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March 12, 2024

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

**Re: FDA-2023-D-4974; Advanced Manufacturing Technologies Designation Program**

Dear Recipient,

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request and comments on the **Advanced Manufacturing Technologies Designation Program Draft Guidance.**

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

The general efforts of the FDA to encourage the early adoption of advanced manufacturing technologies (AMT) are welcome by industry, and this guidance could represent another element of this effort to enable faster launches and a robust supply chain through new manufacturing technology. The guidance aims to mitigate known hurdles or perceived risks of the introduction of new manufacturing technologies, by increasing/accelerating development and approval of a drug (new or already marketed) application that applies an advanced manufacturing technology. However, the guidance is very high-level and would benefit to include further scope and descriptions of the program, along with clarity on its distinct benefits. In addition, this guidance needs further elaboration as to how this designation differs from existing programs and if they can be utilized separately or synergistically.

Suggested benefits of AMT designation include early interaction, timely advice, additional communication, possible coordination with the quality assessment team and prioritization of interactions. However, for the AMT designation program to be of significant value to the public, designated AMTs must provide meaningful changes to approval timelines, supporting data, or other expensive/time consuming activities currently borne by drug manufacturers that can then be transferred to the public through faster access to therapeutic products. The current guidance would be improved by providing specifics as to what regulatory benefits can be expected by the AMT holder. Therefore, BIO recommends providing further clarification on the following various topics listed below to better understand how to best leverage this program.

- Providing further description of how the agency will prioritize AMT designations as compared to other programs; i.e. Fast track, breakthrough therapy designation, regenerative medicine advanced therapy designation, etc.
- Give insight on the review and approval process of an AMT designation request; and clarity on if the AMT designation request can be submitted without an accompanying drug application or if the designation should always be tied to an active drug application.
- The guidance would benefit from listing examples of potential technologies that would qualify for an AMT designation, as well as examples to context of use.
- Defining terminology used with context for the AMT program, i.e. “expedited” and “prioritize.” The term “expedited” is used in several places in different functions; e.g. line 73 vs line 259. However, section IV *“Potential Benefits”* only uses the term *“prioritized”* applicant interactions, and generally describes aspects of timely access, early communication and coordination with appropriate FDA quality assessment teams. It is unclear whether the term “expedited” is used in a formal way (referring to an expedited review of an application to plan to have an action at least 1 month prior to the UFA goal date) and /or refers to acceleration vs. standard timelines because when AMT is used.
- Recommend the Agency provide clarity on how interactions with the ETP and CATT will work in combination with the AMT designation program. i.e. is it likely that an ETT or CATT member would act as the designated lead, or will a standing team be formed for the AMT requests with ad-hoc additions depending on the technology?
- Further description on AMT designation role in the drug application review, as well as details on how CBER and CDER communication will be conducted with each other regarding AMT requests and decisions on designation to ensure consistency in the assessment approach and visibility on designated AMT across centers.
- It would be beneficial for FDA to provide additional detail on submitting AMT designation requests for complex issues such as the following;
    - The process for submitting an AMT designation request that would apply to an advanced manufacturing technology that manufacturers device constituent parts approved under BLAs or NDAs.
    - The applicability of AMT designation to ensure supply of drugs that rely on a method or combination of methods of manufacturing, and include analytical methods or process analytical methods that improve manufacturing processes.

BIO also recommends the agency consider creating a website or other types of communications (e.g. newsletter) to provide information directly to the public and sponsors on the above listed points, as well as details on timely communication on technologies that have graduated from the program – including how the agency will report out on designated technologies, the designation program's progress and lesson learned on technologies that were denied or awarded designation would be beneficial as well.

*Please find BIO's additional specific and line-by-line comments in the pages and table below.*

Sincerely,
/s/
Name
E'Lissa Flores, PhD
Biotechnology Innovation Organization

**Specific Comments**

- Since the primary criteria to determine AMT eligibility is the novelty of the technology, the Agency should consider a mechanism to convey previously accepted AMT applications (while preserving appropriate confidentiality). Such a mechanism will prevent sponsors from submitting redundant applications with little chance of AMT acceptance. Two potential mechanism for this purpose could include transparent resources on the appropriate FDA webpage or an *ad hoc* approach in which the sponsor contacts the Agency (e.g. by email) with a preliminary inquiry on a potentially eligible technology.
- The guidance should address situation where companies may be simultaneously using the same or highly similar novel technology and whether this would preclude another sponsor for getting the AMT designation, as well as whether only one sponsor/company can receive an AMT designation per technology. And address whether a technology can be designated as an AMT if it has already been designated as an AMT for different classes of drugs.
- The guidance should clarify whether new technologies addressing continuous manufacturing would be eligible for an AMT designation.
- The guidance states that technology that can ensure supply of life-supporting, life-sustaining, or of critical importance to health could be considered for this program. We believe that the continued supply of drugs, whether or not they meet these criteria, is important. We recommend that the Agency consider expanding this requirement to ensure supply of additional products that may not meet these criteria.
- The draft guidance states on lines 116-120 that a novel method/novel use of a method may be eligible for AMT designation if it 1) reduces development time or 2) increases or maintains the supply of a drug. We recommend that the Agency also consider novel methods/novel use of methods that decrease the complexity of methods and need for specialized equipment/facilities/personnel, decrease the cost of performing the method, and increase the ability of the method to be automated and high throughput.
- Emphasizing ETT and CATT engagement throughout the draft guidance creates areas of ambiguity. The draft guidance states that *"…designation requests are made independently of application submissions. Therefore, there is no predetermined stage of product development or specific application assessment cycle during which AMT designation requests can be submitted to the FDA"* (Line 92-94). However, the draft guidance then strongly recommends engagement with CDER's Emerging Technology Team (ETT) or CBER's Advanced Technologies Team (CATT) as an initial opportunity to discuss a technology before it has reached a maturity level appropriate for AMT designation (Line 104-106). Recommend the editing Lines 104-106 to avoid confusion.

- The draft guidance also suggests that a proposed AMT "should also generally meet the eligibility criteria described in the ETT and CATT programs (Line 122-125). It is unclear, therefore, how the AMT designation program would be meaningfully different. Instead, AMT applications/requests should be a potential pathway when the manufacturing technology does not necessarily meet ETT or CATT requirements (e.g., no guidance exists or no BLAs submitted).
- Lack of clarity regarding how the Agency will interact with requestors who are not also applicants. The draft guidance acknowledges that AMT designation requests and communications may be made independently of [product] applications (Line 92) or by "requestors who are not also applicants" (Line 182). However, the guidance offers lack of clarity on how these interactions between the Agency and non-applicant requestors are distinctly available under the AMT designation program. [For example, the engagement discussed in Q7 is only centered around "applicants," not "requestors" (Line 496-508).]
- Lack of detail on the AMT designation process; more emphasis on FDA interaction on the use of designated AMT in an application. The draft guidance highlights that a key benefit of the AMT program is to provide early FDA interaction with requestors/applicants regarding the development of drugs that may be manufactured using a designated AMT (Line 267-269). It also notes that the FDA expects to prioritize applicant interactions that are intended to discuss the use of a designated AMT in drug development or commercial manufacturing (Line 279-284). However, there is little detail on how the FDA will interact with requestors regarding the development of advanced manufacturing technologies that seek AMT designation outside a product application request.
- In the AMT request itself, the draft guidance suggests that the robustness of the data or information should be "commensurate with the level of risk inherent to the process and potential product, such that the data and information can be later leveraged in a marketing application" (Line 134-137). How will the Agency assess risk? If the AMT is being designated outside a product application, how is product risk weighted? What types of risks in the manufacturing process are the FDA most concerned about?

**LINE-BY-LINE RECOMMENDED EDITS**

| SECTION/ LINE | ISSUE | PROPOSED CHANGE |
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| **24** | AMT: no clear description on what is in scope of AMT – suggest adding a non-exhaustive list of potential technologies which may be considered an AMT | The guideline does not provide a clear description of what is in scope of an AMT. The guideline would benefit with inclusion of a non exhausting list of potential technologies which may be considered an AMT. For example, are pure software approaches , e.g., digital twins within scope? |
| **71** | Clarification is needed regarding the following issues: (1) Will AMT designations be exclusive to one per technology? Will one AMT designation on a specific technology restrict another party to request and be granted a similar AMT designation if filed shortly after the first AMT is designated.<br>(2) Will AMT provide exclusivity of use to the holder or authorized user?<br>(3) Will AMTs be kept confidential to the applicant/holder? Will designated AMTs be shared publicly? | *"The holder of the AMT designation or another authorized party may reference or rely upon data or information about the designated AMT in an application in the same context of use for which the designation was granted."*<br>Suggest adding: An AMT does not exclude another party with similar overlapping technology to obtain AMT status. AMT applications are confidential and only authorized users of the data in one AMT can rely upon the AMT designation.<br>AMT designation titles and holder names are public and will be published upon granting AMT status |
| **71-73** | The guideline refers to "context of use" as the purpose and manner of use for a designated AMT. It will be helpful that the guideline includes examples of "context of use" for clarity. Can a context of use include a material property space, e.g. all powers with bulk density X or particle size Y, etc.? | |
| **73-75** | FDA indicates it will expedite development and assessment of an application, including supplements, for drugs that are manufactured using a designated AMT as described in section 506L(d)(1) of the FD&C Act. | Clarify the term "expedite", to help developers better understand the benefit of AMT designation Both in the context of drugs and biologics that have BT or FT designation and for those that do not and are under a regular review clock. It will be helpful to provide a timeframe for expediting review. |
| **98-99** | FDA strongly recommends that requestors engage with CDER's Emerging Technology Team (ETT) or CBER's Advanced Technologies Team (CATT), where appropriate, before submitting an AMT designation request. | Clarification about the process to engage with ETT/CATT would be helpful. What is the proposed pathway for engagement and what information is needed from requestors for a discussion with ETT and/or CATT? In addition, seeking ETT or CATT advise |

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| | | before submitting a request for AMT designation makes the overall process very long. Is there a way to abbreviate the transition between ETT/CATT and AMT so that it does not take additional time to the 180 days to assess the AMT designation? This is especially important considering that AMT is aimed to facilitate speed to market and speed to market is in the interest of patients Request that the FDA addresses this concern in the guideline |
| **98-100** | FDA strongly recommends that the first discussion about AMT is done in the context of ETT and CATT. Can an early discussion on AMT be bundled/included in an ETP/CATT meeting discussing other topics or should it be solely devoted to the AMT designation discussion? | |
| **182** | | Suggest FDA provide more clarity on the types of stakeholders that can request an AMT designation. Can an equipment supplier be a requestor? |
| **167-169** | Can an AMT be used to initiate an IND? If so, would this be applicable for AMTs that are cross referenced? | |
| **184-185** | There are several areas of the guideline that refer to the data to be included in the AMT designation request. | FDA should include more clarity on whether an AMT designation request is always expected to include product related data, even when the requestor is not the applicant. It will also be helpful to provide more clarity on the kind of product related data expected to be submitted. |
| **196-197** | The guideline states that "upon receipt of the AMT designation request, FDA intends to acknowledge receipt…" This statement suggests that the FDA will not always acknowledge receipt of the request. Request that FDA always acknowledges receipt of an AMT request and revise the guideline accordingly. This will bring more predictability to the designation process. | |
| **204-205** | It is unclear from the guideline whether there will be a core AMT expert standing team like the ETT and CATT which will add SMEs as needed per application request. Or whether there will be an expert team formed for each AMT designation request. | Need more clarification on this matter. If the latter, how will FDA ensure visibility across Center wide AMT designations? |

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| **212-214** | | Since the AMT is a technology-specific designation, clarity is needed if the existing technology teams ETT and CATT would not just participate but actually take the lead role in the designation determination. |
| **214-215** | The guideline explains that the team of experts that will assess a designation request will designate a lead. | Clarity on if the lead be also involved, as needed, in the assessment of submissions using the designated AMT? |
| **221-226** | The guideline explains that "FDA expects to deny requests that are incomplete or submitted for methods of manufacturing that do not meet the criteria described in 506L(b) of the FD&C Act". | Suggest FDA provide clarity on:<br>1. The FDA will communicate to the requestors the reasons for denying an AMT designation request<br>2. How a requestor whose AMT request has been denied can discuss with FDA the information needed to address the gaps identified in a denied request<br>3. Whether there is an opportunity to discuss with the FDA the path forward to be granted AMT designation.<br>4. It will be helpful if the FDA provides an example of a potential next step if a request is not granted.<br>It will also be helpful if FDA can include examples of potential gaps that could potentially lead to denying AMT designation |
| **221-223** | The review of the AMT designation program by FDA is 180 Days or 6 months. | Suggest that FDA consider a reduced designation review timeline, more in line with the scientific advice and briefing books procedures. |
| **226** | | Suggest to add information on how the dialogue between requestor and FDA AMT team will work, for example informal, case-by-case, or formal following a similar approach as interactions with ETP/CATT |
| **226** | | It would be extremely valuable to include a brief outline of FDA feedback on an AMT request and, ideally, make this accessible for comments again. This would be a great opportunity for requestors to a) understand what the main drivers for FDA will be to assess maturity of the technology and rationale for decision-making, and b) recommend aspects to cover in this feedback, such as:<br>● key information required to describe the technology in process transfer to a commercial facility, |

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| | | • data & digital requirements<br>• risks which need to be mitigated<br>• references to existing guidance describing the above |
| **230-232** | The guideline explains how to communicate proposed changes to the AMT designation to the FDA. | Clarify if AMT designations will be assigned a designation number and if designations will be Center specific. Additional clarity on if CDER and CBER will have access to designated AMTs regardless of the original Center granting the designation would also be helpful. |
| **247-253** | FDA intends to assess the proposed AMT changes, including data to support such changes, to confirm that the designated AMT continues to meet criteria for designation and to evaluate any potential impact on the context of use for which the AMT was designated. | Clarify what the timeline for this review is and whether the submissions of AMT changes are managed independently of applications using the AMT. Additionally, it is unclear how the FDA will ensure communication between the AMT lifecycle management team and a review team reviewing an application utilizing an AMT will proceed. Please include an explanation of how reviewers will become aware of both clinical and/or commercial changes that occur to a designated AMT. |
| **240-253** | Applicants with approved applications that use, reference, or rely upon a designated AMT should evaluate the potential impact of the change on the finished product that is the subject of the application to determine whether a post approval submission is required as described in 21 CFR 314.70 or 252 601.12.19 | Clarify the approach needed for post-approval submissions and whether the AMT change should be included in the appropriate post-approval submission and expected to meet the predefined review timelines. |
| **255 - 262** | A technique will not be considered an AMT after FDA has gained significant experience assessing a designated AMT and the designated AMT has been used in multiple approved regulatory applications. The content of approved regulatory applications is not public knowledge. Hence, the vast majority of sponsors will be unaware of FDA's experience or the fact that the AMT has been the subject of approved regulatory applications. | FDA should provide insight into the communications related to graduating technologies. For example, will these communications come quarterly? Or will there be a database listing graduated technologies? |
| **255-262** | FDA will graduate an AMT technology once FDA has gained significant experience with it and will transfer review of future applications to the standard process. | More clarity is needed on if graduation of an AMT is based on experience gained by a single applicant using the AMT for multiple products or based on experience from multiple applicants using similar AMTs. |

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| **265-341** | Potential Benefits of AMT Designation | Does the FDA foresee AMT designation to confer any additional benefits post-approval, e.g., during process validation activities for technology transfers? |
| **267-272, 279-280** | Potential Benefits" only uses the term "prioritized" applicant interactions, and generally describes aspects of timely access, early communication and coordination with appropriate FDA quality assessment teams. | Clarity is needed on whether the term "expedited" also refers to an acceleration of the review timelines to plan to have an action at least 1 month prior to the UFA goal date because the AMT is used. |
| **269-272** | As resources permit, FDA intends to provide timely advice and to engage in additional communication, in the form of written correspondence or meetings, with requestors, designated AMT holders, and applicants for a drug manufactured using a designated AMT. | Clarify predicted timelines and meeting procedures, and whether AMT meetings will be defined as Type C meetings. |
| **279** | Describe the actual AMT benefits, rather than expectations (e.g. language of "expects" to expedite). Clarify what FDA means by "drugs imminently at risk of being a shortage" Should that be taken that new drugs are excluded and that "shortages" (lack of availability) of new life saving drugs are not considered. | Edit to add: "*FDA expects to prioritize applicant interactions that are intended to discuss the use of a designated AMT in drug development or commercial manufacturing, with higher priority being given to drug development activities and applications using a designated AMT with the potential to significantly improve product quality, address known quality issues for a drug or class of drugs, or increase or maintain the supply of drugs that are currently in shortage or imminently at risk of being in shortage* **or new drugs of significant lifesaving value individually or in aggregate compared to current standard of care**." |
| **284** | How does Fast Track and Break Through status impact AMT review times. | Edit to add: *"Consideration for prioritization may also be given to drug development activities and applications that are accepted into other expedited programs (e.g., fast track, breakthrough therapy)* **but are not required for AMT benefits to be obtained**." |
| **286-289** | For NDAs, BLAs, and ANDAs involving complex generic drugs, these interactions typically occur under the appropriate user fee meeting type and are generally facilitated through the designated lead for the AMT request, in consultation with the application quality assessment team. | The current text describes commercial application but does not include clinical meeting approaches. This comment aligns with a comment in Section V (lines 493-494). |

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| **336-341** | The guideline states that "When a designated AMT no longer meets the eligibility criteria, as described in section III.E of this guidance, appropriate steps…". Is the purpose of this paragraph to say that when an AMT is no longer considered a designated AMT due to changes in its lifecycle, this will be communicated to the review teams? | Clarity is needed on the AMT lifecycle management that FDA is referring to and what are the "appropriate steps" that FDA will take. |
| **390-395** | "In some cases, the designated AMT holder may also be the holder of a drug master file (DMF) that contains the designated AMT. In those circumstances, an applicant submitting an NDA or ANDA can, to support their application and with an appropriate right of reference, generally reference a DMF. However, when a DMF holder is also the holder of a designated AMT, information specifically describing the designated AMT should be shared with the NDA or ANDA applicant." | Clarity around and examples of AMTs that can be part of a DMF and AMTs that cannot. Additionally, clarity is needed on if an AMT can constitute a DMF in itself and the delineation between an AMT in a clinical setting versus a commercial setting. Given the significance of this concept, we suggest moving considerations for using a DMF concurrently with an AMT-designated technology to the main sections of the guidance rather than the Q&A. |
| **410-416** | Q4, it appears that there is a difference between the use of AMT in an NDA vs. a BLA. Lines 412-413 imply that the information about the AMT (including details that were submitted during the AMT designation process) will be subject to a second assessment during the BLA review. This would be a duplicative effort and could result in misalignment of the assessment during the AMT designation and the BLA review. | Clarity is needed from FDA on the review process for BLAs and post-approval changes that contain an AMT. |
| **433-438** | FDA recommends not requesting AMT designation at the same time as ETT/CATT engagement because ETT and CATT discussions generally occur earlier in the technology development process and are intended for less mature methods and technologies compared to AMT designation, which is intended for more mature methods and technologies (e.g., for which model drug-specific data are available). | Clarification to this section and possible addition of a flow chart would be helpful to ensure developers have a clear path to follow. |
| **493-494** | Q7 should be a standalone item in Section III, clearly identifying the meeting requests during clinical development, during commercial application submission and in the post-approval space. | Suggest moving content to Section III with a header of applicant AMT meeting request |