Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

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Procedural

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Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Accelerated approval is one of FDA's expedited programs[2] intended to facilitate and expedite development and review of new drugs[3] to address an unmet medical need in the treatment of a serious or life-threatening condition. The purpose of this guidance is to provide information on FDA's policies and procedures for accelerated approval as well as threshold criteria generally applicable to concluding that a drug is a candidate for accelerated approval. This guidance also describes the procedures for expedited withdrawal of approval of a product approved under accelerated approval and the revisions Congress made through the Consolidated Appropriations Act, 2023 (Public Law 117-328). Additional programs to expedite product development and review are covered in other guidances.[4]

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) and the Oncology Center of Excellence (OCE) at the Food and Drug Administration.

[2] FDA's expedited programs include (1) fast track designation, (2) breakthrough therapy designation, (3) accelerated approval, and (4) priority review designation. Two additional programs described in section 506 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) are more narrowly tailored: the limited population pathway for antibacterial and antifungal drugs (LPAD) and the regenerative medicine advanced therapy (RMAT) program.

[3] In this guidance, all references to *drugs* or *drug products* include both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

[4] See the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014). See also the guidances for industry *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* (February 2019) and *Limited Population Pathway for Antibacterial and Antifungal Drugs* (August 2020) for the Agency's current thinking on these topics. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The accelerated approval pathway, in appropriate cases, provides for the approval of drugs for serious conditions that fill an unmet medical need based on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.[5]

In 1992, FDA issued its accelerated approval regulations.[6] In 1997, Congress codified the accelerated approval program in the Food and Drug Administration Modernization Act (FDAMA) (Public Law 105-115), adding section 506 to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356). In 2012, Congress amended section 506 of the FD&C Act via the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144) to provide that FDA should consider the "severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments." Section 506(c) of the FD&C Act, as amended by FDASIA, provides that FDA may grant accelerated approval to:

> . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

For drugs granted accelerated approval, sponsors conduct confirmatory trials that must be completed postapproval and are intended to verify and describe the anticipated effect on irreversible morbidity or mortality (IMM) or other clinical benefit (see section IV.D of this

[5] A clinical benefit is a positive therapeutic effect that is clinically meaningful in the context of a given disease. The clinical benefit must be weighed against a treatment's risks to determine whether there is an overall benefit for patients (i.e., a positive benefit-risk profile).

[6] Food and Drug Administration, Final Rule, "New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval" (57 FR 58942, December 11, 1992) (21 CFR parts 314 and 601) and Food and Drug Administration, Proposed Rule, "New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval" (57 FR 13234, April 15, 1992).

guidance).[7] If the required confirmatory trial[8] verifies and describes the clinical benefit, FDA considers the confirmatory trial requirement to have been met and therefore released.[9] (The Agency sometimes refers to this determination informally as *conversion* of a product to traditional approval.) FDA may withdraw approval of a drug approved under accelerated approval if, for example, the sponsor fails to conduct a confirmatory trial with due diligence or a confirmatory trial fails to verify and describe the effect on IMM or other clinical benefit, among other reasons (see section V of this guidance).[10]

Section 506(c) of the FD&C Act was most recently amended by the Consolidated Appropriations Act, 2023 (Public Law 117-328), which granted FDA additional authorities and imposed on FDA additional obligations regarding accelerated approval. Among other revisions, section 3210 of the Consolidated Appropriations Act, 2023 provides that not later than the date of approval of a product under accelerated approval, FDA will specify conditions for the confirmatory study or studies sponsors are required to conduct under this section, which "may include enrollment targets, the study protocol, and milestones, including the target date of study completion."[11] Congress also revised the provisions in section 506(c) related to the expedited withdrawal of approval of a product approved under accelerated approval, including by adding new procedures for expedited withdrawal. Section V of this guidance describes the procedures for expedited withdrawal of approval of a product approved under accelerated approval.

Additionally, under the Consolidated Appropriations Act, 2023, Congress gave FDA the authority to require, as appropriate, that a confirmatory trial be underway prior to accelerated approval or within a specified time period after the date of accelerated approval. The Agency intends to address this authority in a separate guidance.

III. OVERVIEW OF ACCELERATED APPROVAL

Accelerated approval is generally used in settings of unmet medical need for drugs intended for the treatment of a serious or life-threatening condition. FDA's accelerated approval regulations state that accelerated approval is available only for drugs that provide a meaningful therapeutic benefit over existing treatments, and the FD&C Act was subsequently amended to require that

[7] Section 506(c)(2)(A)(i); 21 CFR 314.510 and 601.41. The terms *postapproval*, *postmarketing*, and *confirmatory* are used interchangeably throughout this guidance to describe the postapproval studies that are generally required under section 506(c) of the FD&C Act. The terms *trials* and *studies* are used interchangeably in this guidance. Other authorities distinguish between postapproval studies and clinical trials (see, e.g., section 505(o) of the FD&C Act (21 U.S.C. 355(o)). Other Agency guidances relating to other subject matters may also distinguish between trials and other types of studies.

[8] References to a confirmatory trial should be understood to mean one or more trials, as appropriate for the relevant product.

[9] See 21 CFR 314.560 and 601.46.

[10] Section 506(c)(3)(A) of the FD&C Act.

[11] Section 506(c)(2)(C) of the FD&C Act.

FDA consider "the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments" when approving a product under accelerated approval.[12] Accelerated approval allows sponsors to obtain approval with data that demonstrate efficacy based on surrogate or intermediate clinical endpoints that are reasonably likely to predict clinical benefit for the condition. This often allows sponsors to obtain approval for products intended to treat an unmet medical need sooner than would be possible under traditional approval.

Accelerated approval has been used in settings in which the disease course is long or the clinical outcome events intended to be reduced by the drug are infrequent.[13] Surrogate endpoints or intermediate clinical endpoints have the potential to detect the drug effect that may predict clinical benefit earlier than endpoints showing clinical benefit. For example, accelerated approval has been used extensively in the approval of drugs to treat a variety of cancers where an effect on tumor growth can be assessed rapidly, but demonstrating an effect on survival or other endpoint relevant to show clinical benefit for a particular cancer would need longer and sometimes larger trials because of the duration of the typical disease course. Accelerated approval may be considered for a condition 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.

At the time a product is granted accelerated approval, FDA has determined that an effect on the endpoint used to support approval—a surrogate endpoint or an intermediate clinical endpoint—is reasonably likely to predict clinical benefit. The risks of this approach include that patients may be exposed to safety risks from a drug that ultimately does not demonstrate clinical benefit. In addition, because there generally may be smaller or shorter clinical trials than is typical for a drug receiving traditional approval, there may be less information available at the time of accelerated approval about the occurrence of rare or delayed adverse events. These risks inform the Agency's decision-making regarding use of accelerated approval.

There are certain additional conditions and requirements associated with accelerated approval:

- FDA requires sponsors to conduct postapproval studies to verify and describe the anticipated clinical benefit of the drug.[14]

- No later than the date of approval, FDA must specify the conditions for postapproval studies, which may include a deadline to submit the final study protocol, targets for enrollment progress, and other milestones such as the target date for study completion.[15]

[12] 21 CFR 314.500 and 601.40; section 506(c)(1)(A) of the FD&C Act. FDA's accelerated approval regulations were issued prior to the enactment of section 506.

[13] See FDA's web page on Accelerated Approval Program at https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program.

[14] See section 506(c)(2)(A)(i) of the FD&C Act; 21 CFR 314.510 and 601.41.

[15] Section 506(c)(2)(C) of the FD&C Act.

- FDA may require that postapproval studies be underway prior to accelerated approval or within a specified time from the date of accelerated approval.[16]

- The INDICATIONS AND USAGE section of drug labeling must include a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the CLINICAL STUDIES section for a discussion of this available evidence.[17]

- FDA has required sponsors to submit copies of all their promotional materials to FDA within certain time frames.[18]

- Sponsors are required to submit reports on the progress of required postapproval studies to FDA approximately every 180 days, and FDA is required to publish the reported information.[19]

Accelerated approval should not be considered if the completion of an adequate and well-controlled clinical trial to verify and describe clinical benefit will be infeasible. Importantly, FDA may withdraw an accelerated approval using expedited procedures (1) if the sponsor fails to conduct any required postapproval study with due diligence, including with respect to the study conditions set forth by FDA, (2) if a required confirmatory study fails to verify clinical benefit, (3) if other evidence demonstrates that the product is not shown to be safe or effective under the approved conditions of use, or (4) if the sponsor disseminates false or misleading promotional materials with respect to the product.[20]

Given the nature of accelerated approval, communication between the sponsor and Agency is critical. FDA encourages sponsors to communicate with the Agency early in development concerning (1) the potential eligibility of a drug for accelerated approval, (2) proposed surrogate endpoints or intermediate clinical endpoints, (3) clinical trial designs, and (4) the planning and conduct of confirmatory trials.[21] FDA will strive to provide a timely response to a sponsor's inquiry regarding a development program intending to seek accelerated approval, and it is equally important that a sponsor respond promptly to FDA's inquiries. This applies particularly

[16] Section 506(c)(2)(D) of the FD&C Act.

[17] See 21 CFR 201.57(c)(2)(i)(B); guidance for industry *Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway* (January 2019).

[18] Section 506(c)(2)(A)(ii) of the FD&C Act; 21 CFR 314.550 and 601.45.

[19] Section 506B(a)(2) of the FD&C Act.

[20] Section 506(c)(3)(A) of the FD&C Act.

[21] The accelerated approval pathway will not be an option for every serious disease with an unmet medical need, particularly when evidence is insufficient to support use of a surrogate endpoint or intermediate clinical endpoint, or when an adequate and well-controlled confirmatory trial would be infeasible. In such cases, sponsors should discuss alternative approaches with the Agency.

to formal meetings and related inquiries, written correspondence, and other interactions. See sections IV.A.3 and IV.C.1 of this guidance.

The guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014) will continue to represent FDA's current thinking with respect to the following concepts applicable to accelerated approval:[22]

- Serious Condition
- Available Therapy
- Unmet Medical Need[23]

IV. GRANTING OF ACCELERATED APPROVAL

The following sections provide (A) considerations for the use of surrogate and intermediate clinical endpoints in accelerated approval; (B) evidentiary criteria for accelerated approval (including FDA's considerations in determining what makes an endpoint reasonably likely to predict clinical benefit); (C) requirements for confirmatory studies; and (D) other conditions such as those related to labeling, promotional materials, postmarketing recordkeeping, and safety reporting.

A. Accelerated Approval Endpoints

The two types of endpoints that can be used as a basis for accelerated approval are (1) a surrogate endpoint that is considered reasonably likely to predict clinical benefit and/or (2) a clinical endpoint[24] that can be measured earlier than IMM that is reasonably likely to predict an

[22] Information regarding general considerations for expedited programs, including manufacturing and product quality considerations, nonclinical considerations, clinical inspections, and companion diagnostics in the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics*, or successor guidances that are finalized by FDA, will continue to represent FDA's thinking regarding these topics as they pertain to accelerated approval unless specifically noted otherwise.

[23] Section 506(c)(1)(A) of the FD&C Act requires FDA to consider the availability or lack of alternative treatments in determining whether a product should be approved under accelerated approval. Additionally, FDA's accelerated approval regulations state that accelerated approval is available only for drugs that provide a meaningful therapeutic benefit to patients over existing treatments (21 CFR 314.500; 601.40). FDA has generally interpreted these requirements to mean that accelerated approval is only available for products that address an unmet medical need. For example, a new therapy with efficacy expected to be comparable to available therapy, but with a different mechanism of action, could be of added clinical value in a disease setting in which a significant number of patients may respond differently to the new therapy. The discussion of unmet medical need in the guidance for industry Expedited Programs for Serious Conditions—Drugs and Biologics provides examples of situations in which a drug could be shown to provide a meaningful advantage over available therapy.

[24] A clinical endpoint is a characteristic or variable that directly measures a therapeutic effect of a drug in humans—an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives.

effect on IMM or other clinical benefit.[25] For the purposes of this guidance, these categories of endpoints are referred to as reasonably likely surrogate endpoints and reasonably likely intermediate clinical endpoints, respectively.

1. Surrogate Endpoints

A surrogate endpoint is generally a biomarker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit but is not itself a measure of clinical benefit. In general, depending on the strength of the evidence supporting the ability of a biomarker to predict clinical benefit, the biomarker may be (1) a surrogate endpoint that is known to predict clinical benefit (i.e., a validated surrogate endpoint that could be used for traditional approval); (2) a surrogate endpoint that is reasonably likely to predict a drug's intended clinical benefit (i.e., a reasonably likely surrogate endpoint that could be the basis for accelerated approval); or (3) a biomarker for which there is insufficient evidence to support reliance on the biomarker as either kind of surrogate endpoint (i.e., an endpoint that cannot be used to support accelerated or traditional approval of a marketing application).[26] There are many serious diseases with an unmet medical need for which available biomarkers lack the necessary evidence to support a conclusion that they are reasonably likely to predict clinical benefit. Such biomarkers are not suitable to support either accelerated or traditional approval. In these cases, sponsors should consult with the appropriate review division regarding the path forward.

Examples of reasonably likely surrogate endpoints that FDA has used to support accelerated approval include the following:

- Sputum culture conversion from positive to negative during treatment of pulmonary tuberculosis, either as a time-to-conversion analysis or at a fixed time point after randomization, has been considered reasonably likely to predict the clinical benefit of resolution of infection.[27]

- A decrease in iron stores for patients with iron overload caused by thalassemia has been considered reasonably likely to predict a decrease in transfusion-related adverse events caused by iron overload in the body.

- The extent of liver inflammation or fibrosis has been considered reasonably likely to predict long-term clinical benefit in adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis.

[25] A clinical benefit is a positive therapeutic effect that is clinically meaningful in the context of a given disease. The clinical benefit must be weighed against a treatment's risks to determine whether there is an overall benefit for patients (i.e., a positive benefit-risk profile).

[26] See FDA's web page Surrogate Endpoint Resources for Drug and Biologic Development at https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development.

[27] See the draft guidance for industry *Pulmonary Tuberculosis: Developing Drugs for Treatment* (December 2022) for additional information. When final, this guidance will represent FDA's current thinking on this topic.

- An increase in hemoglobin (iron-containing protein in red blood cells) greater than 1 gram per deciliter after 24 weeks of treatment has been considered reasonably likely to predict improvement in how patients with sickle cell disease feel or function.

2. Intermediate Clinical Endpoints

An intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on IMM and may support accelerated approval when it is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit. An important threshold question is whether the demonstrated therapeutic effect on the intermediate clinical endpoint alone would be a basis for traditional approval. Approvals based on clinical endpoints (other than IMM) will be considered under accelerated approval only when it is critical to confirm the effects on IMM or other clinical benefit. FDA believes intermediate clinical endpoints generally could be used to support accelerated approval in certain situations, such as:

- A study demonstrates a short-term benefit for a chronic disease where a longer duration of effect is necessary for clinically meaningful benefit, and the short-term benefit observed is considered reasonably likely to predict a longer duration of effect.

- An intermediate clinical endpoint 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.

An example of a case in which FDA has used an intermediate clinical endpoint to support accelerated approval includes:

- A treatment for active cerebral adrenoleukodystrophy in boys 4–17 years of age was approved based on major functional disability-free (MFD-free) survival at 24 months following first neurologic functional score ≥ 1. Under accelerated approval, the sponsor was required to conduct postmarketing studies to confirm long-term MFD-free survival.

Sponsors considering a development program for accelerated approval based on an intermediate clinical endpoint should discuss their development program with the appropriate review division early in drug development.

3. Early Consultation on Novel Endpoints to Support Accelerated Approval

Early consultation between review teams and sponsors is critical for development programs where a sponsor intends to use a novel surrogate or intermediate clinical endpoint as the basis for accelerated approval.[28] These discussions could occur at milestone meetings (e.g., during Type B end-of-phase 1 and end-of-phase 2 meetings, as well as Type C meetings). Since it may

[28] Sponsors should seek input on endpoints for accelerated approval, whether novel or previously relied-upon, when they interact with the Agency on their development programs.

require additional preclinical or clinical data to provide sufficient support for the proposed surrogate, sponsors should seek early interactions with the Agency.

Given the importance of developing novel endpoints for more-efficient drug development, FDA has also established processes specifically for early consultation on new surrogate endpoints. Sponsors with clinical data for the investigational drug to support a novel biomarker as a surrogate endpoint for accelerated approval can consider submitting a Type C meeting request to discuss the feasibility of using that surrogate endpoint as a primary efficacy endpoint and to identify any gaps in knowledge and how they might be addressed.[29] Sponsors considering novel intermediate clinical endpoints should also contact the appropriate review division for guidance on seeking early consultation. For rare diseases, sponsors may consider submitting a Rare Disease Endpoint Advancement (RDEA) Pilot Program proposal to collaborate with FDA on the development of a novel surrogate or intermediate clinical endpoint intended to support accelerated approval for a rare disease treatment. If the RDEA Pilot Program proposal is selected by FDA, the Agency will conduct an initial meeting and up to three follow-up meetings.[30]

B. Evidentiary Criteria for Accelerated Approval

Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.[31] For effectiveness, the standard is substantial evidence based on adequate and well-controlled clinical investigations.[32] For safety, the standard is having sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.[33] An application for accelerated approval should also include adequate evidence that a proposed surrogate endpoint or an intermediate clinical endpoint is reasonably likely to predict the intended clinical benefit of a drug.

Determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect, and the empirical evidence to support that relationship. Such empirical evidence may include ". . . epidemiological, pathophysiological, therapeutic,

[29] See section K.3 of the PDUFA VII commitment letter (https://www.fda.gov/media/151712/download). To qualify for this consultation, sponsors must submit a complete meeting background package, including preliminary human data indicating impact of the drug on the biomarker at a dose that appears to be generally tolerable, at the time the Type C meeting request is made. Additional information to assist sponsors in submitting a Type C meeting request for discussion of novel surrogate endpoints is available on FDA's web page at https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development.

[30] For additional information on the RDEA Pilot Program, see FDA's web page at https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program.

[31] Sections 505(d) and 506(e)(2) of the FD&C Act.

[32] Section 505(d)(5) of the FD&C Act.

[33] Section 505(d)(1) of the FD&C Act.

pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."[34] Evidence of pharmacologic activity alone is not sufficient.[35] Clinical data should be provided to support a conclusion that an effect on the surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict the intended clinical benefit.[36]

In making the judgment as to whether a drug's effect on a given endpoint is reasonably likely to predict clinical benefit, FDA considers all relevant evidence and may consult external experts, including through consulting advisory committees, as needed and as permitted by law. This guidance provides an overview of some of the important factors to consider in identifying and assessing whether surrogate endpoints or intermediate clinical endpoints are reasonably likely to predict clinical benefit. This guidance does not, however, address the specific clinical evidence needed to support a conclusion that a particular surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict clinical benefit, because such evidence is case-specific and is not readily generalizable.

The extent to which a drug's effect on a surrogate endpoint predicts clinical benefit is critical in determining whether the endpoint might be appropriate to support accelerated approval or traditional approval. Some effects on well-established, disease-related biomarkers may have little or no ability to predict clinical benefit, or their ability to predict benefit may vary depending on the disease or the intervention. For example, in a patient with a fever caused by an infectious disease, a fall in a patient's body temperature in response to a fever-reducing drug does not predict the drug's effect on the disease. On the other end of the spectrum, there may be some instances in which a drug's effect on a surrogate endpoint is well understood to predict positive effects on the disease process. In those cases, the endpoint may be appropriate to support traditional approval. For example, lowering blood pressure has been shown repeatedly, with a wide variety of drugs, to reduce the incidence of stroke and cardiovascular disease in people with hypertension.

In other instances, the relationship between a surrogate endpoint and the disease process may be sufficiently well-understood to conclude that an effect on the surrogate endpoint is reasonably likely to predict clinical benefit, such that the endpoint might be appropriate to support accelerated approval. Data showing that, in studies of interventions that improve a clinical outcome, the extent of change in the proposed surrogate correlates with the extent of improvement typically provide the strongest support for a surrogate endpoint. Such information, however, is often not available or very limited in settings such as rare diseases. In such circumstances, FDA will weigh information from other available sources, including preclinical animal models, epidemiological data, and relevant clinical data, to determine if the convergence of evidence supports the surrogate as reasonably likely to predict the intended clinical benefit.

[34] Section 506(c)(1)(B) of the FD&C Act.

[35] 57 FR 58942.

[36] In certain circumstances, such as development programs for therapies for rare diseases where there is data supporting a relationship between the target of the therapy and a surrogate endpoint, particularly certain gene therapies for genetic disorders, FDA may determine that clinical data are not needed based on the strength of the totality of the evidence provided supporting the surrogate endpoint (i.e., compelling nonclinical data could be supportive).

Examples of factors to consider in identifying and assessing a surrogate endpoint include the following:

- The extent to which the pathophysiology of the disease and the role of the surrogate endpoint in that pathophysiology is understood — In some cases, surrogate endpoints may be well-understood in terms of their relationship to the underlying mechanism of the disease (e.g., elevated uric acid and gout, low thyroxine levels and hypothyroidism, high ammonia levels and certain urea cycle disorders). However, if the disease process is complex, has multiple pathophysiologic or causal pathways, or is poorly understood, it may be difficult to determine whether an effect on a surrogate endpoint would be reasonably likely to translate into a meaningful clinical effect.

- Whether there is reliable and consistent epidemiologic evidence supporting correlation between the surrogate endpoint and the clinical outcome of interest — The source and nature of the evidence are important. For example, more persuasive evidence may come from prospective, longitudinal studies showing strong correlation and precisely defining the relationship. However, such a relationship does not necessarily establish that the drug's effect on either the surrogate or clinical endpoint(s) will be favorable (e.g., failure of drugs that effectively lower premature ventricular beat rates or raise high-density lipoprotein (HDL) cholesterol to have the expected cardiovascular benefits).

- Whether 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 — This factor would generally be more persuasive if the drug is in the same or a closely related pharmacological class.

The evaluation of a surrogate endpoint will also be context-dependent. For example, it may be challenging in some rare disease settings to obtain data from multiple clinical trials of other drugs to support a relationship between drug effects on the surrogate endpoint and drug effects on the clinical endpoint. In the absence of such data, developing a strong understanding of the pathophysiology of the disease and the role of the surrogate endpoint in that pathophysiology becomes even more critical. Furthermore, the evaluation of whether a drug effect on a surrogate endpoint is reasonably likely to predict clinical benefit will also depend on the magnitude and duration of the effect on the surrogate endpoint. There may be an expectation for an effect on the surrogate endpoint to be at least a specific size to be reasonably likely to predict clinical benefit or to support a favorable benefit-risk assessment, particularly if there are potential serious drug risks.

C. Confirmatory Trials

For drugs granted accelerated approval, sponsors conduct confirmatory trials that must be completed postapproval to verify and describe the effect on IMM or other clinical benefit.[37]

1. Timely Conduct of Confirmatory Trials

Confirmatory trials must be completed with due diligence.[38] FDA has interpreted the due diligence requirement to mean that sponsors must commit sufficient resources to conduct the trial(s) intended to verify the clinical benefit expeditiously so that a determination of whether the drug provides the expected clinical benefit can be made as soon as possible.

When sponsors intend to seek accelerated approval, they should consult with FDA regarding postapproval confirmatory trial(s) early in the drug development program, and there should be agreement by FDA on the design and conduct of the confirmatory trial(s) to help ensure interpretable results. The protocol for a confirmatory trial should be developed and submitted to FDA as early as possible, and timelines for the trial should be specified; for example, timelines for enrollment and trial completion should be stipulated. The confirmatory trial's design should ensure that the trial will be completed on timelines specified by FDA. FDA encourages sponsors to submit draft protocols to FDA during their development program to allow for sufficient time to review and discuss in preparation for submitting their final protocol.[39]

Discussions with FDA about using accelerated approval should come early in the development program, and confirmatory trial(s) should generally be underway at the time the marketing application is submitted. Except in limited circumstances, FDA intends to require that confirmatory trial(s) be underway prior to granting accelerated approval.[40]

For all accelerated approvals, no later than the date of accelerated approval, FDA will set forth conditions for the progress of confirmatory trial(s). Such conditions may include enrollment targets, the target date of study completion, or other milestones, to help ensure that the confirmatory trial is completed in a timely manner.[41] Sponsors should ensure that all needed resources are provided to meet the specified timelines. In addition, sponsors should diligently monitor trial progress and be prepared to make appropriate modifications when enrollment is below expected levels or the trial is otherwise not progressing as intended. This may include adding resources, adding sites, or making other appropriate protocol changes.

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[37] Section 506(c)(2)(A)(i) of the FD&C Act and 21 CFR 314.510 and 601.41. Where confirmatory trials verify clinical benefit, FDA generally will terminate the requirement (21 CFR 314.560 and 601.46). References to a confirmatory trial should be understood to mean one or more trials, as appropriate for the relevant product.

[38] Section 506(c)(3)(A)(i) of the FD&C Act and 21 CFR 314.510 and 601.41.

[39] FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

[40] See section 506(c)(2)(D) of the FD&C Act.

[41] See section 506(c)(2)(C) of the FD&C Act.

Sponsors are required to submit reports on the progress of confirmatory trials to FDA approximately every 180 days.[42]

2. Other Aspects of Confirmatory Trial Design

Generally, the confirmatory trial would evaluate a clinical endpoint that directly measures clinical benefit in the same disease population that was studied to support accelerated approval. In some cases, however, the commercial availability of a drug following accelerated approval may make it difficult to enroll patients for whom the drug is indicated. A confirmatory trial may be conducted in a different but related population that is capable of verifying the predicted clinical benefit, such as in a population with a different stage of the same disease. This is often the case in oncology, where at the time of accelerated approval of a drug for late-stage disease, a confirmatory trial is typically underway in an earlier stage of the same cancer.

There are also cases in which, rather than using a clinical endpoint to provide persuasive evidence of clinical benefit, it may be appropriate to use additional evaluation (i.e., longer trial duration) of the same surrogate endpoint that was used to support accelerated approval in the same population. For example, historically, in HIV treatment, an effect on viral load of relatively short duration (24 weeks) was considered reasonably likely to predict clinical benefit, supporting accelerated approval. However, an effect of longer (48 weeks) viral load suppression was more convincingly related to durable clinical benefit in the setting of lifelong therapy and thus was used to verify clinical benefit. Given that HIV-RNA is a now considered a validated surrogate for predicting efficacy of antiretrovirals, a shorter-term effect on HIV-RNA can support traditional approval for antiretrovirals.[43]

Further, it may be possible for the same clinical trial(s) to support accelerated approval and later fulfill the requirement to verify and describe clinical benefit 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. In such a case, the protocol and the statistical analysis plan should clearly account for an analysis of the surrogate endpoint data to provide support for accelerated approval, with continuation of the adequate and well-controlled trial(s) to obtain data on the endpoint that will be the basis for verifying the clinical benefit. The trial design should include planned processes (e.g., firewalls, data access, and communication plans) to maintain blinding to treatment assignment and confidentiality of unblinded interim clinical endpoint results postapproval, as appropriate, and these aspects of the trial design should be discussed with FDA.

Sponsors may be able to use other novel approaches in studies designed to verify and describe clinical benefit, such as adaptive designs, enrichment strategies, trials with pragmatic elements, or decentralized trials. In general, the considerations described in FDA's guidance documents on

[42] See section 506B(a)(2) of the FD&C Act.

[43] See the guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015).

the use of novel trial designs in the development and regulatory review of drugs and biological products can be applied to the design of confirmatory trials.[44] Sponsors considering novel clinical trial designs to verify and describe clinical benefit should discuss their plans with the appropriate review division as they are developing their protocol(s). Because novel trial designs often warrant additional discussions between sponsors and FDA, sponsors should plan to initiate these consultations early enough in the development process to ensure that the confirmatory trial(s) can be underway at the time of accelerated approval. Sponsors can also seek input on novel confirmatory trial designs through FDA's Complex Innovative Trial Design Meeting Program.[45] If a sponsor's confirmatory trial design proposal meets the eligibility criteria for the requested meeting program, FDA may select the submission for participation.

Sponsors should take steps to facilitate high retention of participants in confirmatory trials. Additionally, sponsors are encouraged to incorporate patient perspectives into the design of a confirmatory trial, which may enhance recruitment and retention, especially for rare disease populations.

D. Other Conditions of Accelerated Approval

For a drug approved under accelerated approval, the drug labeling must include a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits in the INDICATIONS AND USAGE section.[46] The information in this section generally should also acknowledge that the drug was approved based upon accelerated approval and that continued approval for the drug may be contingent upon verification and description of clinical benefit in a confirmatory trial or trials.

Unless otherwise informed by the Agency, an applicant must submit to the Agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval.[47] After 120 days following marketing approval, unless otherwise informed by the Agency, the applicant must submit promotional materials at least

[44] See, for example, the guidances for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (December 2019) and *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* (March 2019). See also the draft guidance for industry *Decentralized Clinical Trials for Drugs, Biological Products, and Devices* (May 2023). When final, this guidance will represent FDA's current thinking on this topic.

[45] See FDA's website for additional information on this program, including eligibility criteria and submission processes, available at https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program.

[46] See 21 CFR 201.57(c)(2)(i)(B); guidance for industry *Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway*.

[47] 21 CFR 314.550 and 601.45.

30 days prior to the intended time of initial dissemination of the promotional labeling or initial publication of the advertisement.[48]

As a general matter, unless stated otherwise in law or regulation, sponsors should assume that the requirements applicable to all approved marketing applications, including the postmarketing recordkeeping and safety reporting requirements provided in 21 CFR 314.80 and 314.81, also apply to marketing applications approved under accelerated approval.[49] Questions regarding these requirements should be directed to the relevant review division.

V. WITHDRAWAL OF ACCELERATED APPROVAL

In addition to defining a pathway for accelerated approval, the FD&C Act also provides expedited withdrawal procedures for drugs approved under accelerated approval if certain conditions are met. This section describes the procedures for expedited withdrawal of FDA approval for a drug approved under accelerated approval.

A. Statutory Procedures for Expedited Withdrawal of Accelerated Approval

Section 506(c)(3)(A) of the FD&C Act, as amended by section 3210 of the Consolidated Appropriations Act, 2023, provides that FDA may use expedited procedures to withdraw approval of a drug that has received accelerated approval if:

> (i) the sponsor fails to conduct any required postapproval study of the product with due diligence, including with respect to conditions specified by the Secretary under paragraph (2)(C) [of section 506(c)];
>
> (ii) a study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the product fails to verify and describe such effect or benefit;
>
> (iii) other evidence demonstrates that the product is not shown to be safe or effective under the conditions of use; or
>
> (iv) the sponsor disseminates false or misleading promotional materials with respect to the product.[50]

Section 506(c)(3)(B) provides that the expedited procedures for such withdrawals consist of:

> (i) providing the sponsor with—
> (I) due notice;
> (II) an explanation for the proposed withdrawal;

[48] Ibid.

[49] 21 CFR 314.540

[50] Section 506(c)(3)(A) of the FD&C Act.

(III) an opportunity for a meeting with the Commissioner or the Commissioner's designee; and

(IV) an opportunity for written appeal to—

(aa) the Commissioner; or

(bb) a designee of the Commissioner who has not participated in the proposed withdrawal of approval (other than a meeting pursuant to subclause (III)) and is not subordinate of an individual (other than the Commissioner) who participated in such proposed withdrawal;

(ii) providing an opportunity for public comment on the proposal to withdraw approval;

(iii) the publication of a summary of the public comments received, and the Secretary's response to such comments, on the website of the Food and Drug Administration; and

(iv) convening and consulting an advisory committee on issues related to the proposed withdrawal, if requested by the sponsor and if no such advisory committee has previously advised the Secretary on such issues with respect to the withdrawal of the product prior to the sponsor's request.[51]

B. General Considerations Prior to Proposing Expedited Withdrawal

The Agency generally expects that any proposal to withdraw approval of a drug that has been granted accelerated approval will be issued by the center or centers (hereafter, Center) that approved the drug. When the data or other information received by the Agency raises concerns that one or more of the criteria for withdrawing approval may have been met, responsible officials within the Center should discuss their concerns with the sponsor and seek an appropriate resolution. Such discussions may result in the sponsor's voluntary request for withdrawal of approval under 21 CFR 314.150 or 21 CFR 601.5(a) or other regulatory actions, as appropriate, depending on the circumstances.

If the Center is considering whether to propose withdrawing approval of a drug that has been granted accelerated approval, it should generally convene an advisory committee to request the committee's advice on whether one or more of the criteria for withdrawal in section 506(c) of the FD&C Act has been met and any other issues that may be relevant to whether approval should be withdrawn. Doing so will provide an opportunity for a robust, public discussion of the issues and will provide the committee's advice to the Center before the Center decides whether to propose withdrawing approval. FDA strongly recommends that a sponsor submit, if it had not already, any data and evidence and any objections to withdrawal that the sponsor considers relevant so that they may be considered at this stage.

If the Center concludes that one or more of the conditions for withdrawal under section 506(c)(3)(A) have been met and withdrawal is appropriate, it should issue a proposal to withdraw approval, beginning the withdrawal process under section 506(c)(3)(B).

[51] Section 506(c)(3)(B).

C. Implementation of the Expedited Withdrawal Procedures

As noted previously, the expedited procedures for withdrawing accelerated approval require FDA to provide the sponsor with (1) due notice, (2) an explanation for the proposed withdrawal, (3) an opportunity to meet with the Commissioner or a designee of the Commissioner (Commissioner/designee), (4) an opportunity for written appeal to the Commissioner, or to a designee who has not participated in the proposed withdrawal of approval and is not a subordinate of an individual (other than the Commissioner) who participated in such proposed withdrawal, and (5) the opportunity for an advisory committee meeting on issues related to the proposed withdrawal if requested by the sponsor and an advisory committee has not previously advised FDA on such issues with respect to the withdrawal of the product prior to the sponsor's request. In addition, FDA must provide an opportunity for public comment on the proposal to withdraw approval and publish on FDA's website a summary of public comments received and FDA's response to such comments.

This section provides information on how FDA plans to implement these statutory procedures.[52]

1. Providing the Sponsor With Due Notice and an Explanation for the Proposed Withdrawal

Generally, the proposal to withdraw approval under section 506(c) of the FD&C Act should be issued with the concurrence of the Center director. The Center should send the sponsor a written notice to advise the sponsor of the proposal to withdraw and provide the explanation for the proposed withdrawal.[53]

The written notice to the sponsor should, among other things:

- Advise the sponsor of the statutory opportunity for a meeting with and/or a written appeal to the Commissioner/designee under section 506(c)(3)(B)(i)(III) and (IV) of the FD&C Act.

- State whether an advisory committee has advised on the issues relating to the proposed withdrawal such that it would not be necessary to convene an advisory committee to discuss these issues under section 506(c)(3)(B)(iv).

- Request that the sponsor promptly (or within a definite period specified in the written notice) indicate whether it intends to submit a written appeal, request a meeting with the Commissioner/designee or, if there was not a previous advisory committee meeting on

[52] This section of the guidance focuses on FDA's policies for expedited withdrawal of approval under section 506(c)(3)(B) of the FD&C Act for a drug or biological product granted accelerated approval. However, there may be circumstances when the Agency has identified another drug or biological product (for example, a generic drug or biosimilar product) whose application may be subject to withdrawal if the Agency withdraws approval of the drug or biological product that received accelerated approval. The additional procedures that would apply in a circumstance where another drug or biological product may be subject to withdrawal if the Agency withdraws approval from the accelerated approval drug are beyond the scope of this guidance.

[53] See section 506(c)(3)(B)(i)(I) and (II) and 506(c)(3)(B)(ii) of the FD&C Act.

the issues related to the proposed withdrawal, request an advisory committee meeting on such issues. Request that, alternatively, if the sponsor does not intend to use the procedures available under section 506(c)(3)(B), the sponsor indicate whether it requests voluntary withdrawal of the accelerated approval. If the sponsor requests or indicates an intent to use any of the procedures available under section 506(c)(3)(B), the Center should notify the Office of the Commissioner.

- Inform the sponsor that the Center, in accordance with section 506(c)(3)(B)(ii) of the FD&C Act, plans to publish a *Federal Register* notice (FRN) seeking public comment on its proposal for withdrawal and that the Center will submit to a public docket a copy of the written notice and any attachments provided to the sponsor (see also section V.C.2 for additional details on the FRN).

- Provide a time frame by which the sponsor is required to (1) submit a written appeal (if pursued) and any supporting data and information, (2) request a meeting with the Commissioner/designee, or (3) request the convening of an advisory committee on issues related to the proposed withdrawal if there was not a previous advisory committee meeting on such issues. The Center should choose a time frame that is reasonable under the circumstances. The Agency expects that 30 days from publication of the FRN seeking public comment on the proposed withdrawal should generally be sufficient. As previously noted, the responsible Center will typically have discussed the pivotal issues in the withdrawal proposal with the sponsor before issuing the proposal, and the Agency should avoid undue delay in conducting these proceedings. If the sponsor fails to pursue its statutory opportunities within the time frame specified in the notice, FDA may deem the sponsor to have *waived* its opportunity to submit an appeal and supporting materials, request a meeting with the Commissioner/designee, or when available, request the convening of an advisory committee regarding the proposed withdrawal unless the Center or the Commissioner/designee provides an extension.

- Notify the sponsor how to submit an appeal or any other response to the written notice (e.g., notifying the Agency of an intent to submit an appeal or submitting a request for a meeting). Generally, the appeal and any other response, including supporting materials, should be submitted to the docket opened for the written notice, with a copy provided to the Center. Additional instructions, for example, on submitting redacted materials, will come from the Commissioner/designee should the sponsor elect to pursue its opportunity for an appeal or meeting.

If upon receiving the written notice the sponsor voluntarily requests withdrawal of approval, the Center may decide to suspend the procedures for withdrawal under section 506(c)(3)(B) of the FD&C Act and instead withdraw approval under 21 CFR 314.150 or revoke licensure under 21 CFR 601.5(a), or the Center can, alternatively, decide to continue with withdrawal under the expedited procedures. The Center will generally contact the sponsor to confirm whether it would like to request voluntary withdrawal after the sponsor receives the written notice.

If the Agency determines that the sponsor has waived its opportunity for written appeal and the other procedures provided to the sponsor under section 506(c)(3), the Agency should decide whether to finalize the proposal to withdraw.

2. Providing an Opportunity for Public Comment on the Proposed Withdrawal

If the sponsor does not request voluntary withdrawal or the sponsor requests voluntary withdrawal but the Center decides to continue with withdrawal under the expedited procedures, the Center should publish an FRN providing an opportunity for public comment on the proposal to withdraw approval and also submit to a public docket a copy of the written notice sent to the sponsor and the Agency's explanation for the proposal to withdraw. The FRN should specify the period of time for the public to comment on the proposal to withdraw under section 506(c)(3)(B)(ii). The Agency expects that 30 days from the date of publication of the FRN should generally be sufficient. The Agency generally does not intend to extend the period of time to allow for public comment on any sponsor appeal or other proceedings conducted under section 506(c)(3).

3. Opportunity for a Written Appeal and Opportunity for a Meeting With the Commissioner/Designee

The sponsor's request for a written appeal or a meeting with the Commissioner or their designee under section 506(c)(3)(B)(i) may be addressed by the Commissioner or by a designee of the Commissioner who has not participated in the proposed withdrawal of approval (other than the meeting described in section 506(c)(3)(B)(III)) and who is not a subordinate of an individual (apart from the Commissioner) who has participated in the proposed withdrawal.

If a designee is selected, the Commissioner generally intends to designate FDA's Chief Scientist or one of the center directors of the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, or the Oncology Center of Excellence who was not involved in the proposal to withdraw. The Commissioner/designee may select a team of advisers to assist with review of the proposed withdrawal and any appeal and should select advisers who have not participated in the proposed withdrawal of approval. Generally, for consistency and efficiency, if a designee is selected, the designee for the written appeal will be the same as the designee for the meeting with the sponsor. If a designee becomes unable to act for any reason, a new designee may be selected by the Commissioner.

If the sponsor submits an appeal or requests other proceedings under section 506(c)(3)(B), the Commissioner/designee, as appropriate, may make rulings regarding the conduct of such proceedings. Such rulings regarding the conduct of the withdrawal proceeding should be provided to both the Center and the sponsor and submitted to the docket. During the pendency of the proceeding under section 506(c)(3), the sponsor and Center may direct requests or questions regarding any rulings or the conduct of the withdrawal proceeding to the Commissioner/designee. Apart from the sponsor's written appeal, and as discussed in subsections a and b, below, neither the Center nor the sponsor should submit substantive written materials to the Commissioner/designee that are not requested or otherwise agreed upon by the

Commissioner/designee (for example, the Commissioner/designee may establish a schedule for when materials should be submitted and meetings, if any, will occur).

a. Written appeal

In its written appeal, the sponsor should present its objections to the proposal to withdraw approval. The sponsor may submit any supporting data, information, or evidence on which the sponsor relies for its appeal, except that the sponsor may seek to incorporate by reference any data, information, or evidence submitted to the new drug application (NDA) or biologics license application (BLA) file or presented in briefing materials to an advisory committee convened to provide advice to the Agency on whether to withdraw the accelerated approval.

In general, if the Center convened an advisory committee in considering a proposal to withdraw approval, the sponsor should rely only on data, evidence, or analyses that were presented to such advisory committee, either at the meeting itself or in briefing materials (including information incorporated by reference), unless the data, evidence, or analyses were not reasonably available or their significance was not reasonably foreseeable at the time of the advisory committee meeting. Absent a showing of good cause (i.e., not reasonably available or reasonably foreseeable) for failing to present data, evidence, or analyses to any advisory committee previously convened for the purposes of evaluating whether the Agency should consider proposing withdrawal, the Commissioner/designee in evaluating the sponsor's appeal may decide not to consider such data, evidence, or analyses that was not previously presented. Accordingly, in its written appeal, the sponsor should identify any data, evidence, or analyses on which the written appeal relies that were not previously presented to the advisory committee, if one was convened in considering a proposal to withdraw approval, and explain both why such data, evidence, or analyses were not previously presented and why they are material to the appeal in light of previously considered data, evidence, and analyses.

The Center should be given an opportunity to submit a response to the written appeal, and the Commissioner/designee may specifically request that the Center submit such a response or address specific aspects of the appeal.

b. Meeting with the Commissioner/designee

If the sponsor requests a meeting with the Commissioner/designee, the Commissioner/designee should schedule the meeting to take place after any written appeal is submitted and after any written responses from the Center or sponsor.

The Commissioner/designee should establish the format for the meeting. The sponsor should be provided an opportunity to make a presentation, and the Commissioner/designee may provide in advance specific questions or topics for the sponsor to address. The Commissioner/designee should invite the Center to attend and may also invite the Center to present or to address specific questions. The meeting is not expected to be a decisional meeting. The Commissioner/designee should prepare meeting minutes that summarize the meeting and have them posted to the public docket. The Commissioner/designee may request a subsequent meeting, if necessary, or direct the sponsor and/or Center to address any follow-up questions through written submissions.

741
742 *4. Convening and Consulting an Advisory Committee*
743
744 Section 506(c)(3)(B)(iv) of the FD&C Act provides that the expedited withdrawal procedures
745 include convening and consulting an advisory committee on issues related to the proposed
746 withdrawal if requested by the sponsor and if no such advisory committee has previously advised
747 FDA on such issues with respect to the withdrawal of the product.
748
749 As previously noted, the Center should generally convene and consult an advisory committee on
750 whether one or more of the criteria for withdrawing approval have been met, and whether
751 approval should be withdrawn, before issuing a proposal to withdraw. Such a meeting is
752 expected to fulfill the advisory committee role contemplated by section 506(c)(3)(B)(iv), in
753 which case a second advisory meeting will not be necessary, even if requested by the sponsor. If
754 the sponsor requests that an advisory committee be convened under section 506(c)(3)(B)(iv), the
755 Commissioner/designee will decide whether to grant the request. A request under section
756 506(c)(3)(B)(iv) should not be granted if there was a previous advisory committee convened on
757 the issues related to the proposed withdrawal.
758
759 If the Commissioner/designee decides that an advisory committee should be convened and
760 consulted on issues relating to the proposed withdrawal, whether on the
761 Commissioner/designee's initiative or in response to a request from the sponsor, the
762 Commissioner/designee may request that the Center arrange and conduct the meeting and may
763 request the consideration of particular topics.
764
765 *5. Commissioner/Designee's Decision Including a Summary and Response to Public*
766 *Comments*
767
768 The Commissioner/designee's decision on the appeal should be based on information filed in the
769 docket for the withdrawal proceeding and, as appropriate, information that the sponsor submitted
770 to the NDA or BLA file for the product whose approval is at issue in the withdrawal proceeding,
771 and the record of any advisory committee consulted to consider issues related to the proposed
772 withdrawal (including for any of these sources information incorporated by reference). Upon a
773 finding on appeal that the studies do not verify clinical benefit of the drug or the available
774 evidence does not show the drug to be safe and effective under the conditions of use in the
775 approved labeling, the Commissioner/designee generally intends to withdraw accelerated
776 approval in the absence of unusual circumstances.
777
778 The Commissioner/designee's decision should include all of the following:
779
780 (1) An analysis of the statutory grounds for the proposed withdrawal and the sponsor's
781 objections to those grounds.
782
783 (2) A summary of the public comments and the response to such comments consistent with
784 section 506(c)(3)(B)(iii).
785

(3) An explanation of the basis for the Commissioner/designee's decision regarding whether to finalize the proposal to withdraw approval. If the Commissioner/designee finds that a statutory ground for withdrawal has been satisfied, the Commissioner/designee's decision should not address in detail the sponsor's arguments, if any, regarding why the Agency should nonetheless exercise its discretion to decline to withdraw approval—or the evidence, data, or analyses offered in support of those arguments—unless the Commissioner/designee determines that providing detailed analysis of those arguments is warranted in the interest of completeness and transparency. If the Commissioner/designee determines a detailed analysis is warranted, the Commissioner/designee should consider whether any detailed analysis submitted by the Center in support of the proposed withdrawal adequately addresses the sponsor's policy arguments and, if so, whether adopting the Center's analysis in the decision is appropriate.

The Center should post the Commissioner/designee's decision to the FDA website and take any actions necessary to implement the decision. The Commissioner/designee's decision will generally be considered final and, unless noted otherwise in the decision, will be considered effective upon issuance, including with respect to withdrawal, when applicable.

In the event that the Agency determined that the sponsor waived its opportunity for written appeal and the other procedures provided to the sponsor under section 506(c)(3) and the Agency decided to move forward with the proposal to withdraw by issuing an FRN providing an opportunity for public comment, a written decision should be issued by the Center or by the Commissioner/designee. The written decision should state whether approval will be withdrawn, summarize and respond to the public comments on the proposal to withdraw, and provide the Agency's reasons for the decision. The decision should be posted to the Agency's website, and the Center should take any actions necessary to implement the decision.

6. Communications Between the Commissioner/Designee and the Sponsor or the Center Issuing the Proposed Withdrawal

The Commissioner/designee and any advisers designated for the Commissioner/designee's team should avoid substantive communications regarding the withdrawal proceeding with any individual or parties at the Agency or outside the Agency except on the public record.[54] Substantive oral communications regarding the withdrawal proceeding between the Center or sponsor and the Commissioner/designee's team should take place with both the sponsor and Center present, and a summary of such communications should be developed by the Commissioner/designee and placed in the public docket established for the proceeding. Written communications that the Center or sponsor submit to the Commissioner/designee's team should be posted to the public docket that is established for the proceeding, and the sponsor and Center should provide a copy of such communications to each other.

[54] The Agency is not required by section 506(c)(3)(B) of the FD&C Act or FDA regulations to observe separation of functions during the expedited withdrawal proceedings described in this guidance. The Agency is adopting the policies in section V.C.6 of this guidance to provide transparency around the expedited withdrawal proceedings.