Response to a request for comments Docket No. FDA-2023-D-4974 “Advanced Manufacturing Technologies Designation Program Guidance for Industry”
Comments submitted by the International Society for Pharmaceutical Engineering (ISPE), regulatorycomments@ispe.org

GENERAL COMMENTS ON THE DOCUMENT
ISPE acknowledges the value of the Advanced Manufacturing Technologies Designation Program Guidance for Industry. ISPE appreciates the delineation of criteria and adoption of prioritization used to designate and assess innovations as well as clarification on how industry can approach and engage FDA regarding the initiation and development of advanced manufacturing technologies. ISPE believes that the Advanced Manufacturing Technologies Designation Program Guidance for Industry should serve to encourage industry investment and development in innovative technologies and pharmaceutical products.
Several sections in the draft guidance (lines 113-114, 153-155, 179-180) refer to “superior quality” as a basis for AMT designation. While ISPE acknowledges that the legislation upon which this guidance was drafted explicitly stipulates that “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,” superior quality is not defined and cannot be measured. ISPE believes that a reasonable interpretation of the legislation is to translate the provisions in the guidance as “equivalent or improved quality assurance.” The use of the term ‘superior quality’ as a basis for determining AMT designation could discourage rather than encourage innovation.
ISPE requests clarification that an innovative technology could be established/approved without a formal regulatory application or reference to a Drug Master File. While the Guidance states that AMT designations are made independently of application submissions, it does not explicitly indicate whether a proposed AMT must be accompanied by a formal regulatory application (e.g., IND, BLA, supplement) to be established/approved.
ISPE acknowledges that acceleration and engagement are helpful, however, the seemingly substantial data requested to obtain AMT designation may be prohibitive and discourage innovation. There seems to be a disconnect within the AMT draft guidance between the designation criteria and the expected level of data required to support AMT designation to achieve the intended benefits articulated in the guidance. For many innovative technologies, the data requested to support designation can only be generated late in development prior to an application for a commercial new drug or a post-approval change to an approved pharmaceutical product. In some instances, requisite data may only be generated after approval of a commercial application. The only benefit of AMT designation at this late stage of development would be an accelerated review of the commercial application and subsequent supplements. While ISPE recognizes that some measure of data may be necessary to obtain meaningful responses from FDA regarding the value and substantial impact of an advanced manufacturing technology, few innovative technologies have sufficient data during early development to demonstrate the level of improved manufacturing reliability of quality assurance expected to achieve AMT designation. Therefore, the benefits of AMT designation may not be

fully realized by a sponsor with a potentially innovative technology for which data may be limited to substantially demonstrate improvements in manufacturing reliability or increased quality assurance. ISPE recommends that the guidance states that information including prior knowledge and/or data, where applicable, may be acceptable for determining AMT designation.
While question 6 in the Q&A addresses the differences between AMT Designation and Platform Technology Designation programs it does not provide sufficient guidance on the introduction of an innovative approach to a platform technology, i.e., automated operations, adaptive controls, digitalization, etc., when applied to approved/existing manufacturing processes that could ostensibly improve product quality assurance. ISPE recommends that this guidance reinforce how AMT designation could be applied for continual process improvements that rely on adaptations of platform technologies.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
127-185	The draft guidance uses a narrow definition of "data and information demonstrating that the method of manufacturing meets the criteria"	The section should be rewritten to allow utilization of "information" that is not specifically "data" to justify meeting the criteria in III.B. For example, adding the following statement: "*Data and information may include prior knowledge, anecdotal evidence from analogous innovative technologies, articulated descriptions of the innovative approach and its expected improvement in manufacturing reliability and quality assurance, etc.*"	In early development, data may be limited or not available on manufacturing process details or for demonstrating that the AMT will increase or maintain supply or quality of the drug. However, other information could support justification of meeting the criteria, such as prior knowledge, anecdotal evidence from analogous innovative technologies, articulated descriptions of the innovative approach and its expected improvement in manufacturing reliability and quality assurance, etc.
153	*"A description of proposed process controls, quality information, and, if applicable, proposed controls of critical*	Replace the phrase 'superior drug quality' with 'improved quality assurance'	In early phases of development for most innovative technologies, this level of information is generally not possible with any precision. Only estimated controls and anticipated improvements can be

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	steps intended to ensure equivalent or superior drug quality."		prospectively ascertained, as the requisite development studies, scale-up evaluations and design of experiments will not have been completed to demonstrate unequivocal improvements in quality.
157-158	"*Developmental data and information for the proposed AMT that evaluates and justifies the context of use*."	Replace the word *'evaluates'* with *'describes'*.	The context of how a proposed AMT can be used can be described, but not necessarily evaluated.
223-226	"*Submission of an AMT designation request does not guarantee designation or acceptance into the program*."	Add a statement that a rejected application can be resubmitted once requisite data becomes available.	Submission of an application too early (e.g., at IND phase) should not disqualify legitimate advanced manufacturing technologies from leveraging the benefits of AMT designation once data has been generated to meet AMT criteria.
286	"*For NDAs, BLAs and ANDAs involving complex generic drugs . . .*"	A definition of "*complex generic drug*" should be provided or its relevance to AMT designation clearly referenced.	Please provide an explanation for the meaning of "*complex generic drug"* and its implications for AMT designation.
465 - 491		Suggest introducing examples to indicate platform technologies that would be eligible for AMT designation from those platform technologies that would not be eligible for AMT designation.	It is not clear from the explanation to this question why AMT and Platform Technology programs are different or why novel application of platform technologies in development are not considered the same.
386 - 398	In the case where the requestor is not an applicant for a specific drug or pharmaceutical product, the designation of an AMT is not publicly available as it is considered proprietary which limits applicants interested in leveraging an AMT designation, if they do not know it has been granted.	ISPE suggests providing additional Q&A clarity regarding provisions for leveraging AMT designations.	The absence of provisions describing access to AMT designated technologies could limit their adoption across the industry and, in particular, where those innovations may be most useful at reducing drug shortages and quality compliance issues.

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386 - 398	It does not appear that more than one company may receive an AMT designation for the same manufacturing technology, e.g., continuous manufacturing.	ISPE suggests providing additional Q&A clarity regarding provisions for more than one company to receive AMT designation for the same/similar advanced manufacturing technology.	The absence of guidance regarding access to AMT designation for similar innovative technologies will discourage companies from collaboration and stifle innovation.
386 - 398	Omission of provisions for adoption of an AMT designated technology for another alternative innovative approach.	ISPE suggests additional clarity in the Q&A with provisions regarding whether the 'innovative' use of an advanced manufacturing technology that has 'graduated through ETT/CATT' is eligible for AMT designation.	The absence of guidance for follow-on innovations based on a precedented AMT designated technology could limit adoption and retard innovative development and continual improvement.