March 13, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2023-D-4974 for *Advanced Manufacturing Technologies Designation Program – Guidance for Industry*

Dear Dr. Marks and Dr. Cavazzoni:

The Alliance for Regenerative Medicine (ARM) appreciates the opportunity to comment on the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) draft guidance, *Advanced Manufacturing Technologies Designation Program*. Because of the highly complex and labor-intensive nature of cell and gene therapy (CGT) manufacturing, the development of innovative manufacturing technologies that can increase standardization across the industry is an important topic for ARM members to assist in maximizing development efficiency and timely access to CGTs.

ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis.

We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

We agree with Dr. Marks' recent statement that "*We still have not made the quantum leap forward that we need to in our ability to manufacture cell and gene therapies to help reduce the cost and improve accessibility*."[1] To that end, ARM has supported the creation Section 506L of the Federal Food Drug and Cosmetic Act (FFDCA) enacted by Section 3213 of the Food & Drug Omnibus Reform Act (FDORA) with the goal of enhancing manufacturing innovation, driving down cost, and enhancing standardization in the field, as well as implementing recommendations of the National Academies of Medicine report to FDA on manufacturing

[1] https://event.on24.com/wcc/r/4435866/85E64884655211FFEAA8740B6C120B8A?partnerref=social

innovation.[2] However, this guidance, as drafted, unduly limits this pathway's promise to meet the needs of the CGT field and runs contrary to both the statute and FDA's publicly stated goals of improving understanding and standardization of CGT CMC. We appreciate the agency's attention to correcting the specific issues expounded upon below, especially the limitation on cross-referencing data within BLA applications.

Application to CGT BLAs

We are concerned that, as drafted, the guidance fails to provide a clear framework for the adoption of AMTs across the CGT industry.

The draft guidance makes clear that sponsors of new drug applications (NDAs) or abbreviated new drug applications (ANDAs) can rely on and incorporate by reference an AMT designation held by another entity to support their application, including from a drug master file (DMF). However, FDA states that biologics license application (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 DMF that contains a designated AMT*."

This statement runs contrary to the law, which requires that FDA "***allow the holder of an [AMT] designation, or a person authorized by the [AMT] designation holder, to reference or rely upon, in [an NDA] or [a BLA], data and information about the designated AMT for use in manufacturing drugs in the same context of use for which the designation was granted***."[3] The differing approach for BLAs, if adopted in the final guidance, will limit the utility of this pathway for developers of proprietary technologies intended for use in the manufacturing of CBER- and CDER-regulated biological products.

ARM agrees with the agency that a BLA application holder is, and should be, responsible for ensuring the quality of the product and, therefore, understands the regulatory *intent* behind FDA's requirements that certain CMC information[4] needs to be contained within the BLA and not referenced through a DMF or otherwise. However, these requirements have hindered new technology development and adoption in CGTs and we are disappointed that these

---

[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. Recommendation: ***"[C]reate new mechanisms and evaluate, expand, and consolidate existing pilot programs that allow consideration of innovative technology outside individual product submissions to*** *accelerate implementation, lessen risk, and increase regulatory familiarity in ways that are transparent to the pharmaceutical ecosystem."*

[3] FFDCA Section 506L(d)(2)

[4] 2024 final rule amending 21 CFR 601.2: *…(g) Except as provided in paragraph (h) of this section, an application for a biological product submitted to the Food and Drug Administration for licensure under section 351 of the Public Health Service Act; licensed under section 351 of the Public Health Service Act; or deemed, under section 7002(e) of the Biologics Price Competition and Innovation Act of 2009, to be licensed under section 351 of the Public Health Service Act* ***may not incorporate by reference drug substance, drug substance intermediate, or drug product information contained in a master file,*** *including a drug master file submitted under § 314.420 of this chapter. Amendments and supplements submitted in support of these applications also may not incorporate by reference such information contained in a master file.*

requirements were codified by FDA after the release of this guidance without regard for the statute governing the AMT designation program.[5]

Many CGT product developers rely on contract manufacturing organizations (CMOs) for manufacturing expertise due to the technical complexity and reduced production costs offered by CMOs compared to bespoke in-house approaches. There is a delicate and adequate balance of data sharing that has been facilitated by DMFs for decades. Requiring instead a CMO AMT designation holder to share a complete data package without any financial incentive or legal protection with an application will hinder the development, improvement, and adoption of these technologies. Said another way, requiring disclosure of confidential information from a CMO to an application holder removes incentives for a CMO to invest in novel approaches and creates legal hurdles to a business model that can ultimately help to achieve CBERs goals of improving manufacturing of CGTs.

Because of the in-depth review of an AMT technology, we believe that product quality can be maintained or improved while referencing CMC attributes of AMT-designated technologies in DMFs or other mechanisms as the statue intends. To this end, ARM recommends removing the limitations in this guidance and revisiting the aforementioned rule to appropriately effectuate this programs' authorizing statute to allow for cross citation of manufacturing information supporting a designated AMT.

ARM has provided feedback to the FDA regarding another pathway established as part of FDORA – Section 506K of the FFDCA: Platform technologies – in advance of the release of draft guidance. ARM specifically requested that FDA allow cross-referencing of CMC data between platform technologies and believes that revisiting the 2024 rule should also take this pathway into consideration. Allowing cross-referencing in both pathways will help to meet FDAs stated goals of greater standardization in the manufacturing methods of the industry.

Designation and Application Criteria and Process

We appreciate that the draft guidance provides information about the agency's expectations for data submissions that will support the designation of an AMT. However, there are key aspects of the process that we believe need correction or where we would like further clarification and additional details to effectuate a successful program.

Relationship to ETT and CATT

Section 506L does not reference CDER's Emerging Technology Program (ETP) or CBER's Advanced Technologies Team (CATT), even though the provision that formally authorizes the ETP was passed in the same legislation that created this pathway. Therefore, we do not believe that it is consistent with congressional intent to intertwine these pathways as is outlined by this guidance.

[5] "Biologics License Applications and Master Files," 89 FR 9743 (February 12, 2024).

First, the FDA suggests in the draft guidance that in addition to meeting the statutory criteria for a novel technology, the method "should also generally meet the eligibility criteria" for participation in the ETP and CATT.[6] While the statutory criteria and the ETP criteria are in the same spirit, they are distinct. ARM is concerned that, depending on how strictly FDA adheres to requiring the ETP parameters in addition to the AMT parameters, the agency is limiting the pool of eligible technologies beyond the intent of the provision. If it was the intent of Congress to require eligibility for ETP to enter into the AMT designation program, or to mirror ETP eligibility criteria in the AMT program, the provision would have been drafted as such. ARM recommends deleting this "should" statement in the final guidance.

Second, "FDA strongly recommends that requestors engage with [ETP or CATT], where appropriate, before submitting an AMT designation request. While FDA notes that it may *not* be appropriate to go through the ETP or CATT first when "a method of manufacturing could already be at a stage where it is ready for commercial scale production" or when the person submitting a designation request is not a product application holder[7], ARM is concerned that an expectation of prior engagement with ETP or CATT will create a bottleneck for entry into the AMT program. Meetings with these teams are difficult to obtain, and phase-appropriateness is often cited as a reason for rejecting requests (e.g. the technology is too early in development or not early enough in development).

We recommend FDA remove this recommendation and replace it with a detailed explanation (with examples) of how FDA determines phase appropriateness for the ETP and AMT programs to allow developers to select the correct paradigm by which to engage the agency and the timelines to request such meetings in advance of AMT submission. We also request that ETP/CATT processes be improved more broadly to ensure meetings can be obtained.

Definition of Novelty

---

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

[7] "…[t]he Emerging Technology Program is primarily designed for companies that intend to eventually incorporate an emerging technology into the CMC section of their application."

ARM appreciates that FDA provides additional thinking about the statutory definition of "novel" in Q1 of Section V of the guidance.[8] We agree that a novel technology used in a way that is negligible to the overall manufacturing process (e.g. not "substantially improve") should not be considered novel for the purposes of AMT designation. However, additional detail about how the agency considers whether a novel component "substantially improves" an overall manufacturing process would help to clarify the scope of the technologies that qualify for the pathway, such as improving overall success rate, capacity, or throughput time. For example:

- would applying a production method in a new domain where there are no defined best practices or experience – aligning with the FDAs existing definition of advanced manufacturing – be considered a "substantial improvement"?
- would a closed, integrated system used for e.g., target cell purification, target cell transduction via a viral vector, cell washes and formulation, or filling that is currently a platform technology within manufacturing facilities be considered a "substantial improvement" if such a system were to be created for the use at the patient's bedside?
- would a novel cell line designed to significantly enhance recombinant AAV production by increasing the output of viral particles per cell or increasing the packaging efficiency of each cell would be considered a "substantial improvement"?

ARM also requests that the final guidance address how product approvals or licensures impact the assessment of the novelty of an AMT. It is unclear if the agency will only consider an AMT novel if it has never been used in an approved application, or whether there are other considerations (such as complexity, market penetration, INDs, etc.). It is also unclear how product approvals that happen while an AMT is undergoing assessment for designation will impact such assessment.

Clarification of "Model Drug"

The FDA notes that the AMT should be validated using a 'model drug' and references this as a 'representative drug' and 'developmental candidate molecule' in other parts of the guidance. Given that these terms can be defined differently, we recommend that the FDA use 'model drug' throughout for consistency and define the term. This definition should clarify that a model drug

[8] *A method of manufacturing, or a combination of manufacturing methods, is eligible for designation as an advanced manufacturing technology if such method or combination of methods* ***incorporates a novel technology****, or uses 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…*

is not limited to only approved products or products that are subject to an IND (though it can be).

A true model drug that would support designation for a particular context of use could be, for instance, a demonstration that an AMT can successfully produce a specific viral vector packed with a given gene sequence, or successful transfection efficiency using a GFP-tagged protein, even if these final products are not in themselves drug *candidates*.

Data Requirements

We recommend that the FDA clarify the level of risk inherent to "the process and potential product" refers to manufacturing risk as described in *Q9(R1) Quality Risk Management Guidance for Industry.* Given that the FDA suggests that the "robustness of data and information [submitted] should be commensurate with the level of risk," the agency should be explicit in its assessment of risk given that assessing risk for a model product may have different considerations than within a product application. ARM also requests FDA provide information about the robustness of data requirements as they relate to the stage of AMT development.

Impact of Designation

MAPP

The statute and guidance are clear that one of the benefits of an AMT designation is increased interaction with FDA during the review of a designation request and during the development and review of drug and biologic products that incorporate a designated AMT. ARM appreciates that the granular details of the benefits of other FDA programs, such as Breakthrough Designation, are described in Manuals of Policies and Procedures (MAPPs) rather than the guidance, and therefore recommends a MAPP for this pathway expounding on the details of the AMT designation process. Specifically, we request that the MATT include information about how FDA:

- will interact with requestors (including those who are not application holders);
- will prioritize designation requests; and
- plans to expiate quality assessment of applications containing AMT-designated technologies.

AMT "Lead"

ARM appreciates that one of the benefits of designation is the deployment of the AMT designation lead into the review teams assessing products that are manufactured using AMT-designated technologies. Having consistency in personnel ensures understanding of and expeditious quality assessment. Given the high rate of turnover in FDA staff, ARM suggests this guidance address situations in which the lead is replaced (due to position change or departure

from the agency) and clarifying how new leads will be trained and incorporated into review teams.

Public Listing

While not required by the statute, ARM recommends that the FDA publish a list of AMT-designated technologies and those that have applied for the designation program, with consent from the designation holder, as well as key learnings from the program. This is consistent with another recommendation from the National Academies report referenced above:

> *The compilation and availability of case studies of successful introductions of innovations and even of common themes and characteristics of unsuccessful introductions would also be an extremely useful resource if confidentiality limitations can be overcome.*

We believe that greater transparency will allow the industry to easily understand FDAs positioning on available technologies and inform product development decisions.

Lifecycle

Graduation

The guidance explains a process by which a technology "graduates" from the program after the agency gains "significant experience" with an AMT through its use in multiple regulatory applications. Specifically, the agency notes it will use standard quality assessment processes rather than expedited processes for product applications that use an AMT post-graduation.

ARM is concerned that this approach is contrary to the authorizing statute in Section 506L and limits the utility of the pathway. The underlying law does not give FDA authority to repeal a designation or "graduate" an AMT. It is, in fact, silent on the matter, consistent with other designation programs in the FFDCA. FDA notes that graduation will help the agency focus resources on newer technologies. However, ARM believes that the agency will save time and resources if AMT technologies that are well-understood are adopted widely. Products adopting these technologies should, therefore, be less time-intensive to review and result in more expeditious processes compared to applications with bespoke manufacturing approaches. To that end, we do not believe that "graduating" a technology or removing the designation is appropriate.

If the FDA chooses to proceed with a "graduation" model, ARM recommends a structure that is in accordance with the statute and -

- Follows specific parameters outlined in the guidance that define "sufficient experience." We recommend a specific threshold of regulatory applications that use the AMT (which is greater than a single initial approval) or a timeline.

- Ensures that the quality assessment process is less time-intensive for products utilizing the graduated AMT.
- Maintains the AMT designation. The National Academies notes in its original recommendation for this pathway that the public and binding de-risking of technology is one of the main benefits. Removing the designation undermines the intent of the pathway.
- Become eligible for, or be granted, platform designation for products that meet that program's criteria.
- Includes a public-facing list of all graduated AMTs and the designation holders.

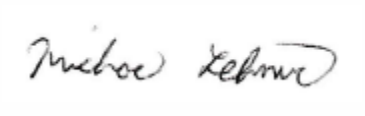
Practical Considerations

The pace of innovation in the CGT field is rapid as the pipeline expands and more players are involved in their production. We therefore recommend that the agency provide its thinking with regards to updating AMT-designated technologies and situations in which there are multiple AMT developers working in parallel. Specifically, we as that FDA address whether:

- only one developer can receive an AMT designation per technology
- situations in which companies may be simultaneously developing a novel technology would preclude each other from getting the AMT designation.
- an individual product approval or licensure using an AMT would preclude the AMT from receiving designation (when developed by the application holder or another party)
- a technology can be designated as an AMT if it has already been designated as an AMT for different context of use
- a technology could be eligible for the platform designation if such technology also meets the criteria for such designation.

ARM appreciates FDAs consideration of these comments. We strive to continue our productive scientific dialogue with the FDA as both the industry and the agency work to improve consistency and standardization in the manufacturing of these products. Please consider ARM a resource as you work to finalize this guidance in a way that promote the continued evolution of the CGT field.

Sincerely,



Michael Lehmicke
Senior Vice President, Science and Industry Affairs