key considerations related to the implementation of the AMTDP and further opportunities to encourage greater adoption of innovative manufacturing technologies.

Regulatory Strategies for Adoption and Next Steps

During this final session, panelists primarily focused on the AMTDP, before providing some additional recommendations for FDA to support the adoption of innovative manufacturing methods through ETP and CATT. 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 (i.e., 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 would 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 applications to 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 prove their suitability compared to product-specific technologies. When possible, they recommended FDA specify the data requirements for these scenarios, but some emphasized that FDA will likely need to provide some flexibility on what type and degree of documentation should be included in applications.

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 holders may receive for future submissions. If the bar for “substantial improvement” is set too low, the Agency could receive more applications than it could process in a timely manner, and many of the submitted technologies might provide only a small improvement over existing manufacturing methods. On the other hand, if the bar is too high, some potential applicants with innovative technologies might be discouraged from applying for a designation.

Speakers also urged FDA to provide as much certainty as possible in defining the “expedited development and review” of future applications using technologies designated as AMTs – they felt this would be critical in demonstrating to industry the concrete benefits of applying for a designation. They echoed the point raised throughout the day that companies would be more willing to prioritize the creation and adoption of innovative manufacturing methods if given evidence of a consistent and supportive regulatory process.

Conclusion

FDA and the Duke-Margolis Center appreciate the input shared by speakers and attendees at this workshop. Within 180 days of this workshop, FDA will issue draft guidance for the Advanced Manufacturing Technologies Designation Program. Within 2 years of the enactment of the Consolidated Appropriations Act of 2023, FDA will issue final guidance for the implementation of the program.