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Client Alert

FDA and Life Sciences

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FDA Ushers in New Program for Drug Products Manufactured Using Innovative Manufacturing Technologies

Under Section 3213 of Food and Drug Omnibus Reform Act, the U.S. Food & Drug Administration ("FDA" or the "Agency") is required to establish the Advanced Manufacturing Technologies Designation Program,[i] an initiative intended to facilitate the development of drugs, biological products, and active pharmaceutical ingredients using a designated "advanced manufacturing technology."[ii] On December 13, 2023, FDA issued a draft guidance (the "Draft AMT Guidance") that describes the program's framework for designating certain drug manufacturing methods as advanced manufacturing technologies ("AMTs").[iii] FDA refers to AMTs as innovative technologies that can improve the manufacturing and supply dependability of drugs and biological products, including those deemed critical or in shortage; optimize product development; and increase timely access.[iv] FDA notes that AMTs can "directly improve product quality," when, for example, better manufacturing controls lead to fewer human interventions.[v]

There are high hopes that the program may help FDA and manufacturers avoid drug shortages, which have been on the rise. In 2022, 150 different manufacturers notified FDA 1,293 times that the manufacture of a drug, biological product, or active pharmaceutical ingredient was being permanently discontinued or interrupted, and that such discontinuances or interruptions were likely to result in a meaningful disruption of the supply of such products.[vi] This marked a nearly 66% increase in notifications from the prior year.[vii]

ELIGIBILITY

The AMT designation is intended to capture those manufacturing technologies that incorporate a "novel technology" or use an "established technique or technology in a novel way," such that it will "substantially

improve the manufacturing process for a drug while maintaining equivalent, or providing superior, drug quality."[viii] The manufacturing process improvement can be the result of, for instance:

i. Reducing the development time for a drug; or

ii. Increasing or maintaining the supply of a drug that is (A) life-supporting, life-sustaining, or of critical importance to providing care, or (B) on FDA's drug shortage list.[ix]

As described in the Draft AMT Guidance, FDA will consider a technology to be "novel" for purposes of the designation if it is "one that has not been used in a previously approved application and for which FDA therefore has limited assessment or inspectional experience."[x] FDA will consider an "established technique or technology" to be novel if "it is used in a way that has not been described in a previously approved application" and that new use "substantially improve[s] the manufacturing process for a drug."[xi]

BENEFITS OF AMT DESIGNATION

AMT designation will come with benefits related to the development and review of drug and biological products that are manufactured using a designated AMT and that seek approval in a new drug application ("NDA") or biologics license application ("BLA").[xii] As with other designation programs, many of the benefits will accrue through increased interactions with the Agency during early product development. But the Draft AMT Guidance also makes clear that FDA will continue engagement all the way through application review, including to address AMT-related questions and issues, and application content related to a designated AMT.

In particular, FDA intends to provide timely advice and interactive communication through written correspondence or meetings with applicants for a drug or biologic manufactured using a designated AMT, as well as to prioritize such interactions involving the use of a designated AMT in product development or commercial manufacturing.[xiii] FDA will assign higher priority to development programs and NDAs/BLAs that use a designated AMT that has the potential to "significantly improve product quality," to "address known quality issues," or to "increase or maintain the supply of drugs that are currently in shortage or imminently at risk of being in shortage."[xiv] The applicant will also receive the benefit of FDA's expedited review.[xv]

Importantly, FDA will facilitate the quality assessment of an NDA or a BLA for a product manufactured using a designated AMT, with the stated goals of improving efficiency in the assessment process and supporting applicants in the development of the NDA/BLA CMC sections "such that the incorporation of a designated AMT will not increase the time or number of assessment cycles required to arrive at a quality-related decision."[xvi] As the Draft AMT Guidance explains, use of a designated AMT is therefore not expected to increase the Agency's review timeline for applications, even when a designated AMT is used "across multiple drugs."[xvii]

FDA will also allow the holder of the AMT designation (or person authorized by the holder), when submitting an application, to reference or rely upon data and information about the designated AMT in the same context of use for which the designation was granted.[xviii] For example, when the designated AMT holder and the applicant are different entities, the designated AMT holder can authorize the applicant to incorporate by reference data and information about the designated AMT in its application. The Draft AMT Guidance notes that, in some circumstances, an "applicant submitting an NDA or an [abbreviated new drug application]" may wish to submit a drug master file to facilitate reference to a designated AMT. This raises interesting questions of data reliance for BLAs specifically (for which drug master files often are not permitted[xix])—an issue we may expect to see raised in comments on the draft guidance.

AMT DESIGNATION REQUESTS

Persons or organizations (e.g., applicants, contract manufacturers, technology developers) can request that a method of manufacturing be designated as an AMT by submitting data and information to FDA that demonstrate that the method meets the statutory criteria in a particular context of use.[xx] FDA will review the request for AMT designation independent of application submissions (i.e., FDA grants a designation outside the context of a specific application) and issue a determination within 180 calendar days after receiving an AMT designation request.[xxi]

FDA recommends that the requestor's submission include:

i. A brief description of the method of manufacturing (or combination of methods) and why it should be considered for AMT designation;

ii. A detailed description of how the method of manufacturing (or combination of methods) meets the eligibility criteria in a particular context of use;

iii. The context of use under which the proposed AMT will be used in drug development;

iv. Perceived regulatory, technical, or other challenges associated with implementing the proposed AMT;

v. The timeline for drug development activities that incorporate the proposed AMT (if known);

vi. Information about previous engagement with the Emerging Technology Team at the Center for Drug Evaluation and Research ("ETT") or the Advanced Technology Team at the Center for Biologics Evaluation and Research ("CATT"), if any; and

vii. For a proposed AMT used to manufacture an existing drug that is life-supporting, life-sustaining, of critical importance to providing health care, or on FDA's drug shortage list, a cross reference to the existing application and data demonstrating that the proposed AMT will increase or maintain the supply of the drug while maintaining equivalent, or providing superior, drug quality.[xxii]

FDA notes that the robustness of the data and information should correspond to the degree of risk associated with the manufacturing process for the drug (and the degree of risk associated with the drug itself), such that the data and information can be leveraged in an associated marketing application.[xxiii] If a requestor is not able to provide drug-specific information, then FDA suggests that the requestor generate data using a model drug to help the Agency understand the parameters, limits, and context of use of the proposed AMT.[xxiv]

The Agency also strongly recommends that requestors engage with the appropriate technologies team (i.e., ETT or CATT) to discuss the technology before submitting an AMT designation request. FDA invites requestors to do this early, at the proof-of-concept, prototype, or hypothetical stage in manufacturing method development.[xxv]

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FDA is soliciting comments on the Draft AMT Guidance by February 12, 2024, and the Agency is expected to issue final guidance before December 29, 2024.[xxvi] King & Spalding LLP regularly counsels manufacturers and other life sciences companies on FDA's regulation of drugs, including biologics, and on the development and submission of marketing applications. Please let us know if you have any questions regarding this draft guidance, or if you would like to consider submitting a comment.

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[i] Food and Drug Omnibus Reform Act of 2022, Pub. L. No. 117-328, § 3213, 136 Stat. 5807, 5826–29 (2022). King & Spalding reported on some of the other, major regulatory reforms under FDORA earlier this year. *See* King & Spalding, Client Alert, *Not Quite the Titanic: The Food and Drug Omnibus Reform Act Rescues Some FDA Policy Initiatives* (Jan. 9, 2023), https://www.kslaw.com/news-and-insights/not-quite-the-titanic-the-food-and-drug-omnibus-reform-act-rescues-some-fda-policy-initiatives; King & Spalding, Client Alert, *Nearly a Century in the Making: Congress Modernizes FDA's Regulation of Cosmetics* (Jan. 9, 2023), https://www.kslaw.com/news-and-insights/nearly-a-century-in-the-making-congress-modernizes-fdas-regulation-of-cosmetics.

[ii] 21 U.S.C. § 356*l*(a)–(b); 88 Fed. Reg. 86333, 86334–35 (Dec. 13, 2023).

[iii] *See generally* U.S. Food & Drug Admin., Guidance for Industry (draft), *Advanced Manufacturing Technologies Designation Program* (Dec. 2023) (hereinafter "Draft AMT Guidance"), https://www.fda.gov/media/174651/download.

[iv] *Id.* at 1.

[v] *Id*.

[vi] U.S. Food & Drug Admin., Report to Congress, *Drug Shortages CY 2022*, at 9, *available at* https://www.fda.gov/media/169302/download?attachment.

[vii] FDA received 777 notifications from 115 different manufacturers in 2021. U.S. Food & Drug Admin., Report to Congress, *Drug Shortages for Calendar Year 2021*, at 6, *available at* https://www.fda.gov/media/159302/download?attachment.

[viii] 21 U.S.C. § 356*l*(b); Draft AMT Guidance, at 3–4.

[ix] 21 U.S.C. § 356*l*(b); Draft AMT Guidance, at 3–4.

[x] Draft AMT Guidance, at 9.

[xi] *Id.* at 9–10.

[xii] 21 U.S.C. § 356*l*(d)(1).

[xiii] Draft AMT Guidance, at 7–8.

[xiv] *Id.* at 8.

[xv] *Id*. at 10–11.

[xvi] *Id*. at 9.

[xvii] *Id.*

[xviii] 21 U.S.C. § 356*l*(d)(2).

[xix] *See* Biologics License Applications and Master Files, 84 Fed. Reg. 30968 (proposed June 28, 2019) (to be codified at 21 C.F.R. pt. 601) (noting that the "proposed rule also codifies FDA's existing practice that a biological product in a biologics license application (BLA) under the PHS Act may rely on a master file, except for information regarding a drug substance, drug substance intermediate, or drug product"); King & Spalding, Client Alert, *FDA Issues Draft Guidance on Use of "Generally Accepted Scientific Knowledge" to Support Drug and Biologic Applications* (June 5, 2023), https://www.kslaw.com/news-and-insights/fda-issues-draft-guidance-on-use-of-generally-accepted-scientific-knowledge-to-support-drug-and-biologic-applications.

[xx] 21 U.S.C. § 356*l*(c)(1); Draft AMT Guidance, at 2.

[xxi] 21 U.S.C. § 356*l*(c)(2); Draft AMT Guidance, at 3, 11.

[xxii] Draft AMT Guidance, at 4–5.

[xxiii] *Id.* at 4.

[xxiv] *Id.* at 5.

[xxv] *Id.* at 3.

[xxvi] 21 U.S.C. § 356*l*(e)(2)(A)(ii); 88 Fed. Reg. at 86334.