American Society of Gene + Cell Therapy

March 5, 2024

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

RE: ADDENDUM - Comments for Docket No. FDA-2023-D-4974 "Advanced Manufacturing Technologies Designation Program; Draft Guidance for Industry."

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on the *Advanced Manufacturing Technologies Designation Program; Draft Guidance for Industry*. ASGCT is a nonprofit professional membership organization comprising more than 6,200 scientists, physicians, clinicians, and other professionals working in gene and cell therapy (CGT) in settings such as universities, hospitals, and biotechnology companies.

This comment serves as an addendum to the Society's submission to this docket on February 9, 2024. On February 12, 2024, the FDA published the final rule Biologics License Applications and Master Files (89 FR 9743) ('BLA DMF rule'). In the original submission, the Society requested that FDA allow BLAs to reference DMFs containing information on designated Advanced Manufacturing Technologies (AMTs) and consider changes to the *proposed* BLA DMF rule that would account for the AMT Designation Program. However, the BLA DMF *final* rule codifies a policy that BLAs cannot incorporate information about drug substance, drug intermediate or drug product through referencing a drug master file – regardless of AMT designation - without accounting for the new provisions of law.

The AMT designation is supposed to represent a new, forward-looking methodology to assessing manufacturing technologies before they are used in an application. Under the effectuating statute of the AMT Designation Program FDA is to "allow the holder of an advanced technology designation, or a person authorized by the advanced manufacturing technology designation holder, to reference or rely upon, in an application submitted under Section 505 ***or Section 351 of the Public Health Service Act*** [emphasis added], 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."

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FDA has continuously noted that bespoke manufacturing processes in the CGT field lead to long and complex CMC reviews – leading to high regulatory burden on both the Agency and CGT developers. ASGCT agrees with, and supports, FDAs efforts to encourage the development and adoption of more standardized, internationally harmonized, and platform manufacturing practices in the industry. Realizing these goals will take collaboration with contract manufacturers and other third parties who can develop and implement new advanced manufacturing techniques in a way that benefits numerous developers. DMFs are the main way that propriety information can be shared with the agency without disclosing it to drug sponsors. By eliminating the ability for BLAs to reference DMFs that contain information about AMT-designated technologies, there is little incentive for a contractor to develop a new technology, or for a product developer to license a technology, which can be deployed across applicants, as there would be no propriety protections on that investment.

If the rule is not revisited to consider the letter and intent of the new law, and the AMT program is finalized as is, this program will not help spur the development and adoption of new manufacturing technologies in the CGT field that are needed for these products to flourish to meet their potential and demands of the patient community. ASGCT respectfully requests that FDA consider changes to the BLA DMF rule that take into account the AMT designation program, and, regardless of the timeline of that effort, make clear in the AMT Final Guidance that FDA will allow the referencing of DMFs containing information on AMT-designated technologies in BLAs.

Sincerely,

David Barrett, J.D.
Chief Executive Officer

February 9, 2024

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The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease. Many of our members have spent their careers in this field performing the underlying research that has led to today's robust pipeline of transformative therapies. Given this mission, we provide the following comments to FDA to ensure that this new designation program can be a catalyst for innovation in CGT manufacturing.

General Comments

In 2023, the pipeline of CGT, and RNA therapies grew by 6%. As a result, there are 3,951 therapies in development, ranging from preclinical through pre-registration.[1] Without a doubt, the pipeline is robust and manufacturing technology needs to keep pace. As more products receive FDA licensure and approval, improvements will be critical to meet real-world patient demand, bring manufacturing closer to the bedside, and reduce production costs. New innovations in manufacturing have lagged behind other areas in the field. One reason for this delay is lack of market incentive to develop new, or manufacture approved products, using a novel technology with inherent regulatory risk- whether perceived or real. The National Academies of Medicine published a report[2] in 2021 which suggested that FDA implement a pathway to review novel advanced manufacturing technologies separately from individual products to de-risk their use in product applications.

The Society was pleased to see the Advanced Manufacturing Technologies (AMT) Designation Program included in the Food and Drug Omnibus Reform Act (FDORA) in 2022.[3] The creation of a product agnostic pathway is an important step toward the field's adoption of new technologies. If implemented properly, the program could help address the challenges currently facing the manufacturers and sponsors of CGTs. ASGCT submitted comments to FDA following the public meeting required in FDORA to capture this promise. We are therefore concerned that this draft guidance limits the utility of the pathway for BLA holders and therefore for the CGT field. The Society's top priority is for FDA to correct the imbalance of the AMT pathway between CBER and CDER in the final guidance. We expand on this concern and others below.

Specific Comments

III. AMT Designation Requests

A. Criteria

While the Society supports the goals of CBER's Advanced Technologies Team (CATT), the AMT program was intended to serve a separate purpose. We are concerned that the Agency has suggested that, in most cases, CATT interaction should happen prior to AMT, and AMT eligibility should align with CATT eligibility. This limits the ability for technologies to qualify for AMT, both definitionally and logistically given the existing limitations and bottlenecks associated with CATT. Furthermore, references to the CATT process were not included in the authorizing statute. The Society requests greater clarity

on the attributes of technologies that are appropriate for the CATT and AMT programs and the removal of the tie between the programs' entry criteria. If FDA does not remove these links, the final guidance should provide information regarding how CATT will help determine and advance the appropriate level of maturity for AMT designation.

The Society acknowledges the statutory criteria in FDORA is broad in scope when referencing novel technologies. We appreciate the Agency's efforts to define novel technologies, as referenced in Q1. However, additional information on how the FDA intends to assess if a technology "substantially improve[s] the manufacturing process for a drug while maintaining equivalent, or providing superior, drug quality," is necessary to understand which novel technologies qualify.

B. Content of the Request
The Society believes that the intent behind the reference to robust data and information commensurate with the level of risk inherent to the potential product is sound. For CGT manufacturing technologies, we believe that general data on complexity of the products within the proposed context of use and process should be sufficient.

In the draft guidance, the Agency recommends the requestor include data generated using a model drug to provide a clear understanding of the proposed AMT's parameters, limitations, and context of use. In the context of CGT development, it is unclear what the Agency views as a model drug, which is also referred to as a "developmental candidate molecule" and a "representative drug" in the guidance. As CBER products are less likely to be well characterized, the Society requests clarification on what qualifies as a model drug, such as whether a technology developer can use a model representative of a class. We suggest that model drugs not be limited to those under active development as this pathway is intended to be product-agnostic and is open to drug application holders as well as independent technology developers.

D. Designation Determination
A number of details regarding the assessment of designation requests and final determinations remain unanswered by the guidance. Like other pathways at the Agency, we recommend that a publicly available CBER standard operating policy and procedure (SOPP) be developed for the review process of an AMT designation request. The SOPP should include information on the composition of the review committee(s), the role of subject matter experts (SMEs), the selection process for and duties of the designated lead, timelines for data requests, meeting formats, and the level of involvement of senior FDA managers and other Agency staff.

ASCGT also recommends that the FDA provide a public list of AMT-designated technologies (with the consent of the requestor). A publicly available list of AMT designations would help product developers to find and consider using designated AMTs in their individual drug development programs; these activities may facilitate the implementation of AMTs in the field. This listing could parallel CDER's Drug Master File Database list which discloses only the Master File (MF) holder, subject, submission date, MF type, and active or inactive status.

E. Lifecycle

The Society appreciates that designated AMT holders will have the opportunity to propose manufacturing changes for review. However, there are logistical questions that remain unanswered, such as when entities who have referenced the original AMT will be notified of proposed changes, and how will products using the referenced AMT be impacted. We suggest greater detail of these steps for AMT holders who are also application holders, as well as those who are not.

ASGCT acknowledges the concept of 'graduating' technologies that were once novel and have since grown into greater use. However, this concept runs counter to the underlying law and the goals of the program. CBER leadership often speaks to the need for greater standardization in the manufacturing of CGT products to reduce the burden of CMC review. If an AMT was widely adopted, it would inherently consume fewer Agency resources because reviewers would be familiar with the technologies being used. In this vein, the bottlenecks that are currently caused by bespoke CMC approaches would be alleviated, while simultaneously helping to achieve the goals of the program. Slowing down application review for more familiar technologies and removing the designation meant to serve as a market driver to adopt standardized manufacturing options reduces the potential benefit of the program.

The Society recommends removing the graduation concept as currently drafted. If the FDA chooses to maintain the concept of graduation, ASGCT requests that graduated technologies maintain their designation and affiliated benefit, as well as receive additional notation in the publicly available list reflecting that FDA has gained "significant experience." We request that, if graduation is maintained, FDA provide concrete metrics to define "significant experience."

IV. Potential Benefits of AMT Designation

ASGCT appreciates that FDA aims to provide "timely advice to, and interactive communication with" AMT developers requesting designation. ASGCT requests that the final guidance reflects that "interactive communication" involves, at minimum, one "in person" meeting.

V. Questions and Answers

Q4. How Designated AMTs are Used, Referenced, Or Relied Upon in a BLA as compared to an NDA or ANDA?

In the draft guidance, FDA states that a BLA "should not incorporate by reference a designated AMT, including by referencing a DMF that contains a designated AMT" because "a BLA holder is expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license." This is directly contrary to the authorizing statute, which "allow[s] the holder of an advanced technology designation, or a person authorized by the advanced manufacturing technology designation holder, to reference or rely upon, in an application submitted under Section 505 ***or Section 351 of the Public Health Service Act*** [emphasis added], 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."

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This policy, if finalized, would be restrictive to the CGT field and against the intent of AMT designation to speed progression of standardized and novel manufacturing methods for CGTs to market. We strongly urge FDA to remove this restriction in the final guidance. We also request that FDA revise the 2019 “Drug Master Files: Draft Guidance for Industry” and the rule proposing changes to 21 CFR 601.2 (h) to clarify that cross-referencing Master Files is permitted for holders of, or those with a right-of-reference to, an AMT-designated technology in BLA applications.

While the draft guidance is a useful primer for the AMT pathway, it unduly limits the scope and potential of the program and lacks the level of detail necessary for AMT development. Given the novelty and complexity of CGT manufacturing processes, ASGCT would also like to request explicit sections in the final guidance outlining the requirements of the AMT Designation Program for CGT manufacturing technologies. The Society would welcome the opportunity to work with the Agency on further developing this pathway to meet its goals for the CGT field.

Thank you for the consideration of these comments. If you have any questions, please do not hesitate to contact Margarita Valdez Martínez, Director of Policy and Advocacy, at mvaldez@asgct.org.

Sincerely,

David Barrett, J.D.
Chief Executive Officer