# Congress of the United States

Washington, DC 20510

February 26, 2024

Dr. Robert Califf
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Califf

We write to regrading FDAs recently released draft *Advanced Manufacturing Technologies Designation Program – Guidance for Industry*. This guidance implements Sections 3213 of Title III of Division FF of the Consolidated Appropriations Act of 2023 (referred to as the Food and Drug Omnibus Reform Act or "FDORA"), which provided FDA with new authorities meant to advance modern manufacturing technologies and reduce drug shortages. These provisions were based on our legislation from the 116th and 117th Congresses – the *Manufacturing API, Drugs, and Excipients (MADE) in America Act* – and we are eager to see these policies become a reality.

Advanced manufacturing technologies (AMTs) have the potential to prevent drug shortages, lower drug manufacturing costs, and improve drug quality. Currently, FDA only reviews manufacturing technologies with binding feedback to product sponsors during the review of a drug or biologic application. This paradigm disincentivizes AMT adoption in new products because it presents additional risk in the development process and in approved products because sponsors need to invest in the infrastructure to manufacture the product in a new way before ever getting binding feedback from the agency.

Section 3213 of FDORA established the Advanced Manufacturing Technologies Designation Program.[1] This provision was based on the *MADE in America Act* and a recommendation the 2021 National Academies of Medicine report commissioned by FDA that recommended the agency review manufacturing technologies separately from individual product applications to facilitate greater adoption of modern drug production techniques.[2] We are pleased that the FDA met the statutory deadline to release draft guidance on this new pathway. However, we are concerned that the draft falls short of the intent of, and contradicts, the statute.

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[1] Section 506L of the Federal Food Drug and Cosmetic Act

[2] National Academies of Sciences, Engineering, and Medicine. 2021. Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations. Washington, DC: The National Academies Press. https://doi.org/10.17226/26009

First, we are concerned that FDA has tied the AMT program to CDER's Emerging Technology Team (ETT) and CBER's Advanced Technologies Team (CATT) with respect to both the qualification criteria and the logistical steps to enter the program. The qualifying criterion for manufacturing methods in the statute is those that –

> "*incorporate a novel technology or use[ ] an established technique or technology in a novel way that will substantially improve the manufacturing process for a drug while maintaining equivalent, or providing superior, drug quality.*"

The statute offers examples of "substantially improve" – including by reducing development time, or bolstering the supply chain for critical drugs. The guidance notes, however, that technologies should also generally meet the eligibility criteria for the ETT –

- *Have the potential to improve product safety, identity, strength, quality, and purity*
- *Include one or more elements subject to quality assessment for which the Agency has limited review or inspection experience, including an innovative or novel:*
    - *Product technology (e.g., dosage form or packaging such as a container and closure system)*
    - *Manufacturing process (e.g., design, scale-up or lifecycle approaches)*
    - *Control strategy (e.g., testing technology or process controls)*

In addition, "FDA strongly recommends that requestors engage with [ETT] or [CATT], where appropriate, before submitting an AMT designation request," FDA does note that it may not be appropriate to go through the ETT or CATT first when "*a method of manufacturing could already be at a stage where it is ready for commercial scale production*," however, there is no detail on how FDA defines this threshold. There is also no detail on how the ETT/CATT processes will be improved to ensure manufacturing technology developers who wish to use the AMT pathway will be afforded meetings. Finally, if a technology does go through the ETT/CATT process as FDA suggests it should, it would no longer meet the ETT criteria at the end, and therefore, under this drafting of the guidance, not be eligible for the AMT designation pathway.

FDORA included a codification of the ETT, and if it was our intent to merge definitions or logistics between the sections, this would have been done in the authorizing statute. These programs, their definitions, and goals are distinct and should not be conflated.

Second, we believe that the FDA has gone beyond the scope of the statute by inserting the concept of designation "Lifecycle" into the guidance. FDA describes a process by which an AMT would eventually lose its designation and drug products utilizing such technologies would move from expedited to standard review timelines. We did not contemplate the removal of the designation during the legislative development process, nor did the National Academies of Medicine suggest removal.[2] It is unclear why, once a technology is better understood, product application review would slow down. The more standardized manufacturing methods become, the fewer resources should be needed to review them – resulting in faster overall application review timelines.

By removing an AMT designation and its benefit to application holders, the FDA is effectively removing the market incentives to adopt AMTs. We suggest that the Lifecycle process reflect maintenance of the

designation and continuing expedition of product applications, with an additional "bonus" of the proposed 'graduation' label that can validate the agency's experience with the technology within the marketplace.

Third, we are concerned that FDA has unduly narrowed the provision contradictory to the statute by excluding biologic license applications (BLAs), such as those for gene and cell therapies, from cross-referencing AMT data contained in drug master files (DMFs). The statute clearly states that FDA shall –

> *"allow the holder of an [AMT] designation, or a person authorized by the [AMT] designation holder, to reference or rely upon, in an application submitted under Section 505 [NDAs] or Section 351 of the Public health Service Act [BLAs], including a supplemental application, data and information about the designated advanced manufacturing technology for use in manufacturing drugs in the same context of use for which the designation was granted."*

However, FDAs position in the guidance run contrary to the intent and the plain reading of the law and states that BLA sponsors –

> "*should have access to the supportive data and information for drug substance, drug substance intermediate, and drug product manufacturing relevant to the AMT and should not incorporate by reference a designated AMT, including by referencing a [drug master file] that contains a designated AMT."*

The intent of this pathway was, in part, to help FDA meet its own stated goals of improving standardization and consistency among CGT manufacturing. If BLA holders are not able to cross reference information about AMT designated technologies, it removes a major incentive for application holders to utilize designated AMTs and for contract manufacturers to develop designated AMTs for use across the industry. We strongly suggest removing this limitation that is not driven by law.

We appreciate your attention to these concerns and look forward to the timely issuance of a final guidance which better reflects Congressional intent.

Sincerely,

Tim Scott
U.S. Senator

Earl L. "Buddy" Carter
U.S. Representative

Cc
Dr. Peter Marks, Director, Center for Biologics Evaluation and Research
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