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Client Alert

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FDA Issues Draft Guidance on Accelerated Approval Focused on How the Agency Will Implement New Authorities

On December 5, 2024, the U.S. Food and Drug Administration (FDA or Agency) issued a draft guidance entitled *Expedited Program for Serious Conditions—Accelerated Approval of Drugs and Biologics* (Draft Accelerated Approval Guidance).[i] In 1997, the Food and Drug Administration Modernization Act codified FDA's accelerated approval program by adding Section 506 to the Federal Food, Drug and Cosmetic Act (FDCA),[ii] and Congress amended Section 506 in 2012.[iii] The accelerated approval program helps get necessary therapies to patients who need them quickly by speeding the development of drugs and biologics that treat serious and life-threatening conditions, where there is an unmet need. To that end, accelerated approval allows FDA to approve drugs and biologics that demonstrate a reasonable likelihood of a clinical benefit based on a surrogate endpoint or an intermediate clinical endpoint. Sponsors of accelerated approval applications are required to conduct a post-approval confirmatory trial to verify the clinical benefit.

Recently, in the Consolidated Appropriations Act of 2023[iv] (often referred to as the Food and Drug Omnibus Reform Act (FDORA)), Congress amended Section 506 of the FDCA again – this time to grant FDA the authority (1) to specify conditions and procedures for confirmatory trials, (2) to help expedite the withdrawal of approval of a drug or biologic approved through the accelerated approval pathway, and (3) to require (as appropriate) that confirmatory trials be underway at the time of approval or within a specified time period thereafter.

In the draft guidance, FDA describes how the Agency plans to implement the first and second of these new authorities and promises to issue guidance on the third new authority soon. The draft guidance is intended to be used in conjunction with a guidance entitled *Expedited Programs*

for Serious Conditions—Drugs and Biologics issued in May 2014, which will continue to represent the Agency's latest thinking on concepts such as "serious condition," "available therapy," and "unmet medical need."[v]

OVERVIEW OF ACCELERATED APPROVAL REQUIREMENTS

The *Draft Accelerated Approval Guidance* provides an overview of the accelerated approval program, the key tenets of which are described above and likely familiar to many readers. In addition, FDA's overview of the program provides examples of the types of circumstances in which the Agency believes that accelerated approval may be appropriate and the types of circumstances in which it may not be warranted.

- **Potentially Appropriate Settings/Conditions for Accelerated Approval**
  - Settings where the "disease course is long or the clinical outcome events intended to be reduced by the drug are infrequent," and where "[s]urrogate endpoints or intermediate clinical endpoints have the potential to detect the drug effect that may predict clinical benefit earlier than endpoints showing clinical benefit" (e.g., endpoints that can assess the effect on tumor growth, rapidly, and that are reasonably likely to predict improvement in overall survival for a particular cancer).[vi]
  - Conditions "where an effect on a surrogate endpoint could be shown in a smaller number of patients, but a much larger study would be needed to show the effect on a clinical outcome, such as survival."[vii]
- **Inappropriate Settings for Accelerated Approval** include settings where "the completion of an adequate and well-controlled clinical trial to verify and describe clinical benefit will be infeasible."[viii]

In the overview, FDA also (1) discusses specific risks associated with accelerated approval, i.e., exposing patients to safety risks from a drug or biologic that ultimately may not demonstrate clinical benefit, with limited information regarding the occurrence of rare or delayed adverse events, and (2) notes that those risks will inform the Agency's decision-making regarding whether accelerated approval is appropriate.[ix]

CONSIDERATIONS REGARDING SURROGATE ENDPOINT AND INTERMEDIATE CLINICAL ENDPOINT SELECTION

As mentioned, either surrogate endpoints or intermediate clinical endpoints can be the basis for accelerated approval. In the *Draft Accelerated Approval Guidance*, FDA offers what amounts to do's and don'ts regarding endpoint selection. According to FDA:

- **Do Use Accelerated Approval If There Are:**
  - Validated surrogate endpoints (i.e., those that are known to predict clinical benefit);
  - Surrogate endpoints that are reasonably likely to predict clinical benefit; or
  - Intermediate clinical endpoints that, alone, cannot support traditional approval, e.g., (a) endpoints that show short-term benefit for a chronic disease where a longer duration of effect is necessary for clinically meaningful benefit, and the short-term benefit is reasonably likely to predict a longer duration effect, or (b) an "intermediate clinical endpoint [that] demonstrates clinical benefit on a less serious or earlier symptom of a serious disease, but the benefit observed is anticipated to predict a favorable disease outcome."[x]
- **Don't Use Accelerated Approval If There Are:**
  - Surrogate endpoints are neither known to predict clinical benefit or reasonably likely to predict clinical benefit;
  - Intermediate clinical endpoints that alone could support traditional approval; or

- Intermediate clinical endpoints that are not reasonably likely to predict clinical benefit.[xi]

In addition, FDA reminds readers that drugs and biologics granted accelerated approval must meet the same standards for safety and effectiveness as those approved via the traditional approval pathway.[xii] In other words, to be approved via the accelerated approval pathway, drugs and biologics must be supported by "substantial evidence" that is based on adequate and well-controlled clinical investigation(s) and constitutes "sufficient information to determine that the drug or biologic is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling."[xiii]

That said, FDA notes that "[d]etermining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend upon the biological plausibility of the relationship between the disease, the endpoint, the desired effect, and the empirical evidence to support that relationship."[xiv] FDA also reminds readers that Section 506(c)(1)(B) of the FDCA states that empirical evidence may include "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."[xv] Factors to consider in assessing whether an endpoint is reasonably likely to predict clinical benefit include: (1) the "extent to which the pathophysiology of the disease and the role of the surrogate endpoint in that pathophysiology is understood," (2) "[w]hether there is reliable and consistent epidemiologic evidence supporting correlation," and (3) "[w]hether there is evidence from clinical trial data supporting that the effect on the surrogate endpoint has been shown to predict a clinical benefit with another drug or drugs."[xvi]

FDA also states in the draft guidance that the Agency's evaluation of the appropriateness of a surrogate endpoint will be context dependent. For example, FDA will take into account the magnitude of the effect that the drug or biologic has on a surrogate endpoint and may require that effect to be "at least a specific size . . . , particularly if there are potential serious drug risks."[xvii]

CONFIRMATORY TRIAL DESIGN

FDA's *Draft Accelerated Approval Guidance* advises readers that:

- Confirmatory trials must be completed with due diligence, meaning that sponsors must commit sufficient resources to completing the trial as quickly as possible;
- Sponsors seeking accelerated approval should consult with FDA on clinical trial design as early as possible during the development program;
- The clinical trial design should specify timelines for enrollment and trial completion, and it should ensure that the clinical trial will meet the timelines specified;
- Confirmatory trials should generally be underway at the time the marketing application is *submitted*, and, except in limited circumstances, FDA will require the confirmatory trial to be "underway *prior to granting accelerated approval*";
- FDA will set forth conditions (e.g., enrollment targets) for the progress of the confirmatory trial no later than the date of accelerated approval;
- Sponsors should diligently monitor trial progress and add resources or make appropriate protocol changes to help ensure that the confirmatory trial stays on track to meet timelines; and
- Sponsors are required to submit progress reports on confirmatory trials approximately every 180 days.[xviii]

FDA also notes that for some confirmatory trials it may be appropriate (1) for the trial to be conducted in a different but related population than the population that was used in the trial supporting accelerated approval if it would otherwise be difficult to enroll the confirmatory trial, (2) to design a confirmatory trial that uses the same surrogate endpoint that was

used to support accelerated approval, or even (3) to use the *same* clinical trial to support accelerated approval and to confirm the clinical benefit, post accelerated approval, if a "relevant surrogate or intermediate clinical endpoint can be measured earlier in the trial and the expected clinical benefit demonstrated later in the same trial."[xix]

EXPEDITED WITHDRAWAL OF APPROVAL

The recent amendments to Section 506 of the FDCA established that FDA may use expedited procedures to withdraw approval of a drug or biologic that has received accelerated approval if:

- The sponsor fails to conduct required post-approval confirmatory trials with due diligence;
- The confirmatory trial fails to verify and describe the intended clinical benefit;
- The evidence shows that the drug or biologic is not safe or not effective for its intended use; or
- The sponsor disseminates false or misleading promotional materials related to the drug or biologic.[xx]

Expedited withdrawal procedures include: (1) providing the sponsor with notice of the proposed withdrawal, an opportunity to meet with the FDA Commissioner or the Commissioner's designee, and an opportunity for a written appeal, (2) providing the public with an opportunity to comment on the proposed withdrawal, review a summary of the public comments received, and review a response to such comments on FDA's website, and (3) providing an opportunity for the sponsor to request that an advisory committee be consulted on relevant issues, subject to certain exceptions.[xxi]

FDA's *Draft Accelerated Approval Guidance* explains in detail how FDA will conduct each of these procedures. In addition, the draft guidance provides that, as a general matter, proposals to withdraw accelerated approval will be issued by the relevant Center, and that the relevant Center should in most instances hold an advisory committee meeting prior to proposing to withdraw a drug or biologic's accelerated approval.

CONCLUSION AND KEY TAKE-AWAYS

While FDA has yet to address all aspects of its new statutory authority for accelerated approval, the draft guidance helps sponsors better understand the Agency's current thinking on acceptable endpoint selection, considerations for the design and conduct of confirmatory trials, and the conditions and procedures for expedited withdrawal of approval. Sponsors should engage FDA early regarding the potential eligibility of a drug or biologic for accelerated approval, proposed surrogate endpoints or intermediate clinical endpoints, clinical trial designs, and steps to facilitate timely initiation and completion of confirmatory trials. Feedback from FDA early in the development process will better inform accelerated approval applications and may help circumvent expedited withdrawal of approval.

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[i] *See* U.S. Food & Drug Admin., *Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics: Draft Guidance for Industry* (2024) (Draft Accelerated Approval Guidance), https://www.fda.gov/media/184120/download.
[ii] *See* Food and Drug Administration Modernization Act (FDAMA), Public Law 105-115 (enacted Nov. 21, 1997).
[iii] *See* Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144 (enacted July 9, 2012).
[iv] *See* Consolidated Appropriations Act, 2023, Public Law 117-328 (enacted Dec. 29, 2022).
[v] *See Draft Accelerated Approval Guidance* at 6.
[vi] *Id.* at 4.
[vii] *Id.*
[viii] *Id.*
[ix] *See id.*
[x] *Id.* at 7-8.
[xi] *See id.* at 8.
[xii] *See id.* at 9.
[xiii] *Id.*
[xiv] *Id.*
[xv] *Id.* at 9-10 (citing 21 U.S.C. § 356(c)(1)(B)).
[xvi] *Id.* at 11.
[xvii] *Id.*
[xviii] *Id*. at 12-13.
[xix] *Id.* at 13.
[xx] *See id.* at 15.
[xxi] *See id.* at 15-16.