Considerations for FDA's New Advanced Pharmaceutical Manufacturing Programs
Steps Forward from the 2023 U.S. Omnibus Spending Bill
TABLE OF CONTENTS

Introduction ........................................................................................................... 4

Summary of Considerations for:

• Centers of Excellence in Advanced and Continuous Pharmaceutical Manufacturing ......................................................................................... 5

• FDA’s New Advanced Manufacturing Technologies Designation Program ............................................................................................................ 6

Advanced Manufacturing Definition .................................................................... 7

National Centers of Excellence in Advanced and Continuous Pharmaceutical Manufacturing

• Program Overview ............................................................................................... 8

• Key Considerations for the Program ................................................................ 9

Advanced Manufacturing Technologies Designation Program

• Program Overview ............................................................................................... 12

• Key Considerations for the Program ................................................................ 13

Opportunities for Alignment between Centers of Excellence, AMTDP and other FDA Priorities ................................................................. 15

Conclusion ........................................................................................................... 16
A persistent drug shortage crisis in the U.S. is associated with higher mortality rates, medication errors, medication rationing, delays in life-saving cancer treatment and other critical medical procedures, and significant financial costs to the health care system.

The leading cause of drug shortages is manufacturing quality issues, especially for older generic drugs that are complex to manufacture. Factors such as the use of outdated, less reliable manufacturing technologies and a lack of mature quality management practices contribute to these quality issues. Additionally, incentives exist for manufacturers of low-cost generic drugs to outsource manufacturing to a concentrated group of foreign countries. Globalized supply chains introduce efficiencies and provide access to global talent and manufacturing capabilities but also come with exposure to geopolitical risks, such as military conflict and trade constraints.

Advanced manufacturing technologies (AMTs), such as continuous manufacturing, real-time process monitoring and release, novel container-closure systems, and many other technology types, can help to address some of these risks by increasing quality assurance and reducing manufacturing downtime when quality issues are detected. The U.S. has significant expertise in AMTs—more than 80 percent of drugs currently made using AMTs are produced in the U.S. After initial investment, AMTs can reduce per-unit production costs, thus enabling domestic pharmaceutical manufacturing to be more cost-competitive.

Despite this strong potential, the vast majority of recent new drug applications still use traditional manufacturing techniques. For example, the U.S. Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research only approved 19 new drug applications using AMTs from 2015 through April 2023. Adoption of AMTs in the production of generic drugs has been lower than for branded drugs. As generics drugs represent 90 percent of all prescriptions dispensed in the U.S. and more frequently experience shortages, increasing adoption of AMTs in generic drug manufacturing is critical. However, generic manufacturers frequently cite barriers to implementing AMTs, such as prohibitively high upfront investment costs and regulatory barriers.

The Consolidated Appropriations Act of 2023 directed the FDA to designate National Centers of Excellence in Advanced and Continuous Manufacturing (CoEs) and implement an Advanced Manufacturing Technologies Designation Program (AMTDP). These programs have a strong potential to increase adoption of AMTs among new innovative drugs.

Other policy steps to increase AMT adoption to appropriate levels among generic manufacturers, such as providing direct financial support to help cover upfront implementation costs, are likely needed as well; however, these other steps are outside of the scope of this issue brief.
This issue brief discusses considerations for FDA, academia, manufacturers, and other stakeholders as the new CoEs and AMTDP are designed and implemented.

### BOX A  Policy Steps to Address Barriers to AMT Adoption

<table>
<thead>
<tr>
<th>Barrier to Adoption</th>
<th>Policy Step to Overcome Barrier</th>
<th>Example Federal Programs/Offices That Could Help Address Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>High upfront financial costs to implement AMTs</td>
<td>Provide direct financial support, such as forgivable loans, grants, and contracts to manufacturers, especially generic manufacturers, to help cover upfront implementation costs.</td>
<td>HHS Supply Chain Resilience and Shortage Coordinator&lt;br&gt;White House Executive Office of the President&lt;br&gt;ASPR Industrial Base Management and Supply Chain Office</td>
</tr>
<tr>
<td>Insufficient availability of technical expertise</td>
<td>Invest in development of a workforce that is proficient in AMTs and enable improved knowledge-sharing.</td>
<td>FDA Centers of Excellence in Advanced and Continuous Manufacturing</td>
</tr>
<tr>
<td>Uncertainty around whether use of AMTs will impact FDA review timelines and time-to-market</td>
<td>Enable expedited FDA review for drugs using AMTs, including quantification of the extent to which expedited review is achieved.</td>
<td>FDA Advanced Manufacturing Technologies Designation Program</td>
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</tbody>
</table>
Leverage synergies and cross-cutting goals between the CoEs and AMTDP and other programs, such as the Quality Management Maturity program, CDER Emerging Technologies Program (ETP), CBER Advanced Technologies Team (CATT), as well as programs at other federal agencies with potential to support advanced manufacturing efforts within the U.S. Department of Health and Human Services (HHS), such as ASPR’s Industrial Base Management and Supply Chain Office, and agencies external to HHS, such as the National Science Foundation (NSF) and Department of Defense (DoD). Additionally, FDA should consider the optimal structure (potentially a “hub-and-spoke” model), key priorities (dividing into New Drug Development and Existing Drugs units), funding and incentive mechanisms, and impact metrics that would best enable the program to have its intended impact.

Identify opportunities to drive development and adoption of advanced manufacturing technologies to produce essential generic medicines, prioritize technologies that can best enable achievement of higher levels of quality management maturity (QMM), facilitate involvement with industry, create and deliver new training programs, and encourage diversity in workforce. Collaborate with industry in the development of business cases for investment in advanced pharmaceutical manufacturing and its successful implementation.

Establish relationships with CoEs for potential research, identify business needs aligned with CoE efforts and collaborate to develop business cases for AMT investment, clearly communicate manufacturer participation needs and constraints, and identify workforce development opportunities that increase diversity and promote continuing education in advanced manufacturing.

Expediently appropriate funding for CoEs as authorized in the Consolidated Appropriations Act of 2023. Consider additional means of incentivizing the adoption of AMTs in future legislation, such as investments in AMTDP technologies that de-risk startup costs associated with AMT equipment and practice adoption. Allocate more funding to FDA for reviewing applications to ensure timely review of applications using AMTs without delaying review for other applications.

Payers and purchasers could provide incentives to manufacturers that disclose that their drug is manufactured using a designated advanced manufacturing technology.
Summary of Considerations for FDA’s New AMTDP

Duke-Margolis has identified the following considerations for FDA when implementing the AMTDP:

• **Expediting Review** and Other Potential Incentives to Spur Adoption. FDA should consider:
  - Providing increased clarity and certainty for applicants referencing an AMT designation regarding how applications will be expedited.
  - Expediting other clinical and non-clinical elements of review in addition to CMC elements for applicants referencing an AMT designation.
  - Providing a standardized method that designation holders can use to indicate to payers, purchasers, and others that their drug was approved using an advanced manufacturing technology designated by FDA.
  - Using other regulatory flexibility options, such as less burdensome postapproval change filing categories, for certain manufacturing changes that are lower risk as the result of utilizing advanced manufacturing technology.

• **Clarifying Who Should Engage Which FDA Team, and When**: FDA should make clear that ETP and CATT will engage with any entity seeking a potential AMT, even if FDA familiarity with the technology may have historically precluded ETP or CATT engagement, and even if the entity does not intend to submit a drug application and does not yet have data on a model drug.

• **Measuring Impact**: FDA may consider tracking the following metrics in the years following the program’s implementation, including:
  - The number and quantity of products manufactured using a designated advanced manufacturing technology.
  - The types of approved products used in designated advanced manufacturing technologies.
  - Time from Submission to FDA Action/approval.

• **Defining Advanced Manufacturing in the Context of the AMTDP**: FDA familiarity with a technology should likely not preclude a technology from being considered “advanced” in the context of the AMTDP. FDA should instead consider levels of uptake of the technology in commercial production for key domains or product categories, such as in essential generics, when determining whether a technology should qualify for AMT designation. While technologies may “graduate” from the ETT/CATT after FDA becomes familiar with the technology, technologies should still be eligible for AMT designation and should not lose the benefits of designation until the technology has achieved significant levels of uptake in commercial production for key domains and product categories, including in generic products.

• **Aligning Opportunities for CoEs and Other FDA Priorities**: FDA could encourage industry partners in CoEs to seek Advanced Manufacturing Technology Designations for the technologies they develop.
Advanced Manufacturing Definition

Varying definitions of advanced manufacturing exist, and establishing a clear and workable definition for the purposes of the CoE and AMTDP programs is critical. Box B includes a few useful definitions from different sources.

BOX B Advanced Manufacturing Definitions

**Advanced Manufacturing Technologies Designation Program Draft Guidance:** defines advanced manufacturing as a term for an innovative pharmaceutical manufacturing technology or approach that has the potential to improve the reliability and robustness of the manufacturing process and supply chain and increase timely access to quality medicines for the American public. Advanced manufacturing can integrate novel technological approaches, use established techniques in an innovative way, or apply production methods in a new domain where no defined best practices or experience exist.

**Consolidated Appropriations Act of 2023:** defines advanced and continuous pharmaceutical manufacturing as a pharmaceutical manufacturing method or combination of methods that incorporates a novel technology or uses an established technique in a novel way, specifically emphasizing continuous manufacturing processes where multiple simultaneous unit operations allow for continuous input, transformation, and product output. This legislative definition of advanced manufacturing, however, is not specific to continuous manufacturing, allowing for a broader interpretation of technologies that could fall within the program.

**2013 President’s Council of Advisors of Science and Technology (PCAST) Report on Advanced Manufacturing**

Defines advanced manufacturing as “manufacturing that makes extensive use of computer, high precision, and information technologies integrated with a high-performance workforce in a production system capable of furnishing a heterogeneous mix of products in small or large volumes with both the efficiency of mass production and the flexibility of custom manufacturing in order to respond quickly to customer demands.” Notably, the PCAST definition does not reference novelty or newness in the definition and is not specific to pharmaceuticals.

**Advanced Pharmaceutical Manufacturing: A Functional Definition (Journal of Advanced Manufacturing and Processing, 2022)**

Describes advanced manufacturing as “a system that is designed using predictive models, where automation minimizes human intervention while enabling closed loop process control and real time quality assurance, where performance has been optimized to maximize desired process goals, where flexible amounts of product with equivalent attributes can be manufactured, and where equivalent processes can be implemented at multiple locations to manufacture products with equivalent critical quality attributes.” Notably, this definition also does not reference novelty or newness.

For the purposes of the CoEs and the AMTDP, the FDA should define AMTs broadly enough to account for the variability of manufacturing approaches used in pharmaceuticals and encourage diverse manufacturer participation, but narrowly enough to make efficient use of agency resources by focusing on the highest-impact candidates. Consideration should be given to the relative state of the manufacturing field for a product or product category (i.e., in a domain, such as generics) when assessing whether a manufacturing method should qualify as “advanced.” For example, if manufacturing processes across the industry for essential generic drugs do not utilize the most advanced technologies (compared to newer branded drugs) but could benefit from some form of modernization, those upgrades could qualify as AMTs. In practice, this approach could include relatively simple upgrades that already are well understood by FDA, such as the use of improved container-closure systems or automated visual inspection equipment.

As detailed in the AMTDP section below, the AMTDP draft guidance describes how FDA may decide to “graduate” technologies that were once deemed advanced to the standard quality assessment process when FDA has gained significant experience in assessing the technology. **FDA familiarity with a technology likely should not preclude a technology from being considered “advanced” in the context of the AMTDP.** Some technologies with which FDA is familiar have not seen adequate adoption in all the relevant domains (i.e., in essential generics). Our recommendations describe options for appropriately defining AM to ensure maximum impact from the AMTDP and other AM programs.
Overview of National Centers of Excellence in Advanced and Continuous Pharmaceutical Manufacturing

The Consolidated Appropriations Act of 2023 directed FDA to designate and fund up to five National Centers of Excellence in Advanced and Continuous Manufacturing. The Act set forth high-level goals for the CoEs, including:

- Expanding research capacity for advanced manufacturing technologies,
- Accelerating drug development to respond to public health threats,
- Mitigating or preventing drug shortages, and/or
- Addressing other priorities as identified by the HHS Secretary.

The legislation authorized $100 million in funding from 2023 to 2027 for the CoEs, each to be led by an institution of higher education or consortium of institutions of higher education in close collaboration with industry partners and the FDA. Funding for the CoEs will support expanding capacity for advanced research, implementing advanced research capacity and capabilities suitable for accelerating the development of drug products, and establishing best practices in line with the FDA mission.

BOX C CoE Eligibility Criteria

For an institution to be eligible to receive a CoE designation, it must include a description of the institution’s:

**Physical capacity and technical capabilities** to conduct advanced research on, and to develop and implement, advanced and continuous pharmaceutical manufacturing;

**Collaboration or partnerships** with other institutions of higher education, nonprofit organizations, and large and small pharmaceutical manufacturers, including generic and nonprescription manufacturers, contract manufacturers, and other relevant entities;

**Proven capacity** to design, develop, implement, and demonstrate new, highly effective technologies for use in advanced and continuous pharmaceutical manufacturing;

**Proven ability** to facilitate training of a qualified workforce for advanced research on, and development and implementation of, advanced and continuous pharmaceutical manufacturing;

**Experience in** participating in and leading advanced and continuous pharmaceutical manufacturing technology partnerships with other institutions of higher education, nonprofit organizations, and large and small pharmaceutical manufacturers, including generic and nonprescription manufacturers, contract manufacturers, and other relevant entities to support the implementation of advanced or continuous pharmaceutical manufacturing for companies manufacturing or seeking to manufacture in the United States.

FIGURE 1 Center of Excellence Timeline of Upcoming Events

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2022</td>
<td>DEC. 2022 Consolidated Appropriations Act becomes law</td>
</tr>
<tr>
<td>2023</td>
<td>DEC. 2023 FDA may designate one or more CoEs</td>
</tr>
<tr>
<td>2024</td>
<td>2024 – 2027 Center of Excellence reports submitted to FDA and to Congress annually</td>
</tr>
<tr>
<td>2025</td>
<td></td>
</tr>
<tr>
<td>2026</td>
<td></td>
</tr>
<tr>
<td>2027</td>
<td>DEC. 2027 End of currently authorized funding for CoEs</td>
</tr>
</tbody>
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**Key Considerations for the Centers of Excellence in Advanced and Continuous Manufacturing**

**Structure of the Center(s) of Excellence**

The FDA should consider the most effective structure to ensure the FDA and CoE aims are supported by all accountable parties and that the structure supports an appropriate balance between consolidation and specialization. Designating just a single CoE housed at one institution could eliminate the need to divide funding among CoEs, avoid challenges that could stem from coordinating amongst competing CoEs, and provide an identifiable centralized point of contact for partnerships with industry and other interested stakeholders. However, this model would limit the distribution of CoE funding and ability to foster research activities across diverse areas of expertise. An alternative model could include multiple CoEs housed at different institutions, which would allow for more diversity of expertise and approaches to research, foster productive competition, and help ensure funding opportunities are more broadly distributed – though challenges related to competition and coordination could arise.

To capture the benefits of both of these approaches, FDA should consider a “hub-and-spoke” model for the CoEs. In this model, a central institution serves as the “hub” for coordination of internal efforts and external partnerships. Importantly, the centralized hub should have demonstrated experience engaging successfully with industry partners and be well-equipped to leverage the expertise of academic and industrial resources to synergize CoE efforts. The “spokes” would be other institutions of higher education or groups of institutions with more specific focus areas. These spokes could lend specialized technical expertise in various categories of research, technology development, product types, and industry partners. They could be specialized based on types of industry partners or products (such as API and finished dosage form manufacturers or branded and generic manufacturers), technology type (such as continuous manufacturing, process analytical technologies, distributed manufacturing, etc.) or other priorities.

**Learning from Structures of Other Government-funded Collaborations**

In 2011, the FDA designated the first Centers of Excellence in Regulatory Science and Innovation (CERSIs). The program has since expanded to include five CERSIs. Lessons learned from the CERSI model can be taken into consideration in the structuring of the CoEs in Advanced and Continuous Pharmaceutical Manufacturing.

**BOX D Lessons Learned from the CERSI Model**

- FDA direction can set priorities with emphasis on knowledge sharing
  - Clear areas of focus and communication between centers are essential to avoid waste
  - However, CERSIs seem to have limited engagement with industry/manufacturer stakeholders – the Advanced Manufacturing CoEs should have significant industry/manufacturer leadership in key projects as these collaborations are central to the CoE design. Industry sponsors are needed to implement relevant technologies.
  - CERSIs center around Focus Areas under the FDA Regulatory Science Framework
  - Projects expected to achieve Outcomes of Interest, such as disseminating scientific knowledge; catalyzing action among relevant stakeholders including technology transfer; and using research outcomes in pre-market submission. The Advanced Manufacturing CoEs should similarly be focused on well-defined Outcomes of Interest

- Five-year grants provide stability
  - Infrastructure funds support principal investigators (PI), leadership, and critical staff
  - Resource and data sharing plans in place
  - Supplemented by institutional fundraising

- Funding structure tied to projects
  - Provides view into the focus of upcoming work
  - Can discourage collaboration among regional CoEs, creating potential inefficiencies
Another model that could inform the CoEs in Advanced and Continuous Pharmaceutical Manufacturing is the National Science Foundation’s (NSF) Engineering Research Centers (ERCs), which began in the 1980s and now includes 15 active Centers that enable innovations in research and education across numerous technological target areas while engaging industry partners.

**BOX E Lessons Learned from the NSF’s Engineering Research Centers Model**

- Industry-academia partnerships can effectively drive adoption:
  - Application of the ERC model helped the Center for Structured Organic Particulate Systems (C-SOPS) successfully integrate AMTs into pharmaceutical manufacturing through a consortium of over 50 companies, including technology component suppliers, integrators, and technology customers.
  - The C-SOPS launched the implementation of continuous manufacturing of oral solid dose products, leading to adoption by dozens of companies and more than 15 FDA approvals.
  - C-SOPS drove activities based on intended technology adoption outcomes and operated in a largely pre-competitive fashion, maximizing industry freedom to operate over intellectual property considerations.

- Again, long-term funding provides necessary stability:
  - ERC funding consists of an initial five-year award with typical extension to 10 years pending proposal renewal and review.

Other collaborations that could provide learnings that may be applicable to the CoEs include the Medicines 4 All Institute (M4ALL), the Center for Pharmaceutical Processing Research (CPPR), and the Critical Path Manufacturing Sector Initiative. When designing the CoEs, FDA, academia, and others should be cognizant of the potential for synergies and redundancies with the other above collaborations. Having been created in the same legislation as the AMTDP, the CoEs should have a unique focus on enabling development and implementation of technologies that can benefit from and help to achieve the goals of the AMTDP.

**Focusing Efforts on Key Priorities**

FDA should establish focus areas that appropriately guide CoE efforts toward preventing drug shortages and shoring up supply chain vulnerabilities. The CoEs should engage with both the research teams at innovator drug companies to help accelerate drug development and the supply network planning teams at generic drug companies to help mitigate and prevent drug shortages.

Most of the drugs dispensed in the United States are generic drugs. As detailed in other Duke-Margolis publications, manufacturers of older generic products compete for buyers primarily based on lowest price, and the market does not significantly reward investments in reliable manufacturing processes. The dependence on generic drugs contributes to trends, such as offshoring to cheaper production locations and lower levels of investment in upgrades, including the adoption of advanced manufacturing methods.

CoEs should help to drive adoption of AMTs in the production of generic essential medicines to meet the goal of mitigating and preventing drug shortages. A need also exists to drive adoption of AMTs for innovative drugs that have not yet lost patent exclusivity but have been approved by FDA using traditional manufacturing methods. Close partnerships with manufacturers and stakeholders involved in drug purchasing, such as group purchasing organizations (GPOs), wholesalers, and distributors, in these CoEs would be beneficial for identifying products for which adoption would be most feasible and most likely to bring a more reliable supply of essential medicines to patients.

In recognition of the need for different approaches, CoEs could be subdivided into New Drug Development units that focus on innovative drugs (including APIs) and accelerating drug development and Existing Drugs units that focus on technology transfers for existing drugs (including APIs), especially generics.
CoEs also should work to enable implementation of technological advancements that can help CoE participants to achieve higher levels of quality management maturity (QMM) as will be measured in FDA’s QMM program.

Another important priority for the CoEs is the development of a diverse, innovative, highly skilled pharmaceutical manufacturing workforce prepared for success in an industry that will increasingly shift toward more AMTs rather than traditional manufacturing. Building a highly skilled manufacturing workforce has been identified as a critical step toward reducing vulnerabilities in drug supply chains, and the CoEs are uniquely positioned to further this aim. The CoEs should support workforce training programs through the host institutions, community colleges, and trade schools, both for students considering entering the field and for those already in the workforce, with an emphasis on real-world experience and knowledge of innovative manufacturing methods. The CoEs should ensure opportunities for historically underrepresented groups and incorporate these social goals into their efforts.

**Funding and Incentive Structures**

A longer-term funding model, such as those used in the NSF ERCs or FDA CERSI programs, would improve the longevity of research and partnerships, enable long-term strategic planning, and decrease administrative burden. As technology development, demonstration, and successful implementation is a multi-year endeavor requiring sustained efforts, Congress should consider appropriating the entire funding for the program at the outset.

To augment the CoEs’ capacity beyond what is possible based on federal funding alone, the CoEs could implement a fee-based membership program, as has been used for some NSF ERCs, to help support focused projects and foster industry collaboration. To mitigate potential conflicts of interest, these projects should remain separate from FDA funded projects. CoEs should consider how to establish operating models that allow synergistic, but largely independent activities, respectively funded by FDA, industry, or both, as appropriate. This approach will enable the CoEs to develop the large network of industry interactions that is essential for their mission.

FDA should allocate funding to reflect the priorities described in the previous section, particularly regarding the importance of adoption among generic drug manufacturers. FDA should explore funding options that help to target generic industry participation in the CoEs or for adoption of advanced manufacturing technologies in target product categories, such as products at high risk of shortage or important in public health emergencies. Generic manufacturer participation could be measured by the number of generic manufacturer partners, demonstration of concrete progress toward driving adoption and technology transfers in priority product categories, and identification of projects that modernize manufacturing for essential generics with a high risk of shortage. Additional federal funding could be made available through cost-sharing to de-risk the initial participation of generic manufacturers applying to participate in the CoEs’ work.

**Measuring Impact**

Metrics are needed to measure the success of the CoEs’ work. The measures described below build upon those detailed in the Center of Excellence reporting requirements of the Consolidated Appropriations Act of 2023 to provide a more holistic understanding of the CoEs’ impact. The metrics should be SMART (Specific, Measurable, Actionable, Relevant, Time-Bound), and ideally could be agreed upon in collaboration with the HHS Supply Chain Resilience and Shortage Coordinator, also including input from industry partners in the CoEs.

The following metrics can be used to assess impact.

- **The number of Advanced Manufacturing Technology Designations achieved through a CoE:** see the following section for more detail on the Advanced Manufacturing Technologies Designation Program and opportunities for alignment with the CoEs.

- **The number of technology transfers facilitated by a CoE for existing products to be made using advanced manufacturing technologies.**

- **Workforce development metrics.** These metrics can include graduation and training from universities, community colleges, and trade schools that are engaged with a CoE. Scholarship and structured trainee program graduates can be recorded as well. This measurement also can track the number of employees who complete other educational options like certificate and continuing education programs, employee turnover rates, and workplace diversity metrics.
The number of Biologics License Applications and New andAbbreviated Drug Applications that incorporate a technology or method developed through a CoE. This metric could include details on product types and priority categories (products that have experienced shortages in recent years, products essential to PHE response).

Additional measures could include reductions in facility footprint, environmental impact, impact on efficiency in the form of reduced production costs, proportion of AMT methods used versus traditional manufacturing in certain product categories, number of investigational new drug (IND) applications and FDA consults resulting from CoE activity, additional non-governmental funding raised, and total number of industry partnerships.

Overview of Advanced Manufacturing Technologies Designation Program

The Advanced Manufacturing Technologies Designation Program (AMTDP) also was established by the Consolidated Appropriations Act of 2023.\(^1\) The legislation requires FDA to create a pathway for manufacturers to submit information around a manufacturing technology to potentially receive an Advanced Manufacturing Technology (AMT) Designation. FDA will expedite development and assessment of applications for drugs that are manufactured using a designated AMT.

In June 2023, Duke-Margolis hosted a public meeting that enabled FDA to gain input from stakeholders regarding the goals and scope of the AMTDP, along with the framework, procedures, and requirements suitable for such a program. The meeting included presentations and panel discussions by FDA and industry experts regarding initiation and implementation of the AMTDP, along with other related topics, such as best practices and lessons learned from the CDER Emerging Technology Team and CBER Advanced Technology Team programs and case studies from sponsors of previous submissions using innovative manufacturing approaches. In December 2023, FDA issued draft guidance for the AMTDP that outlines the eligibility criteria, submission and assessment process, and benefits of the program. The draft guidance provides some important clarifications regarding FDA’s potential interpretations of various concepts in the context of the AMTDP. FDA is required to issue a final guidance by December 2024.

For this issue brief, we focus primarily on the AMTDP. The 2023 Consolidated Appropriations Act also directed FDA to create a platform technology designation for drugs or biologics that use technologies already found in an approved product. This is an agency-wide initiative that is aiming to increase efficiencies in drug development, manufacturing, and regulatory review. FDA is due to release draft guidance on the platform designation program by the end of 2023. Key differences exist between the platform designation and the AMTDP (although they are also related).
FIGURE 3  Timeline of Activities for the Advanced Manufacturing Technologies Designation Program*

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>DEC. 2022</td>
<td>Consolidated Appropriations Act becomes law</td>
</tr>
<tr>
<td>JUN. 2023</td>
<td>Margolis-FDA workshop on innovative manufacturing and AMTDP</td>
</tr>
<tr>
<td>DEC. 2023</td>
<td>FDA issued draft guidance for AMTDP</td>
</tr>
<tr>
<td>MAR. 2024</td>
<td>Public Comment Period Ends</td>
</tr>
<tr>
<td>DEC. 2024</td>
<td>FDA to issue final guidance for AMTDP</td>
</tr>
<tr>
<td>DEC. 2025</td>
<td>FDA to issue report on progress of AMTDP</td>
</tr>
<tr>
<td>2032</td>
<td>Program sunset unless extended by future legislation</td>
</tr>
</tbody>
</table>

* The legislation directs FDA to issue a draft guidance for the AMTDP by December 2023, final guidance by December 2024, and by December 2025 a report that evaluates the types of innovative manufacturing approaches supported under the program; the number of designations awarded; the number of methods that have been granted designations; and the average time used to evaluate the technologies.

Key Considerations for Advanced Manufacturing Technologies Designation Program

Advanced Manufacturing Definition in the Context of the AMTDP

The 2023 draft guidance states that FDA generally considers a novel technology to be one that has not been used in a previously approved application and for which FDA therefore has limited assessment or inspectional experience. FDA considers an established technique or technology to be novel if it is used in a way that has not been described in a previously approved application. Once FDA has gained significant expertise assessing a designated AMT, and the designated AMT has been used in multiple approved regulatory applications, FDA may decide to “graduate” the technology to the standard quality assessment process.

While this may be an appropriate approach in some cases, **FDA familiarity with a technology should likely not preclude a technology from being considered “advanced” in the context of the AMTDP.** Technologies that have been used in a previously approved application often still have limited to no actual usage in commercial production in key domains or product categories. For example, **continuous direct compression has “graduated,”** but there are still “domains,” like essential generics, in which there is no defined experience in continuous direct compression.

**FDA also should consider levels of technology uptake in commercial production for key domains or product categories when determining whether a technology should qualify as an AMT.** This approach could include providing flexibility to applications for essential generic drugs that use graduated AMTs to still be provided with the benefits of AMT designation. Generic manufacturers seeking to implement graduated technologies would benefit from still being able to participate in CoE and AMTDP activities. Ultimately, FDA definitions of AMTs should ensure appropriate focus on technologies that can best advance the aims of the AMT programs.
Clarity Around Who Should Engage Which FDA Team, and When

The draft guidance describes a stepwise process in which early engagement regarding a potential technology would occur with ETP or CATT, and later, when the technology is more mature, a request for an AMT designation follows. Importantly, AMTDP requests are not limited to sponsors only—meaning that any individual or organization that develops a technology can request a designation, even if they do not plan to submit a Biologics License Application (BLA), a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA).

While AMT designation applies to a method of manufacturing rather than a specific application, the data that will be required of AMT requestors will need to include development data, including batch analysis data generated using either a developmental candidate molecule or a model drug. Requestors do not need to find a partner with a developmental candidate molecule—they can, for example, utilize data generated using an existing generic drug. Requestors ultimately will need to determine how to generate adequate data to demonstrate that their technology meets the criteria for designation, which may vary significantly on a case-by-case basis.

FDA should make clear that ETP and CATT will engage with any entity seeking a potential AMT, even if FDA familiarity with the technology may have historically precluded ETP or CATT engagement, and even if the entity does not intend to submit a drug application and does not yet have data on a model drug. In addition, requestors can seek an AMT designation even if they do not have a developmental candidate molecule identified (although in this case, they will need data on a model drug). Confusion in the industry still exists on these points, and FDA should consider listing examples of types of entities that could request AMT designations, including contract and development manufacturing organizations (CDMOs), equipment manufacturers, software and other technology developers, academia, and others.

Expediting Review and Other Potential Incentives

Expedited regulatory review provides a significant financial incentive to new drug applicants by potentially speeding time to market. New drug applicants using advanced manufacturing technologies have seen revenue benefits ranging from $171 million to $537 million, and further opportunities for expedited review only augment potential incentives for adoption of AMTs.

As required by the Consolidated Appropriations Act of 2023, the AMTDP draft guidance describes how FDA intends to provide timely advice and to engage with requestors, designated AMT holders, and applicants in an effort to expedite development and assessment of applications for drugs that are manufactured using a designated AMT. Importantly, the extent to which expedited review will occur is unclear—applications referencing a designated AMT will still be subject to the same user fee goal dates (i.e., FDA goal to act on 90 percent of applications within a certain number of months of submission) as any other application. Since funding was not specifically appropriated for the AMTDP, FDA’s ability to expedite review of applications using a designated advanced manufacturing technology may be limited by available resources for initial designation requests.

The draft guidance details how FDA plans to prioritize interactions with designation holders with the intention to shorten chemistry, manufacturing, and controls (CMC) review timelines for the most promising technologies but does not address prioritization in other clinical or non-clinical elements of review. While accelerating the CMC review may improve time to market, if it is the only aspect of the full review that is shortened, then the total time of review may still be limited by the speed of review in the clinical or other review elements.

FDA should provide as much clarity and certainty as possible for applicants using an AMT designation regarding how applications will be expedited. To achieve the legislative requirement to expedite review of applications that reference a designated AMT, FDA should prioritize other clinical and non-clinical elements of review in addition to CMC elements.
Designation holders or others using a designated AMT in their manufacturing processes might wish to disclose their use of the designated AMT publicly, to purchasers, or to others outside their organization for various reasons. To facilitate disclosure, FDA should consider how to provide a standardized method that designation holders can use to indicate to payers, purchasers, and others that their drug was approved using an advanced manufacturing technology designated by FDA. This approach could help to enable payers and purchasers to provide incentives to manufacturers that utilize modernized technologies that may be more reliable.

For generic manufacturers, a potentially slight decrease in review time for Prior Approval Supplements (PASs) may not be a significant incentive in many cases. FDA should consider other regulatory flexibility options, such as less burdensome filing categories for certain manufacturing changes that are lower risk to support the use of AMTs.

**Measuring Impact**

The Consolidated Appropriations Act of 2023 established important metrics for FDA to include in a three-year AMTDP progress report, but additional metrics could provide a more holistic view of the program's impact. In addition to the points laid out in the legislation, FDA may consider tracking the following metrics in the years following the program's implementation:

- **The number and quantity of products manufactured using a designated AMT** — While tracking designations granted is worthwhile, tracking the number of approved products that use designated AMTs will assess more accurately whether the designation program is having a meaningful impact on production processes. If a designation is granted but no application uses the designated technology and/or no manufacturer uses the technology to supply the market, then that designation had little impact. The impact measure should capture when the designation program application leads to a designated technology being used for a significant proportion of the supply of a product.

- **The types of products approved using designated AMTs** — Driving adoption of advanced manufacturing may be more impactful in certain product categories. Historically, adoption has been more common for newer, branded products, and less common for older, generic products. Driving adoption in manufacturing of generic essential medicines should be a goal of the program. Adoption in the manufacturing of products that help respond to a public health emergency (PHE) should also be a priority, since the increased capacity and flexibility of advanced manufacturing will help meet any rapidly rising demand from a PHE.

- **Time from Submission to FDA Action/Approval** — To help provide clarity around the extent to which expedited review is achieved and time-to-market reduced, actual dates of FDA action/approval for applications that reference an AMT designation could be compared to the standard user fee goal dates.

**Opportunities for Alignment with AMTDP and Other FDA Priorities**

Numerous opportunities exist for synergies between the many current and developing FDA initiatives that seek to increase the adoption of AMTs. Linking the CoEs and the AMTDP could augment the impact of both programs. For example, FDA could encourage industry partners in CoEs to seek Advanced Manufacturing Technology Designations for the technologies they develop, thereby giving CoE participants the potential added incentive of expedited review for future applications, while simultaneously increasing participation in the AMTDP. The ETP and CATT could likewise engage the CoEs in identifying industry applicants with technologies that could result in AMT Designations. CoEs could participate in extramural research through an agency-wide Broad Agency Announcement (BAA) for research and development to support regulatory science and innovation.
CONCLUSION

The establishment of Centers of Excellence (CoEs) in Advanced and Continuous Manufacturing has strong potential to increase adoption of AMTs among new innovative drugs. The proposed “hub-and-spoke” model and additional aspects inspired by successful government-academia collaborations, like the CERSIs and NSF’s ERCs, could provide an effective structure for these CoEs.

The CoEs should have clearly defined focus areas, including innovative drug development and technology transfers for existing drugs, particularly generics. An initial Congressional appropriation, along with a fee-based membership program, could provide stability for the program’s duration and foster productive industry collaboration.

The Advanced Manufacturing Technologies Designation Program also has strong potential to increase adoption of AMTs among new innovative drugs. FDA should strive for clarity and certainty in its AMTDP design ensuring clearly defined expedited review as an incentive for manufacturers. Impact can be measured through various metrics, such as the number of AMTs achieved, technology transfers facilitated, and applications incorporating a CoE-developed technology or method.

Linking the CoEs and the AMTDP could further enhance the impact of both programs. As these programs progress, it is crucial that the FDA ensures clarity around application and assessments.
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The Duke-Margolis RevAMP Drug Supply Chain Consortium consists of a group of experts in supply chain, manufacturing, regulatory science, national security, and drug shortages from academia, private industry, governmental agencies, and additional relevant stakeholder groups. The Consortium’s mission is to generate effective policy solutions that promote a reliable drug supply chain with advanced manufacturing capabilities and, ultimately, to improve patient outcomes by reducing the frequency and severity of drug shortages.

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Disclosures

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