Guidance for Industry

Expedited Programs for Serious Conditions—Drugs and Biologics

DRAFT GUIDANCE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)

June 2013
Procedural

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Expedited Programs for Serious Conditions—Drugs and Biologics

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TABLE OF CONTENTS

Guidance for Industry[1]
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The following four FDA programs are intended to facilitate and expedite development and review of new drugs[2] to address unmet medical need in the treatment of a serious or life-threatening[3] condition: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation (see Section IV for an overview of the programs). This guidance for industry provides a single resource for information on FDA's policies and procedures for these four programs as well as threshold criteria generally applicable to concluding that a drug is a candidate for these expedited development and review programs.

The provisions of this guidance, when finalized, will replace the current guidance for industry entitled *Fast Track Drug Development Programs—Designation, Development, and Application Review* (issued January 2006). The provisions of this guidance relating to available therapy, when finalized, will replace the current guidance for industry entitled *Available Therapy* (issued July 2004).[4]

FDA's guidance documents, including this guidance, 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.

[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) at the Food and Drug Administration.
[2] For the purposes of 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.
[3] Section III.A.1 explains that all references to serious conditions include life-threatening conditions.
[4] We update and issue guidances periodically. We recommend you check the FDA Web site to ensure that you have the most up-to-date version of a guidance. The guidances referenced in this document are available on the Drugs guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and the Biologics guidance page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

The programs described in this guidance are intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks. The Agency first formally articulated its thinking on expediting the availability of promising new therapies in regulations codified at 21 CFR part 312, subpart E.[5] The subpart E regulations are intended to speed the availability of new therapies to patients with serious conditions, especially when there are no satisfactory alternative therapies, while preserving appropriate standards for safety and effectiveness. The regulations call for earlier attention to drugs that have promise in treating such conditions, including early consultation with FDA for sponsors of such products, and efficient trial design, potentially relying on well-controlled Phase 2 studies for evidence of effectiveness. The subpart E regulations specifically recognize that patients and physicians are generally willing to accept greater risk (and uncertainty about benefit) for a treatment for a serious condition where there is an unmet medical need.

III. CONCEPTS FOR EXPEDITED PROGRAMS

The programs that are the subject of this guidance, fast track designation, breakthrough therapy designation, accelerated approval, and priority review, are summarized in Section IV and described in more detail below. As referenced above, the criteria for all four of these expedited programs draw on the same principle of addressing unmet medical need in the treatment of a serious condition, which is discussed below.

A. Serious Condition

1. Whether a Condition Is Serious

FDA generally intends to interpret the term "serious" consistent with how it has done so in the past for the purposes of accelerated approval,[6] fast track designation,[7] and expanded access to investigational drugs for treatment use.[8] A serious disease or condition is defined in the expanded access regulations as:

> "a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on

[5] 21 CFR part 312, subpart E; Food and Drug Administration, Interim Rule, Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses (53 FR 41516, October 21, 1988).

[6] Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992).

[7] Guidance for Industry: FastTrack Drug Development Program — Designation, Development, and Application Review (which will be superceded by this final guidance and withdrawn).

[8] 21 CFR part 312, subpart I.

such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."[9]

This definition is derived from and consistent with the descriptions of the term in the preamble to the accelerated approval proposed rule and the fast track guidance.

Note: For the purposes of this guidance, FDA considers the term *condition* to include a disease or illness. All conditions meeting the definition of life-threatening as set forth at 21 CFR 312.81(a) would also be serious conditions.

2. Whether the Drug Is Intended to Treat a Serious Condition

As referenced in Section IV, as a general matter, the statutory and regulatory eligibility criteria for expedited programs require that a drug be intended to treat a serious condition. To satisfy this criterion, a drug must be intended to have an effect on a serious aspect of a condition, such as a direct effect on a serious manifestation or symptom of a condition, or other intended effects, including:

- A diagnostic product intended to improve diagnosis or detection of a serious condition in a way that would lead to improved outcomes
- A product intended to improve or prevent a serious treatment-related side effect (e.g., serious infections in patients receiving immunosuppressive therapy)
- A product intended to avoid a serious adverse effect associated with available therapy for a serious condition (e.g., less cardiotoxicity than available cancer therapy)

B. Available Therapy

For purposes of this guidance, FDA generally considers *available therapy* (and the terms *existing treatment* and *existing therapy*) as a therapy that:

- Is approved or licensed in the United States for the same indication being considered for the new drug and
- Is relevant to current U.S. standard of care (SOC) for the indication

Approval or Licensure: Only in rare cases will a treatment that is not approved for the indicated use or is not FDA-regulated (e.g., surgery) be considered available therapy. In those cases, FDA may consider an unapproved or unlicensed therapy to constitute "available therapy" if the safety and effectiveness of the use is supported by compelling evidence, including evidence in the published literature (e.g., certain established oncologic treatments).

[9] 21 CFR 312.300(b)(1).

U.S. Standards of Care: There may be a substantial number of approved therapies with varying relevance to how a serious disease is currently treated in the United States, including therapies that are no longer used or are used rarely. FDA's available therapy determination generally focuses only on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive Cancer Network, American Academy of Neurology) based on clinical evidence and other reliable information that reflects current clinical practice. In the absence of a well-established and documented SOC, FDA may consult with special government employees or other experts for advice in assessing whether an approved therapy is relevant to the current SOC. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic or proteomic marker), the SOC for the broader population, if there is one, generally is considered available therapy for the subset.

Over the course of new drug development, it is foreseeable that the SOC for a given condition may evolve (e.g., because of approval of a new therapy or new information about available therapies). FDA will determine what constitutes available therapy at the time of the relevant regulatory decision for each expedited program the sponsor intends to use (e.g., generally early in development for fast track and breakthrough therapy designations, at time of biologics license application (BLA) or new drug application (NDA) submissions for priority review designation, during BLA or NDA review for accelerated approval).

A drug granted accelerated approval based on a surrogate or clinical endpoint and for which clinical benefit has not been verified is not considered available therapy.

A drug approved under accelerated approval with restricted distribution and a drug approved with a risk evaluation and mitigation strategy (REMS) that includes elements to assure safe use (ETASU) under section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) would be considered available therapy only if the study population for the new drug would be eligible to receive the approved drug under the restricted distribution program or ETASU REMS.

C. Unmet Medical Need

An unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs).

1. Where There Is No Available Therapy

If no therapy exists for a serious condition, there is clearly an unmet medical need.

2. Where There Is Available Therapy

When available therapy exists for a condition, a new treatment generally would be considered to address an unmet medical need if the treatment:

- Has an effect on a serious outcome of the condition that is not known to be influenced by available therapy (e.g., progressive disability when the available therapy has shown an effect on symptoms but has not shown an effect on progressive disability)

- Has an improved effect on a serious outcome(s) of the condition compared to available therapy (e.g., superiority of the new drug used alone or in combination with available therapy in an active- or historically-controlled trial assessing an endpoint reflecting mortality or serious morbidity)

- Has a benefit for patients who are unable to tolerate available therapy or whose disease has failed to respond to available therapy, or the treatment can be used effectively with other critical agents that cannot be combined with available therapy

- Provides efficacy similar to those of available therapy, while (1) avoiding serious toxicity that occurs with available therapy, (2) avoiding less serious toxicity that is common and causes discontinuation of treatment of a serious condition, or (3) reducing the potential for harmful drug interactions

- Provides similar safety and efficacy as available therapy but with another documented benefit, such as improved compliance, that is expected to lead to an improvement in serious outcomes

- Addresses an emerging or anticipated public health need, such as a drug shortage

In some disease settings, a drug that is not shown to provide a direct efficacy or safety advantage over available therapy may nonetheless provide an advantage that would be of sufficient public health benefit to qualify as meeting an unmet medical need. For example, in a condition for which there are approved therapies that have a modest response rate or significant heterogeneity in response, a drug with a novel mechanism of action (but comparable safety and effectiveness) could have the potential to provide an advantage over available therapy. In such a case, the novel mechanism of action should have a well-understood relationship to the disease pathophysiology. In addition, there should be a reasonable basis for concluding that a significant number of patients may respond differently to the new drug compared to available therapy. For example, mechanistic diversity, even without a documented efficacy or safety advantage, could be advantageous in disease settings in which drugs become less effective or ineffective over time. For example, infectious disease drugs or targeted cancer therapies with novel mechanisms of action, although appearing to have comparable efficacy across the disease population, could benefit patients who no longer respond to available therapy. Accordingly, FDA intends to consider a range of potential advantages over available therapy beyond those shown in head-to-head comparisons.

3. Where the Only Available Therapy Was Approved Under the Accelerated Approval Program Based on a Surrogate or Clinical Endpoint and Clinical Benefit Has Not Yet Been Verified

As discussed in Section VII, FDA recognizes, as a general matter, that it is preferable to have more than one treatment approved under the accelerated approval provisions because of the possibility that clinical benefit may not be verified in post-approval confirmatory trials. FDA may therefore consider products as addressing unmet medical need notwithstanding the availability of therapies with accelerated approval.

IV. OVERVIEW OF EXPEDITED PROGRAMS

The table provides an overview of the four expedited programs. Additional details on the specific programs are found in the sections that follow.

Comparison of FDA's Expedited Programs for Serious Conditions

	Fast Track	**Breakthrough Therapy**	**Accelerated Approval**	**Priority Review**
Nature of program	Designation	Designation	Approval Pathway	Designation
Reference	• Section 506(b) of the FD&C Act, as added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), and amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)	• Section 506(a) of the FD&C Act, as added by section 902 of FDASIA	• 21 CFR part 314, subpart H • 21 CFR part 601, subpart E • Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA	• Prescription Drug User Fee Act of 1992
Qualifying criteria	• A drug that is intended to treat a serious condition **AND** nonclinical or clinical data demonstrate the potential to address unmet medical need[a] **OR** • A drug that has been designated as a qualified infectious disease product[b]	• A drug that is intended to treat a serious condition **AND** preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies[a]	• A drug that treats a serious condition **AND** generally provides meaningful advantage over available therapies **AND** demonstrates 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 an effect on irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	• An application (original or efficacy supplement) for a drug that treats a serious condition **AND** if approved, would provide a significant improvement in safety or effectiveness **OR** • Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A[c] **OR** • An application for a drug that has been designated as a qualified infectious disease product[d] **OR** • Any application or supplement for a drug submitted with a priority review voucher[e]

Comparison of FDA's Expedited Programs for Serious Conditions

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Nature of program	Designation	Designation	Approval Pathway	Designation
When to submit	• With IND or after • Ideally, no later than the pre-BLA or pre-NDA meeting	• With IND or after • Ideally, no later than the end-of-Phase 2 meeting	• The sponsor should ordinarily discuss the possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned endpoint as a basis for approval and discussing the confirmatory trials.	• With original BLA, NDA, or efficacy supplement
Timelines for FDA response	• Within 60 calendar days of receipt of request	• Within 60 calendar days of receipt of request	• Not specified	• Within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement
Features	• Actions to expedite development and review • Rolling review	• All fast track designation features • Intensive guidance on efficient drug development during IND, beginning as early as Phase 1 • Organizational commitment involving senior managers	• Approval based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	• Shorter clock for review of marketing application (6 months compared to the 10-month standard review)
Additional considerations	• Designation may be withdrawn if it no longer meets fast track qualifying criteria	• Designation may be withdrawn if it no longer meets breakthrough therapy qualifying criteria	• Submission of copies of promotional materials for review • Conduct any required postapproval trials to verify and describe the anticipated clinical benefit or effect on IMM • Subject to expedited withdrawal	• Designation will be assigned at the time of original BLA, NDA or efficacy supplement filing

[a] Designation applies to a combination of a drug (either alone or in combination with other drugs) and the specific use for which it is being studied. Where appropriate, designation may be granted to development of a new use of an FDA-approved drug.

[b] Title VIII of FDASIA entitled "Generating Antibiotic Incentives Now (GAIN)" provides incentives for the development of antibacterial and antifungal drugs for human use intended to treat serious and life threatening infections. Under GAIN, a drug may be designated as a *qualified infectious disease product (QIDP)* if it meets the criteria outlined in the statute. A drug that receives QIDP designation is eligible under the statute for fast track designation and priority review. However, QIDP designation is beyond the scope of this guidance.

[c] Any supplement to an application under section 505 of the FD&C Act that proposes a labeling change pursuant to a report on a pediatric study under this section shall be considered to be a priority review supplement per section 505A of the FD&C Act as amended by section 5(b) of the Best Pharmaceuticals for Children Act.

[d] See footnote b above.

[e] Any application or supplement that is submitted with a priority review voucher will be assigned a priority review. Priority review vouchers will be granted to applicants of applications for drugs for the treatment or prevention of certain tropical diseases, as defined in section 524(a)(3) and (4) of the FD&C Act and for treatment of rare pediatric diseases as defined in section 529(a)(3) of the FD&C Act.

V. FAST TRACK DESIGNATION

Section 506(b) of the FD&C Act provides for the designation of a drug as a fast track product "if it is intended, whether alone or in combination with one or more other drugs, for the treatment of a *serious or life-threatening disease or condition*, and it *demonstrates the potential to address unmet medical needs* for such a disease or condition." This section describes the qualifying criteria (italicized terms) and the features (e.g., benefits) of fast track designation. Appendix 1 describes the fast track designation process.

A. Qualifying Criteria for Fast Track Designation

1. Serious Condition

See Section III.A.

2. Demonstrating the Potential to Address Unmet Medical Need

The type of information needed to demonstrate the potential of a drug to address an unmet medical need will depend on the stage of drug development in which fast track designation is requested. Early in development, evidence of activity in a nonclinical model, a mechanistic rationale, or pharmacologic data could be used to demonstrate such potential. Later in development, available clinical data should demonstrate the potential to address an unmet medical need. See Section III.C.

B. Features of Fast Track Designation

1. Actions to Expedite Development and Review

There are opportunities for frequent interactions with the review team for a fast track product. These include FDA-sponsor meetings, including pre-IND, end of Phase 1, and end of Phase 2 meetings to discuss study design, extent of safety data required to support approval, dose-response concerns, use of biomarkers, and other meetings as appropriate (i.e., to discuss accelerated approval, the structure and content of an NDA, and other critical issues).

In addition, such a product could be eligible for priority review if supported by clinical data at the time of BLA, NDA, or efficacy supplement submission.

2. Submission of Portions of an Application (Rolling Review)

If FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective, the Agency shall evaluate for filing, and may consider

reviewing portions of a marketing application before the sponsor submits the complete application (see Appendix 2).[10]

VI. BREAKTHROUGH THERAPY DESIGNATION

Section 506(a) of the FD&C Act provides for designation of a drug as a breakthrough therapy "if the drug is intended, alone or in combination with 1 or more other drugs, to treat a *serious or life-threatening disease or condition* and *preliminary clinical evidence* indicates that the drug may demonstrate substantial improvement over *existing therapies* on 1 or more *clinically significant endpoints*, such as substantial treatment effects observed early in clinical development." This section describes the qualifying criteria (italicized terms) and the features (e.g., benefits) of breakthrough therapy designation. Appendix 1 describes the breakthrough therapy designation process.

A. Qualifying Criteria for Breakthrough Therapy Designation

1. Serious Condition

See Section III.A.

2. Existing (or Available) Therapies

See Section III.B.

3. Preliminary Clinical Evidence

Unlike the information that could support fast track designation, which could include theoretical rationale, mechanistic rationale (based on nonclinical data), or evidence of nonclinical activity, breakthrough therapy designation requires preliminary clinical evidence of a treatment effect that would represent substantial improvement over available therapies for the treatment of a serious condition. Assessment of the treatment effect for the purposes of breakthrough therapy designation will be based on preliminary clinical evidence, which could include early clinical evidence of both clinical benefit and an effect on a mechanistic biomarker (generally derived from Phase 1 and 2 trials). Nonclinical information could support the clinical evidence of drug activity. In all cases, preliminary clinical evidence demonstrating that the drug may represent a substantial improvement over available therapy should involve a sufficient number of patients to be considered credible. However, FDA recognizes that the data cannot be expected to be definitive at the time of designation.

Ideally, preliminary clinical evidence would be derived from a study that compares the investigational drug to an available therapy (or placebo, if there is no available therapy) in clinical testing and shows superiority, or from a study that compares the new treatment plus SOC to the SOC alone. FDA encourages sponsors to obtain some preliminary comparative data of

[10] Section 506(d)(1) of the FD&C Act.

this kind early in development. Other types of clinical data that could also be persuasive include studies comparing the new treatment with historical experience (generally, FDA expects such data would be persuasive only if there is a large difference between the new treatment and historical experience).[11]

4. May Demonstrate Substantial Improvement on Clinically Significant Endpoint(s)

To support a breakthrough therapy designation, the preliminary clinical evidence must show that the drug may demonstrate "substantial improvement" over available therapy on one or more "clinically significant" endpoints.

Substantial Improvement: To determine whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, which could include duration of the effect, and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy. Such improvement will be clear when there is no available therapy or when available therapy shows only a modest response and the new therapy shows an effect on an important outcome. Where there is an effective available therapy, showing substantial improvement is more challenging.

Approaches to demonstrating preliminary clinical evidence of substantial improvement include:

- Direct comparison of a new drug to available therapy (or to no treatment if none exists) showing a much greater or more important response (e.g., complete response where the control treatment results in partial response). Such a trial could be conducted in treatment naïve patients or in those whose disease failed to respond to available therapies either as a comparison with the failed therapy (if ethically acceptable) or as a no-treatment controlled study.

- The new drug added to available therapy results in a much greater or more important response compared to available therapy in a controlled study or to a historical control. This trial also could be conducted in treatment naïve patients or in those whose disease failed to respond to available therapies.

- The new drug treats the underlying cause of the disease, in contrast to available therapies that treat only symptoms of the disease, and preliminary clinical evidence shows significant efficacy. In this case, the treatment effect is entirely new (i.e., has not been observed with available therapies). For example, a drug that targets a defective protein that is the underlying cause of a disease (whereas current therapies only treat the symptoms of the disease).

[11] Sponsors contemplating the use of historical controls should consult FDA's guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001, ICH) for more detailed discussions.

- The new drug reverses disease progression, in contrast to available therapies that only provide symptomatic improvement.
- The new drug has an important safety advantage that relates to serious adverse events compared to available therapies and has similar efficacy.

Clinically Significant Endpoint: For purposes of breakthrough therapy designation, FDA considers *clinically significant endpoint* generally to refer to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. It can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- An effect on an established surrogate endpoint

- An effect on a surrogate endpoint or intermediate clinical endpoint (see Section VII.B.2) considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)

- An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease

- A significantly improved safety profile compared to available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy

In a breakthrough therapy designation request, the sponsor should provide justification for why the endpoint, biomarker, or other findings should be considered clinically significant.

B. Features of Breakthrough Therapy Designation

1. All Fast Track Designation Features

Section 902 of FDASIA instructs FDA to take actions appropriate to expedite the development and review of a breakthrough therapy. Because a drug that qualifies for breakthrough therapy designation would also meet the standard for fast track designation, FDA has determined that it would be appropriate for the features of fast track designation to be available to a drug designated as a breakthrough therapy (see Section V.B).

2. Intensive Guidance on an Efficient Drug Development Program, Beginning as Early as Phase 1

As discussed previously, breakthrough therapy designation will usually mean that the effect of the drug will be large compared to available therapies. In such cases, the development program for the breakthrough therapy could be considerably shorter than for other drugs intended to treat the disease being studied. However, FDA notes that a compressed drug development program still must generate adequate data to demonstrate that the drug is safe and effective in order to

meet the statutory standard for approval.[12] Omitting components of the drug development program that are necessary for such a determination can significantly delay, or even preclude, marketing approval.

Sponsors can design an efficient clinical trial or trials in a number of ways. FDA will seek to ensure that the sponsor of a product designated as a breakthrough therapy receives timely advice and interactive communications in order to help the sponsor design and conduct a development program as efficiently as possible. During these interactions, the Agency may suggest, or a sponsor can propose, alternative clinical trial designs (e.g., adaptive designs, an enrichment strategy, use of historical controls) that may result in smaller trials or more efficient trials that require less time to complete. Such trial designs could also help minimize the number of patients exposed to a potentially less efficacious treatment (i.e., the control group treated with available therapy).

FDA anticipates that the review team and the sponsor will meet throughout drug development to address these and other important issues at different phases of development. In addition, a sponsor should be prepared for a more rapid pace for other aspects of the drug development (e.g., manufacturing (see Section IX.A), development of a necessary companion diagnostic).

3. Organizational Commitment Involving Senior Managers

FDA intends to expedite the development and review of a breakthrough therapy by, where appropriate, intensively involving senior managers and experienced review staff in a proactive collaborative, cross-disciplinary review. Where appropriate, FDA also intends to assign a cross-disciplinary project lead for the review team to facilitate an efficient review of the development program. The cross-disciplinary project lead will serve as a scientific liaison between the members of the review team (e.g., clinical; pharmacology-toxicology; chemistry, manufacturing, and controls (CMC); compliance; biostatistics) for coordinated internal interactions and coordinated communications with the sponsor through the review division's Regulatory Health Project Manager.

If a sponsor has not requested breakthrough therapy designation, FDA may suggest that the sponsor consider submitting a request if: (1) after reviewing submitted data and information (including preliminary clinical evidence), the Agency thinks the drug development program may meet the criteria for breakthrough therapy designation and (2) the remaining drug development program can benefit from the designation.

[12] Section 505(d) of the FD&C Act; Section 351(a) of the Public Health Service Act.

VII. ACCELERATED APPROVAL

The accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to:

> a product for a *serious or life-threatening condition* . . . upon a determination that the product has an effect on a *surrogate endpoint* that is *reasonably likely to predict clinical benefit*, or an effect on a *clinical endpoint that can be measured earlier than an effect on 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*.

Accelerated approval is usually contingent on a sponsor's agreement to conduct additional post-approval studies to verify and describe the drug's clinical benefit (see Sections VII.D.2 and VII.D.3).[13]

This section describes the qualifying criteria, relevant terms (italicized terms), and the conditions of accelerated approval. The FDASIA provisions facilitate somewhat broader use of accelerated approval to expedite patient access to important treatments for serious conditions. FDA believes the new provisions provide additional flexibility concerning the implications of available therapy on eligibility for accelerated approval (see Section VII.A.2). They also provide clarification concerning the use of clinical endpoints (herein referred to as intermediate clinical endpoints) as a basis for accelerated approval (see Section VII.B.2). Finally, the new provisions make clear that FDA has the authority to consider pharmacologic or other evidence developed using biomarkers or other scientific methods or tools, in conjunction with other data, in determining whether an endpoint is reasonably likely to predict clinical benefit (see Section VII.C.1).[14]

The accelerated approval pathway is most often useful in settings in which the disease course is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. For example, accelerated approval has been used extensively in drug development for a variety of cancers and human immunodeficiency virus (HIV) disease—diseases in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

Accelerated approval is generally less useful in more acute disease settings in which therapy is intended to provide a more near-term clinical benefit. In such settings, even if there are

[13] FDCA 506(c)(2)(A).

[14] FDCA 506(c)(1)(B). FDA regulations provide that the agency may consider "epidemiologic, therapeutic, pathophysiologic or other evidence" in determining whether an endpoint is reasonably likely to predict clinical benefit. FDASIA provides that FDA may consider "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

potentially predictive surrogate endpoints or intermediate clinical endpoints, there may be little or no time advantage for studies evaluating a surrogate or intermediate endpoint compared to studies evaluating the intended clinical benefit.

FDA encourages sponsors to communicate with the Agency early in development concerning the potential eligibility of the drug for accelerated approval, proposed surrogate or intermediate clinical endpoints, clinical trial designs, and study planning and conduct of confirmatory trials.

A. Qualifying Criteria for Accelerated Approval

At the time a product is given accelerated approval, there generally will be uncertainty about whether a surrogate endpoint or intermediate clinical endpoint predicts the drug's ultimate anticipated clinical benefit. The principal risk of this approach is the possibility that patients will be exposed to a drug that will ultimately not be shown to provide an actual clinical benefit. In addition, there may be fewer, smaller, or shorter clinical trials than is typical for a drug with traditional approval, which for example could mean there is less information about the occurrence of rare adverse events. For these reasons, accelerated approval is limited to a drug intended to treat a serious condition which appears to provide some meaningful advantage over available therapy.

1. Serious Condition

See Section III.A.

2. Meaningful Advantage Over Available Therapy

The accelerated approval regulations state that accelerated approval is available only for drugs that provide a meaningful therapeutic benefit over existing treatments.[15] The accelerated approval provision of section 901 of FDASIA (amending section 506 of the FD&C Act) requires FDA to "tak[e] into account . . . the availability or lack of alternative treatments."

Amended section 506(c) may reasonably be interpreted as providing additional flexibility as compared to the regulations. Specifically, section 506(c) broadens use of the accelerated approval pathway to cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective. The discussion of unmet medical need in Section III.C.2 provides examples of situations in which a drug could be shown to provide a meaningful advantage over available therapy, including some in which there may not be a demonstrated direct therapeutic advantage. Section III.B describes what constitutes available therapy for purposes of determining whether a drug provides a meaningful advantage.

[15] 21 CFR 314.500 and 601.40.

B. Accelerated Approval Endpoints

There are two types of endpoints that can be used as a basis for accelerated approval: (1) a surrogate endpoint that is considered reasonably likely to predict clinical benefit; and (2) a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (also see Section VII.D.2). For purposes of this guidance, these categories of endpoints are referred to as surrogate endpoints and intermediate clinical endpoints, respectively.

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

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).

1. Surrogate Endpoints

For purposes of accelerated approval, a surrogate endpoint is a marker, 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. Depending on the strength of the evidence supporting the ability of a marker to predict clinical benefit, the marker may be a surrogate endpoint that is known to predict clinical benefit (a validated surrogate endpoint, which could be used for traditional approval), a surrogate endpoint that is reasonably likely to predict a drug's intended clinical benefit (which could be used for accelerated approval), or a marker for which there is insufficient evidence to support reliance on the marker as either kind of surrogate endpoint (and thus cannot be used to support traditional or accelerated approval of a marketing application).

HIV viral load, as evidenced by a laboratory measure of HIV in plasma, has been shown to correlate with morbidity and mortality associated with HIV disease, but is not a direct measure of clinical benefit. Prolonged suppression of viral load is known to reliably predict an effect on survival.

2. Intermediate Clinical Endpoints (clinical endpoints that can be measured earlier than an effect on irreversible morbidity or mortality)

For purposes of accelerated approval, an intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM.

A threshold question is whether the demonstrated therapeutic effect alone would be a basis for traditional approval. For example, traditional approval would be appropriate where the effect is modest, but a sufficiently meaningful benefit within the context of the disease to provide a

favorable risk-benefit profile. If the therapeutic effect is not a clinical benefit and a basis for traditional approval, accelerated approval could be an option if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a drug. FDA has limited experience with accelerated approvals based on intermediate clinical endpoints. However, we believe intermediate clinical endpoints generally would be used to support accelerated approval in the following types of situations:

- The study results for a clinical endpoint demonstrate a therapeutic effect that would not support traditional approval because:
    - The effect is not a clinical benefit
    - The effect is only a modest benefit within the context of the disease that alone would not justify the risks associated with the drug, but there is an evidentiary basis to conclude that the effect is reasonably likely to predict an effect on IMM or other clinical benefit that would be a basis for traditional approval
- A clinical endpoint demonstrates a relatively short-term clinical benefit in a chronic disease setting in which it is essential to confirm longer-term durability of the clinical benefit for traditional approval but the short-term benefit is reasonably likely to predict long-term benefit
- A clinical endpoint demonstrates a clinical benefit that is reasonably likely to predict an effect on IMM in a disease setting in which it is essential to confirm the effect on IMM, (e.g., because available therapy has established effects on IMM)

FDA expects that most demonstrations of clinical benefit would be a basis for traditional approval. 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.

C. Evidentiary Criteria for Accelerated Approval

Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.[16] For effectiveness, the standard is substantial evidence based on adequate and well-controlled clinical investigations.[17] For safety, the standard is having sufficient information to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling.[18] Under accelerated approval, FDA can rely on a particular kind of evidence, such as a drug's effect on a surrogate endpoint, as a basis for approval (and ensure that remaining doubts about the relationship of the

[16] Section 505(d) of the FD&C Act.
[17] Section 505(d)(5) of the FD&C Act.
[18] Section 505(d)(1) of the FD&C Act.

effect on the surrogate to clinical benefit are resolved by additional post-approval studies).[19] An application for accelerated approval should also include evidence that a surrogate or intermediate clinical endpoint is reasonably likely to predict the intended clinical benefit of a drug.

1. Whether an Endpoint Is "Reasonably Likely to Predict" Clinical Benefit

Whether an endpoint is reasonably likely to predict clinical benefit is a function of the biological plausibility of the relationship between the disease, endpoint, and the desired effect, and the empirical evidence to support that relationship. The empirical evidence may include "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."[20] Evidence of pharmacologic activity alone is not sufficient, however.[21] Clinical data should be provided to support the assertion that a relationship of the surrogate or intermediate clinical endpoint to the outcome is reasonably likely, and should be relevant to the relationship between the specific endpoint to be used and the specific intended clinical benefit of the drug.

Whether a drug effect on a given endpoint is reasonably likely to predict clinical benefit is a matter of judgment. FDA considers all relevant evidence and weighs the uncertainty against the severity of the disease to be treated and the lack of available therapy. On a case-by-case basis, FDA will make informed judgments using both internal and external expertise. This guidance provides an overview of some of the important factors to consider in identifying and assessing the predictive potential of surrogate or intermediate clinical endpoints. However, this guidance does not address clinical evidence requirements because they are not readily generalizable.

a. Understanding of the disease process

Surrogate endpoints are often thought to be a measure of, for example:

- The underlying cause of the disease (e.g., elevated uric acid and gout, elevated blood pressure and hypertensive cardiovascular disease, low thyroxin levels and hypothyroidism)

- An effect that predicts the ultimate outcome (e.g., tumor shrinkage could be expected to delay symptomatic progression and improve survival, diuresis could be expected to improve symptoms of heart failure)

- The state of the pathophysiologic pathway leading to the clinical outcome (e.g., replacement of a missing enzyme or clotting factor)

[19] Section 506(c) of the FD&C Act. Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR at 58948, December 11, 1992).
[20] Section 506(c)(1)(B) of the FD&C Act, as amended by section 901 of FDASIA.
[21] Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992).

In such cases, the extent to which the pathophysiology of a disease is understood is an important factor in determining whether an endpoint is reasonably likely to predict clinical benefit. If the disease process is complex, has multiple pathophysiologic or causal pathways, and is poorly understood, it may be difficult to identify a surrogate endpoint. For example, for some reasonably well-understood enzyme deficiencies, replacement of the deficient enzyme reliably predicts clinical benefit. In contrast, other enzyme deficiencies may involve a defect for which the pathophysiologic or causal pathways are not well understood and where enzyme replacement alone will not reasonably predict the disease course or treatment results.

Some effects on well-established, disease-related markers may have little or no ability to predict clinical benefit. For example, fever occurs with most infectious diseases but lowering a patient's body temperature with a non-steroidal anti-inflammatory drug does not predict the drug's effect on the disease (although it could be a pertinent biomarker for an antibiotic). Similarly, in prostate cancer, increased levels of prostate-specific antigen (PSA) are the result of advancing tumor burden. Therefore, PSA is correlated with the progression of prostate cancer and risks of mortality. However, PSA is not the mechanism through which the disease causes morbidity; so, the effect of a drug on lowering PSA cannot necessarily be relied upon to predict the drug's clinical benefit.

b. Understanding of the relationship between the drug's effect and the disease process

The extent to which a drug's effect on the surrogate endpoint is known to predict an effect on the disease is critical. Sometimes this relationship can be assessed epidemiologically but it is most persuasively established by knowing that a drug that affects the surrogate also affects a clinical outcome. Thus, lowering blood pressure has been shown repeatedly to reduce the incidence of stroke and cardiovascular disease in people with hypertension. Similarly, killing infecting bacteria or viruses leads to cure of infectious disease and shrinking a tumor for a sustained period can lead to improved survival in patients with some cancers. These surrogate endpoint responses are thus understood to have positive effects on the disease process.

Following are examples of factors to consider in identifying and assessing a surrogate endpoint:

- Whether there is reliable and consistent epidemiologic evidence supporting the relationship between the endpoint and the intended clinical benefit[22]

- How precisely the epidemiologic relationship between the endpoint and clinical outcome is defined. (The more precise the relationship, the stronger the basis for concluding that an effect on the endpoint would have a reasonably well-defined effect on the clinical outcome)

[22] Such a relationship does not always predict a favorable effect, as illustrated by failure of drugs that effectively lower premature ventricular beat rates or raise high-density lipoprotein (HDL) cholesterol to have the expected cardiovascular benefits.

- Whether the effect on the endpoint has been shown to predict a clinical benefit with drugs in the same or a closely related pharmacological class

- Whether the effect on the endpoint has been shown to predict clinical benefit with other drugs in the class for the disease being treated

If an endpoint has failed to predict clinical benefit in a properly designed trial for a drug in the same pharmacologic class, or in the same disease or a related disease, that weighs against reliance on the endpoint as a basis for accelerated approval.

D. Conditions of Accelerated Approval

1. Promotional Materials

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.[23] After 120 days following marketing approval, unless otherwise informed by the Agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.[24]

2. Confirmatory Trials

For drugs granted accelerated approval, postmarketing confirmatory trials are generally required to verify and describe the anticipated clinical benefit or effect on IMM. These trials must be completed with due diligence.[25] Where confirmatory trials verify clinical benefit, FDA will generally terminate the requirement.[26]

Generally, the confirmatory clinical trial would evaluate a clinical endpoint that directly measures the clinical benefit. It is a possibility in some cases, however, that additional evaluation of a surrogate endpoint (e.g., for a longer period), could be persuasive evidence of a clinical benefit. For example, an effect of relatively short duration on a surrogate endpoint may be reasonably likely to predict clinical benefit, supporting accelerated approval. A trial demonstrating that the effect on the same surrogate endpoint persists for an extended duration may be known to reliably predict such clinical benefit.

FDA's accelerated approval regulations provide that postmarketing confirmatory trials to verify clinical benefit would usually be underway at the time of accelerated approval.[27] Ideally,

[23] 21 CFR 314.550 and 601.45.
[24] 21 CFR 314.550 and 601.45.
[25] FD&C Act 506(c)(3)(A); 21 CFR 314.510 and 601.41.
[26] 21 CFR 314.560 and 601.46.
[27] 21 CFR 314.510 and 601.41.

confirmatory trials will be underway even earlier -- at the time a marketing application is submitted. This will help to ensure the confirmatory trials are completed with due diligence and that it will be known as soon as possible whether the drug provides actual clinical benefit.

The design of confirmatory trials should be part of a comprehensive drug development plan and should be discussed with FDA early in the development process. Applicants should include timelines in their development plans to help ensure postapproval confirmatory trials are completed with due diligence. There is concern that the availability of drugs to patients following accelerated approval may interfere with patient accrual to a confirmatory trial, especially when the confirmatory trial is in the same disease population as the population for the drug's accelerated approval indication. For this reason, a confirmatory trial may be conducted in a study population that differs from the population for which accelerated approval was granted. This is the usual case in oncology.

Another approach is to use an interim analysis of the surrogate endpoint data as the basis for accelerated approval, with continuation of the randomized trials during the time period when the surrogate endpoint and interim safety data are being: (1) analyzed, (2) prepared for submission to FDA, and (3) reviewed by FDA. When the ultimate clinical outcome can be expected over this additional timeframe, the data to verify the clinical benefit may be nearly complete by the time of accelerated approval.

3. Withdrawal of Accelerated Approval

FDA may withdraw approval of a drug or indication approved under the accelerated approval pathway if [28], for example:

- A trial required to verify the predicted clinical benefit of the product fails to verify such benefit
- Other evidence demonstrates the product is not shown to be safe or effective under the conditions of use
- The applicant fails to conduct any required postapproval trial of the drug with due diligence
- The applicant disseminates false or misleading promotional materials relating to the product

Approval of a drug may be withdrawn if trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug (e.g., show a significantly

[28] FDCA 506(c)(3). There are additional grounds for withdrawal in Subparts E and H. See 21 CFR 314.530(a) and 601.43(a).

smaller magnitude or duration of benefit than was anticipated based on the observed effect on the surrogate).

If FDA determines there are grounds for withdrawal, the agency may ask the applicant to voluntarily request withdrawal of approval under 21 CFR 314.150(d) or notify the applicant of FDA's proposal to withdraw approval in a notice of opportunity for hearing (NOOH). The NOOH will generally state the proposed grounds for withdrawal of approval.[29] Upon receipt of an NOOH, an applicant has 15 days to file a written request for a hearing. If an applicant does not request a hearing within 15 days, the applicant waives its opportunity for hearing.[30] An applicant may also voluntarily request the Agency to withdraw approval of an application approved under accelerated approval.[31]

VIII. PRIORITY REVIEW DESIGNATION

An application for a drug will receive priority review designation if it is for a drug that treats a *serious condition* and, if approved, would *provide a significant improvement in safety or effectiveness*. In addition, there are specific statutory provisions that provide for priority review for various types of applications, described in Section IV. A priority designation is intended to direct overall attention and resources to the evaluation of such applications. This section describes the qualifying criteria (italicized terms) and the features (e.g., benefits) of priority review designation. Appendix 1 describes the priority review designation process.

A. Qualifying Criteria for Priority Review Designation

1. Serious Condition

See Section III.A.

2. Demonstrating the Potential To Be a Significant Improvement in Safety or Effectiveness

On a case-by-case basis, FDA determines whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. Significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting drug reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes

[29] 21 CFR 314.530(b) and 601.43(b).
[30] 21 CFR 314.530(c)(1) and 601.43(c)(1).
[31] 21 CFR 314.150(c) and 21 CFR 601.5(a).

- Evidence of safety and effectiveness in a new subpopulation

Although such evidence can come from clinical trials comparing a marketed product with the investigational drug, a priority review designation can be based on other scientifically valid information. Generally, if there is an available therapy (see Section III.B), sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority related to either safety or effectiveness. Alternatively, sponsors could show the ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy. Although such showings would usually be based on randomized trials, other types of controls could also be persuasive, for example, historical controls.[32]

B. Features of Priority Review Designation

A priority review designation means FDA's goal is to take action on the marketing application within 6 months (compared to 10 months under standard review).

IX. GENERAL CONSIDERATIONS

Communication with the Agency is a critical aspect of expedited programs. FDA will strive to provide a timely response to a sponsor's inquiry regarding an expedited development program. It is equally critical that the sponsor respond promptly to FDA's inquiries. This applies to formal meetings and related inquiries, written correspondence, and other interactions. In addition to the many types of formal meetings[33] and correspondence the Agency offers to sponsors, additional considerations for sponsors of expedited programs are highlighted in this section.

A. Manufacturing and Product Quality Considerations

The sponsor of a product that receives an expedited drug development designation will probably need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program. The sponsor's product quality team and CMC teams should initiate early communication with FDA to ensure that the manufacturing development programs and timing of submissions meet the Agency's expectations for licensure or marketing approval.[34]

[32] Sponsors contemplating the use of historical controls should consult the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001, ICH) for more detailed discussions.

[33] See the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applications*. Also see the *CDER 21st Century Review Process Desk Reference Guide* accessible at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf.

[34] See the guidance for industry *IND Meetings for Human Drugs and Biologics Chemistry, Manufacturing, and Controls Information*.

When sponsors receive an expedited drug development designation, they should be prepared to propose a commercial manufacturing program that will ensure availability of quality product at the time of approval. The proposal should consider estimated market demand and the commercial manufacturing development plan, especially with regard to manufacturing facilities, lifecycle process validation (including scale-up and comparability), methods validation, stability studies, and potency studies if applicable. The proposal should also include a timeline for development of the manufacturing capabilities with goals aligned with the clinical development program. The applicant should ensure that the manufacturing process is sufficiently developed in order to support the CMC section. After the initial discussion following designation, frequent communication during development will generally facilitate meeting manufacturing development and product quality goals.

The sponsors of such products should allow for an earlier submission of the CMC section (including product quality information) for timely review, and, critically, for inspection planning. Coordination with the sponsor and contract manufacturers may be necessary to ensure facilities (e.g., the manufacturing process and equipment) are ready for inspection (e.g., during review of the clinical section of the application). A comprehensive meeting with FDA's product quality review and evaluation offices in advance of submission may facilitate quality assessment of products designated for expedited programs.

B. Nonclinical Considerations

To ensure timely submission and review of nonclinical data, sponsors should initiate early communication with FDA for their nonclinical study programs. Considerations, such as study protocol modifications, sequence and scheduling of studies, and the need for specific studies (e.g., long-term toxicity), may be important in the context of expedited drug development. FDA will provide guidance to sponsors on the development of appropriate and timely nonclinical data needed to support an application for marketing approval or licensure.

C. Clinical Inspection Considerations

Sponsors should anticipate the Agency's need to inspect clinical trials, including, if applicable, the analytical component of bioavailability or bioequivalence studies. Inspections should be scheduled early in the application review process so inspection results are available to inform the review division and to allow time for the sponsor to address significant inspection findings. To select sites for clinical inspections, it is important for reviewers to have timely access to adequate and accurate data in BLA, NDA, or supplement submissions. Sponsors should initiate early communication with FDA about information required for inspection planning and conduct.

APPENDIX 1: PROCESSES FOR FAST TRACK, BREAKTHROUGH THERAPY, AND PRIORITY REVIEW DESIGNATIONS

This appendix describes general processes applicable to the submission and review of fast track, breakthrough therapy, and priority review designations.

A. Process for Fast Track Designation

1. When to Send a Designation Submission

Sponsors may submit fast track designation requests when the IND is first submitted or at any time thereafter before receiving marketing approval of its BLA or NDA. The IND and potential fast track designation may be discussed before an IND submission in a pre-IND meeting, but a decision on designation would await submission of the IND. As a practical matter, requests should ordinarily occur no later than the sponsor's pre-BLA or pre-NDA meeting with the Agency because many of the features of fast track designation will not apply after that time.

2. Where to Send a Designation Submission

The IND or amendment should be sent to the attention of the appropriate review division or office in CBER or CDER.

3. Content of a Designation Submission

Fast track designation requests should contain the following information (in most cases, this information could be captured in approximately 10 to 20 pages):

- If the fast track designation request is submitted to the sponsor's IND as an amendment, the cover letter should indicate the submission as a **REQUEST FOR FAST TRACK DESIGNATION** in bold, uppercase letters. If the request is submitted with an initial IND, the cover letter should indicate the submission as both an **INITIAL INVESTIGATIONAL NEW DRUG SUBMISSION** and **REQUEST FOR FAST TRACK DESIGNATION** in bold, uppercase letters.

- In the cover letter of the submission include the name of the sponsor's contact person, including the person's address, email address, telephone number, and fax number.

- If applicable, the IND application number should be noted.

- If available, include, for drug products, the proprietary name and active ingredient and, for biological products, the proper name and trade name.

- The division or office to which the IND is being submitted or in which it is active.

- The proposed indication(s).

- A concise summary of information that supports the fast track designation request for the indication being studied, including:
    - The basis for considering the drug to be one intended to treat a serious condition
    - The basis for considering the drug to have the potential to address an unmet medical need and an explanation of how this potential is being evaluated in the planned drug development program (e.g., a description of the trials intended to evaluate this potential)
- If applicable, include a list of documents previously submitted to the IND that are considered relevant to the designation request, with reference to submission dates. Paper submissions can be resubmitted to FDA as appendices to the designation request.

4. FDA Response

FDA will respond to fast track designation requests within 60 calendar days of receipt of the request.

a. Designation letter

If the Agency determines that the criteria for designation as a fast track drug development program have been met, the designation letter will:

- State that fast track designation is granted for development of the product for use in treating the specific serious condition
- Point out that the sponsor should design and perform studies that can show whether the product fulfills an unmet medical need
- Alert the sponsor to the need for the drug development program to continue to meet the criteria for fast track designation

b. Nondesignation letter

If the Agency determines that a fast track designation request was incomplete or that the drug development program failed to meet the criteria for fast track designation, the Agency will send a nondesignation letter to the sponsor. The nondesignation letter will state that fast track designation is not granted and explain the reasons for the Agency's decision.

5. Continued Fast Track Designation

Over the course of drug development, it is foreseeable that certain products in fast track drug development programs will not continue to meet the criteria for fast track designation. A drug product in a fast track development program may not continue to meet the criteria if the drug: (1)

no longer demonstrates a potential to address unmet medical need or (2) is not being studied in a manner that shows the drug product can treat a serious condition and fulfills an unmet medical need. The drug product may no longer demonstrate a potential to address unmet medical need, for example, if a new product was approved under a traditional approval that addressed the same need, or if emerging clinical data failed to show that the product in a fast track development program had the anticipated advantage over available therapy. For products in fast track drug development programs, the Agency expects that the appropriateness of considering particular drug development plans as part of the fast track program will be discussed and evaluated during the drug development process, including at the end-of-Phase 2 meeting and the pre-BLA or pre-NDA meeting. If the sponsor recognizes that the fast track drug development program will no longer be pursued, the sponsor should inform the Agency of this change.

When fast track designation is no longer supported by emerging data or the designated drug development program is no longer being pursued, the Agency may choose to send a letter notifying the sponsor that the program is no longer designated as a fast track drug development program.

B. Process for Breakthrough Therapy Designation

1. When to Send a Designation Submission

Although sponsors may request breakthrough therapy designation at the time of IND submission, or at any time afterward, they should not send breakthrough therapy designation requests until they have preliminary clinical evidence indicating that "the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints."[35] FDA expects that in most cases breakthrough therapy designation requests would be submitted as an amendment to the IND, but a sponsor could also submit its request with the original IND. Ideally, a breakthrough therapy designation request should be received by FDA no later than the end-of-Phase-2 meetings if any of the features of the designation are to be obtained. Because the primary intent of breakthrough therapy designation is to develop evidence needed to support approval as efficiently as possible, FDA does not anticipate that breakthrough therapy designation requests will be made after the submission of an original BLA or NDA or a supplement.

2. Where to Send a Designation Submission

The IND or amendment should be submitted to the attention of the appropriate review division or office in CBER or CDER.

3. Content of a Designation Submission

Breakthrough therapy designation requests should contain the following information (in most cases, this information could be captured in approximately 10 to 20 pages):

[35] Section 506(a)(1) of the FD&C Act, as amended by section 902 of FDASIA.

- If the breakthrough therapy designation request is submitted to the sponsor's IND as an amendment, the cover letter should indicate the submission as a **REQUEST FOR BREAKTHROUGH THERAPY DESIGNATION** in bold, uppercase letters. If the request is submitted with an initial IND, the cover letter should indicate the submission as both an **INITIAL INVESTIGATIONAL NEW DRUG SUBMISSION** and **REQUEST FOR BREAKTHROUGH THERAPY DESIGNATION** in bold, uppercase letters.

- In the cover letter of the submission, the name of the sponsor's contact person, including the person's address, email address, telephone number, and fax number.

- If applicable, the IND application number should be noted.

- If available, include, for drug products, the proprietary name and active ingredient and, for biological products, the proper name and trade name.

- The division or office to which the IND is being submitted or in which it is active.

- The proposed indication(s).

- A concise summary of information that supports the sponsor's breakthrough therapy designation request for the indication being studied, including:

    - The basis for considering the drug to be one intended to treat a serious condition

    - The preliminary clinical evidence that the drug may demonstrate substantial improvement over available therapies. A sponsor should describe the preliminary clinical evidence, including, for example, justification for the clinical study endpoint used and a brief description of statistical analyses

- If applicable, include a list of documents previously submitted to the IND considered relevant to the designation request, with reference to submission dates. Paper submissions can be resubmitted to FDA as appendices to the designation request.

4. FDA Response

FDA will respond to breakthrough therapy designation requests within 60 calendar days of receipt of the request.

a. Designation letter

If the Agency determines that the criteria for designation as a breakthrough therapy development program have been met, the designation letter will:

- State that breakthrough therapy designation is granted for development of the product for use in treating the specific serious condition

- Explain that FDA will work closely with the sponsor to provide guidance on subsequent development, including providing advice on generating evidence needed to support the drug approval in an efficient manner

- Alert the sponsor to the need for the drug development program to continue to meet the criteria for breakthrough therapy designation

b. Nondesignation letter

If the Agency determines that a breakthrough therapy designation request was incomplete or failed to meet the criteria for breakthrough therapy designation, the Agency will send a nondesignation letter to the sponsor. The nondesignation letter will state that a breakthrough therapy designation is not granted and explain the reasons for the Agency's decision.

5. Continued Designation as a Breakthrough Therapy Development Program

Over the course of drug development, it is foreseeable that certain products in breakthrough therapy development programs will no longer be considered a breakthrough therapy. For example, a drug's development program may be granted breakthrough therapy designation using early clinical testing that shows a much higher response rate than available therapies. However, subsequent interim data derived from a larger study may show a response that is substantially smaller than the response seen in early clinical testing. Another example is where breakthrough therapy designation is granted to two drugs that are being developed for the same use. If one of the two drugs gains traditional approval, the other would not retain its designation unless its sponsor provided evidence that the drug may demonstrate substantial improvement over the recently approved drug. Additionally, if the sponsor recognizes that the development program designated as breakthrough therapy will no longer be pursued, the sponsor should inform the Agency of this change.

When breakthrough therapy designation is no longer supported by emerging data or the designated drug development program is no longer being pursued, the Agency may choose to send a letter notifying the sponsor that the program is no longer designated as a breakthrough therapy development program.

C. Process for Priority Review Designation

FDA determines whether an application qualifies for priority review (versus standard review) for every application, not just when requested by the applicant. However, an applicant may expressly request priority review as described in the following sections.

1. When to Send a Designation Submission

Sponsors may request priority review designation when they submit an original BLA, NDA, or efficacy supplement. The Agency does not anticipate that priority review designation requests will be made after the filing of a BLA, NDA, or efficacy supplement.

2. Where to Send a Designation Submission

Priority review designation requests may be submitted with the original BLA, NDA, or efficacy supplement.

3. Content of a Designation Submission

Priority review designation requests should contain the following information:

- The cover letter included with the request should be clearly identified as a **REQUEST FOR PRIORITY REVIEW DESIGNATION** in bold, uppercase letters.

- In the cover letter of the submission include the name of the sponsor's contact person, including the person's address, email address, telephone number, and fax number.

- If available, include, for drug products, the proprietary name and active ingredient and, for biological products, the proper name and trade name.

- The proposed indication(s).

- A concise summary of information that supports the priority review designation request, including:

    - The basis for considering the drug to be intended to treat a serious condition

    - The basis for the assertion that the drug would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition

4. FDA Response

The Agency will inform the applicant in writing of a priority review designation by Day 60 of the review. The division will inform the applicant in writing of a standard review designation by Day 74 of the review. Applications that are not filed do not receive a review designation.

5. Continued Priority Review Designation

After priority review designation is assigned, the timeline will not change during the first review cycle, even if a redetermination of review status is made because of approval of other drugs,

availability of new data, or submission of a request for dispute resolution by the applicant. In addition, applications filed over protest are assigned a standard review. If the application is resubmitted after FDA's refuse-to-file decision or if the application is withdrawn before FDA's action and then resubmitted, FDA will make its determination of review designation based on the resubmitted application.

APPENDIX 2: PROCESSES FOR ROLLING REVIEW

This appendix describes general processes applicable to the submission and review of portions of an application, a feature of fast track designation (see Section V.B.2).

A. Agreement on Proposal

Sponsors obtain preliminary Agency agreement on the proposal at the pre-BLA or pre-NDA meeting. At the meeting, the sponsor and the review division should discuss: (1) the data that will be used to support effectiveness, (2) the schedule for submission of each portion of the BLA or NDA, and (3) a description of portions of the application to be submitted separately. A request to submit portions of an application ordinarily should be included in the information package for the pre-BLA or pre-NDA meeting. If a sponsor seeks to submit portions of an application to the IND after the pre-BLA or pre-NDA meeting, the sponsor should make such a request and provide a proposed schedule for submission of portions of an application to the IND as soon as possible.

A request for submission of portions of an application should be sent as an amendment to the IND for the product in a fast track drug development program; attach Form FDA 1571. The amendment should be clearly identified as a "**REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION**" in bold uppercase letters. A sponsor may apply for fast track designation and submission of portions of a BLA or NDA at the same time. In such cases, sponsors should submit requests as one amendment to the IND. FDA responds to sponsors' requests for submission of portions of an application by letter. FDA also responds to changes to an agreement to accept portions of an application by letter.

B. Portions of an Application Eligible for Early Submission

Generally, the Agency accepts for submission a complete section of a BLA or NDA only, such as the entire CMC section, toxicology section, or clinical section.[36] A section of a BLA or NDA should be submitted for review in a form adequate to have been included in a complete BLA or NDA submission. Drafts should not be included in a submission; if final reports need to be updated, the applicant should submit a formal amendment to the BLA or NDA with the revised information. Occasionally, the Agency may, in its discretion, accept less than a complete section if the Agency determines that such a subsection would constitute a reviewable unit and be useful in making the review process more efficient (e.g., less than a complete section could be a CMC section lacking final consistency lot data and long term stability data, an acute toxicology section lacking chronic toxicology data, final study reports for some or all of the principal controlled trials without integrated summaries). The sponsor should confirm these subsections are final reports.

At the pre-BLA or pre-NDA meeting, the Agency and the sponsor should work together to clearly define the parameters of accepting an incomplete section and to determine whether

[36] Form FDA 356h may be a useful guide to items in a BLA or NDA.

FDA could conduct a meaningful review of the submission before receiving the missing information.

C. Submission of User Fees

A sponsor is required to pay applicable fees as stated in section 736 of the FD&C Act before FDA may commence review of any portion of an application. The applicant should submit Form FDA 3397 with applicable user fees and follow the same procedures as those followed when a complete application is submitted.

D. Commencement of Review

If FDA accepts a portion of an application, this does not necessarily mean that review will commence or proceed before we receive the complete application. Actual commencement and scheduling of review depends on many factors, including staffing, workload, competing priorities, timeline for completion of applications, and the perceived efficiency of commencing review before receipt of the complete submission.

E. Calculation of Review Time

The review clock will not begin until the applicant informs the Agency that a complete BLA or NDA was submitted.[37] After the Agency is notified of the complete application, we will make a filing determination within the usual time.[38]

[37] Section 506(d)(2) of the FD&C Act provides that any time period for review of human drug applications shall not apply until the date on which the application is complete.

[38] 21 CFR 314.101 and CBER SOPP 8404, *Refusal to File Procedures for Biologic License Applications* (August 27, 2007), available on the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073474.htm.