Guidance for Industry

Expedited Programs for Serious Conditions – Drugs and Biologics

U.S. Department of Health and Human Services
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Guidance for Industry[1]
Expedited Programs for Serious Conditions – Drugs and Biologics

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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). The purpose of this guidance for industry is to provide 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.

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.

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 part 312, subpart E (21 CFR part 312).[4] 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

[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] Whether a Condition Is Serious explains that all references to serious conditions include life-threatening conditions.
[4] 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).

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 risks and side effects from treatment of life-threatening and severely debilitating diseases than they would for other diseases. The four principal programs that support these principles are fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation (referred to in this guidance as the Agency's *expedited programs*).

FDA has a history of applying the philosophy underlying subpart E to drugs for rare diseases through use of the Agency's expedited programs. FDA recognizes that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of the disease. FDA will continue to apply flexibility in these situations to address particular challenges posed by each disease.

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 individually in detail in sections V, VI, VII, and VIII. All four expedited programs represent efforts to address an unmet medical need in the treatment of a serious condition, which is discussed in the following paragraphs.

A. Serious Condition

1. Whether a Condition Is Serious

FDA intends to interpret the term *serious* as it has done in the past for the purposes of accelerated approval[5] and expanded access to investigational drugs for treatment use.[6] A serious disease or condition is defined in the expanded access regulations as follows:

> . . . 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 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.[7]

[5] Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992) and Food and Drug Administration, Proposed Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 13234, April 15, 1992).
[6] Part 312, subpart I.
[7] 21 CFR 312.300(b)(1).

Note: For the purposes of this guidance, the terms *condition, disease*, and *illness* are used interchangeably. All conditions meeting the definition of life-threatening as set forth at § 312.81(a) would also be serious conditions.

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

As referenced in section IV, 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 condition or 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 the following:

- 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 mitigate or prevent a serious treatment-related side effect (e.g., serious infections in patients receiving immunosuppressive therapy)
- A product intended to avoid or diminish a serious adverse event associated with available therapy for a serious condition (e.g., product that is less cardiotoxic than available cancer therapy)[8]
- A product intended to prevent a serious condition or reduce the likelihood that the condition will progress to a more serious condition or a more advanced stage of disease

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[9] and
- Is relevant to current U.S. standard of care (SOC) for the indication

[8] Sponsors considering an expedited drug development designation or program for a drug intended to avoid a serious adverse event associated with available therapy or diminish its severity should be aware that they will need to provide data that directly support the effect corresponding to the level of evidence needed to meet the qualifying criteria for the relevant designation or program (e.g., phase 3 data demonstrating lower incidence or severity of the serious adverse reaction compared to available therapy for priority review). The requisite data may be very difficult to obtain in early development, particularly for purposes of breakthrough therapy designation.

[9] 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. Only in exceptional 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 extensive evidence in the published literature (e.g., certain well-established oncologic treatments).

FDA's available therapy determination generally focuses 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. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic mutation), the SOC for the broader population, if there is one, generally is considered available therapy for the subset, unless there is evidence that the SOC is less effective in 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 a 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). FDA encourages sponsors to discuss available therapy considerations with the Agency during interactions with FDA.

As appropriate, FDA may consult with special Government employees or other experts when making an available therapy determination.

When determining whether a drug granted accelerated approval or 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) (21 U.S.C. 355-1), is considered available therapy, the following principles will be applied:

- A drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by postapproval studies. (See section III.C.3.)

- A drug would be considered available therapy if the drug is granted accelerated approval because of restricted distribution and the study population for the new drug under development is eligible to receive the approved drug under the restricted distribution program. Similarly, a drug would be considered available therapy if the study population for the new drug under development is eligible to receive the approved drug under the 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 there is no available therapy 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 or disease progression when the available therapy has shown an effect on symptoms, but has not shown an effect on progressive disability or disease progression)

- Has an improved effect on a serious outcome(s) of the condition compared with available therapy (e.g., superiority of the new drug to available therapy when either used alone or in combination with available therapy (i.e., as demonstrated in an add-on study))

- Has an effect on a serious outcome of the condition in patients who are unable to tolerate or failed to respond to available therapy

- Can be used effectively with other critical agents that cannot be combined with available therapy

- Provides efficacy comparable 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 safety and efficacy comparable to those of available therapy but has a 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 some patients. 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 with available therapy. Thus, 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 efficacy similar to available therapy 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 Endpoint or an Intermediate Clinical Endpoint and Clinical Benefit Has Not Yet Been Verified

As discussed in sections VII and III.B., 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 postapproval confirmatory trials. FDA will therefore consider products as addressing an unmet medical need if the only approved treatments were granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by postapproval studies.

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. Note that a drug development program may qualify for more than one expedited program.

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 **OR** • A drug that has been designated as a qualified infectious disease product[a]	• 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 drug that treats a serious condition **AND** generally provides a 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 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[b] **OR** • An application for a drug that has been designated as a qualified infectious disease product[c] **OR** • Any application or supplement for a drug submitted with a priority review voucher[d]

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 request	• 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, which should usually be already underway at the time of approval	• With original BLA, NDA, or efficacy supplement
Timelines for FDA response	• Within 60 calendar days of receipt of the request	• Within 60 calendar days of receipt of the 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	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Other actions to expedite review	• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	• Shorter clock for review of marketing application (6 months compared with the 10-month standard review)[e]
Additional considerations	• Designation may be rescinded if it no longer meets the qualifying criteria for fast track[f]	• Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy[g]	• Promotional materials • Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit • Subject to expedited withdrawal	• Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

[a] Title VIII of FDASIA, *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.
[b] 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 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.
[c] See footnote a above.
[d] 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 (a)(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.
[e] As part of its commitments in PDUFA V, FDA has established a review model, *the Program.* The Program applies to all new molecular entity NDAs and original BLAs, including applications that are resubmitted following a Refuse-to-File action, received from October 1, 2012, through September 30, 2017. For applications filed by FDA under the Program, the PDUFA review clock will begin at the conclusion of the 60 calendar day filing review period that begins on the date of FDA receipt of the original submission.
[f] A sponsor may also withdraw fast track designation if the designation is no longer supported by emerging data or the drug development program is no longer being pursued (see section A.5. of Appendix 1).
[g] A sponsor may also withdraw breakthrough therapy designation if the designation is no longer supported by emerging data or the drug development program is no longer being pursued (see section B.5. of Appendix 1).

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 provision is intended to facilitate development and expedite review of drugs to treat serious and life-threatening conditions so that an approved product can reach the market expeditiously. This section describes the qualifying criteria and the features of fast track designation. Appendix 1 describes the process for fast track designation.

A. Qualifying Criteria for Fast Track Designation

Fast track designation applies to the drug (either alone or in combination with other drugs) and the specific use for which it is being studied. The term *drug* refers to the combination of two or more drugs if the combination is the subject of the fast track designation or request. Where appropriate, FDA may grant designation to the development of a new use of an approved drug.

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 at 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 meetings with FDA, including pre-IND meetings, end-of-phase 1 meetings, and end-of-phase 2 meetings to discuss study design, extent of safety data required to support approval, dose-response concerns, and use of biomarkers. Other meetings may be scheduled as appropriate (e.g., 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 (see section VIII).

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

If FDA determines, after preliminary evaluation of clinical data submitted by a sponsor, that a fast track product may be effective, the Agency 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." It is important to recognize that the standard for breakthrough therapy designation is not the same as the standard for drug approval. The clinical evidence needed to support breakthrough designation is preliminary. In contrast, as is the case for all drugs, FDA will review the full data submitted to support approval of drugs designated as breakthrough therapies to determine whether the drugs are safe and effective for their intended use before they are approved for marketing. This section describes the qualifying criteria and the features of breakthrough therapy designation. Appendix 1 describes the process for breakthrough therapy designation.

Not all products designated as breakthrough therapies ultimately will be shown to have the substantial improvement over available therapies suggested by the preliminary clinical evidence at the time of designation. If the designation is no longer supported by subsequent data, FDA may rescind the designation.[11] Because FDA commits significant resources to work particularly closely with sponsors of breakthrough therapy products, the Agency needs to focus its resources on breakthrough therapy drug development programs that continue to meet the program's qualifying criteria (see section B.5. in Appendix 1).

A. Qualifying Criteria for Breakthrough Therapy Designation

Breakthrough therapy designation applies to the drug (either alone or in combination with other drugs) and the specific use for which it is being studied. The term *drug* refers to the combination of two or more drugs if the combination is the subject of the breakthrough therapy designation or request. Where appropriate, FDA may grant designation to the development of a new use of an approved drug.

1. Serious Condition

See section III.A.

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

[11] After the sponsor completes the development program, the product may still have sufficient evidence to support marketing approval.

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 may represent substantial improvement over available therapies for the treatment of a serious condition. For purposes of breakthrough therapy designation, *preliminary clinical evidence* means evidence that is sufficient to indicate that the drug may demonstrate substantial improvement in effectiveness or safety over available therapies, but in most cases is not sufficient to establish safety and effectiveness for purposes of approval. FDA expects that such evidence generally would be derived from phase 1 or 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 indicating a substantial improvement over available therapies 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 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 this type early in development. Other types of clinical data that also could be persuasive include single-arm studies comparing the new treatment with well-documented historical experience. Generally, FDA expects that such historically controlled data would be persuasive only if there is a large difference between the new treatment and historical experience. For example, where lung function decline is a major manifestation of a disease, single-arm study data showing that a new drug significantly increases lung function could be persuasive if there is no available therapy that increases lung function. Data demonstrating that a cancer drug substantially increases overall response rate compared with historical controls (e.g., historical response rate with available therapy), with consideration of duration of the response, also could be persuasive. Sponsors contemplating the use of historical controls should consult FDA's ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* for more-detailed discussions.[12]

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

[12] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and the Biologics guidance Web page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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: The determination of whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the drug's effect on a clinically significant endpoint (which could include duration of the effect) and the importance of the observed effect to the treatment of the serious condition or serious aspect of the condition. In general, the preliminary clinical evidence should show a clear advantage over available therapy.

Approaches to demonstrating substantial improvement include the following:

- Direct comparison of the new drug to available therapy shows a much greater or more important response (e.g., complete responses where the control treatment generally results only in partial responses). 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.

- If there is no available therapy, the new drug shows a substantial and clinically meaningful effect on an important outcome when compared with a placebo or a well-documented historical control.

- 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 well-documented 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 has a substantial and clinically meaningful effect on the underlying cause of the disease, in contrast to available therapies that treat only symptoms of the disease, and preliminary clinical evidence indicates that the drug is likely to have a disease-modifying effect in the long term (e.g., a sustained clinical benefit compared with a temporary clinical benefit provided by available therapies).

- The new drug reverses or inhibits 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 reactions (e.g., those that may result in treatment interruption) compared with 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 that typically would be used to support traditional approval

- 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)

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

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

In rare cases, a pharmacodynamic (PD) biomarker may be considered a clinically significant endpoint if it strongly suggests the potential for a clinically meaningful effect on the underlying disease. In such cases, a sponsor should provide evidence supporting the use of the PD biomarker. Such evidence should include, for example, (1) the extent of understanding of the disease pathophysiology, (2) whether the biomarker is on a causal pathway of the disease process, and (3) the time course of the drug's effect on the biomarker (e.g., the biomarker can be measured earlier than a surrogate endpoint used for accelerated approval). In addition, strong evidence of the drug's effect on the PD biomarker generally is expected. FDA is more likely to rely on a PD biomarker for breakthrough therapy designation in a disease setting in which there is no available therapy, if the evidence supports such use.

B. Features of Breakthrough Therapy Designation

1. 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 with 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 to meet the statutory standard for approval.[13] 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 efficient clinical trials in a number of ways. FDA will seek to ensure that a sponsor of a product designated as a breakthrough therapy receives timely advice and interactive communications to help the sponsor design and conduct a drug development program as

[13] Section 505(d) of the FD&C Act and section 351(a) of the Public Health Service Act.

efficiently as possible.[14] During these interactions, the Agency may suggest, or a sponsor may propose, alternative clinical trial designs (e.g., adaptive designs, an enrichment strategy, crossover or N-of-1 design, use of historical controls) or use of an interim analysis by a data monitoring committee.[15] These trial designs may result in smaller trials or more efficient trials that require less time to complete and may help minimize the number of patients exposed to a potentially less efficacious treatment (i.e., the control group treated with available therapy). Such approaches may be especially useful in studies in rare diseases. For example, single-arm trials may be an important option in rare diseases with well-understood pathophysiology and a well-defined disease course.

FDA anticipates that the review team and the sponsor will meet and interact 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 (see section IX.D.)).

2. Organizational Commitment Involving Senior Managers

FDA intends to expedite the development and review of a breakthrough therapy by intensively involving senior managers and experienced review and regulatory health project management 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 drug development program. The cross-disciplinary project lead will serve as a scientific liaison between members of the review team (e.g., medical; clinical pharmacology; pharmacology-toxicology; chemistry, manufacturing, and controls (CMC); compliance; biostatistics), facilitating coordinated internal interactions and communications with a sponsor through the review division's regulatory health project manager.

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

FDA has determined that it is appropriate for a drug designated as a breakthrough therapy to be able to obtain rolling review. Therefore, if FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a breakthrough therapy product may be effective, the Agency may consider reviewing portions of a marketing application before the sponsor submits the complete application (see Appendix 2).

4. Other Actions to Expedite Review

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[14] As noted in IX. GENERAL CONSIDERATIONS, it is important that sponsors respond promptly to FDA inquiries, which may include, for example, requests for information on various aspects of the drug development program.

[15] For more discussion of alternative clinical trial designs, see the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* and the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. When final, these guidances will represent FDA's current thinking on these topics. See also the ICH E10 and the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

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.

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 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, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on IMM or other clinical benefit (see sections VII.D.2. and VII.D.3.).[16]

This section describes the qualifying criteria, relevant terms, and the conditions of accelerated approval. The provisions of FDASIA facilitate somewhat broader use of accelerated approval to expedite patients' 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.). In addition, 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.).[17] By indicating that FDA should take into account, ". . . the severity, rarity, or prevalence of the condition . . ." in considering whether to grant accelerated approval, FDASIA reinforces the Agency's longstanding commitment to regulatory flexibility regarding the evidence required to support product approval for the treatment of serious or life-threatening diseases with limited therapeutic options.

The accelerated approval pathway has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug. For example, accelerated approval has been used extensively in the approval of drugs to treat a variety of cancers and human immunodeficiency virus (HIV) disease where an effect

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

[17] Section 506(c)(1)(B) of the FD&C Act. 21 CFR 314.510 and 601.41 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."

on tumor growth or viral load can be assessed rapidly, but demonstrating an effect on survival or morbidity generally requires lengthy and sometimes large trials because of the duration of the typical disease course. Accelerated approval is also potentially useful in acute disease settings where the intended clinical benefit can be demonstrated only in a very large study because the clinical event that would need to be evaluated to demonstrate clinical benefit occurs rarely. For example, accelerated approval could be used for an acute condition where an effect on a surrogate endpoint could be shown in a small number of patients, but a much larger study would be needed to show the effect on a clinical outcome, such as survival.

FDA encourages sponsors to communicate with the Agency early in development concerning the potential eligibility of a drug for accelerated approval, proposed surrogate endpoints or intermediate clinical endpoints, clinical trial designs, and planning and conduct of confirmatory trials. A sponsor seeking accelerated approval may also need to prepare 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 (see section IX.D.)).

A. Qualifying Criteria for Accelerated Approval

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 principal risk of this approach is the possibility that patients will be exposed to a drug that ultimately will not be shown to provide an actual clinical benefit. In addition, there generally will be fewer, smaller, or shorter clinical trials than is typical for a drug receiving traditional approval, which may generally mean there is less information about the occurrence of rare or delayed adverse events. Uncertainty about whether clinical benefit will be verified and the possibility of undiscovered risks are the primary reasons that accelerated approval is reserved for drugs intended to treat a serious condition and that appear to provide a 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.[18] The accelerated approval provisions of section 901 of FDASIA (amending section 506 of the FD&C Act) require FDA to ". . .tak[e] into account . . . the availability or lack of alternative treatments."

Amended section 506(c) clarifies the Agency's flexibility in administering the accelerated approval program. For example, an alternative therapy with efficacy 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 section III.C.2. provides examples of situations in

[18] 21 CFR 314.500 and 601.40.

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 efficacy or safety advantage. Section III.B. describes what constitutes available therapy when determining whether a drug provides a meaningful advantage.

3. Demonstrates an Effect on an Endpoint That Is Reasonably Likely to Predict Clinical Benefit

These endpoints are discussed in section VII.B. The basis for determining whether an endpoint is reasonably likely to predict clinical benefit is discussed in section VII.C.

B. 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 (2) a clinical endpoint that can be measured earlier than 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 that could be used for traditional approval), a surrogate endpoint that is reasonably likely to predict a drug's intended clinical benefit (and that could therefore be used as a basis 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 that therefore cannot be used to support traditional or accelerated approval of a marketing application).

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

- Prolonged suppression of HIV viral load in plasma has been shown to reduce the morbidity and mortality associated with HIV disease and has been the basis for

traditional approval. Shorter-term suppression of viral load has been used in the past as a surrogate to support accelerated approval because it was considered reasonably likely to predict an effect on morbidity or mortality. Data now demonstrate that short-term suppression of viral load may support full approval, in some circumstances.[19]

- Clearance of bacteria from the blood stream as evidenced by a laboratory measurement of bacteria in the blood has been considered reasonably likely to predict the clinical resolution of infection.

- Outcomes of 6-month follow-up treatment (i.e., sputum culture status and infection relapse rate) have been considered reasonably likely to predict the resolution of pulmonary tuberculosis.

- 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.

- Radiographic evidence of tumor shrinkage (response rate) in certain cancer types has been considered reasonably likely to predict an improvement in overall survival.

2. Intermediate Clinical Endpoints

For purposes of accelerated approval, an intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on IMM and is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit. An important question is whether the demonstrated therapeutic effect alone would be a basis for traditional approval. Approvals for products for serious conditions based on clinical endpoints other than IMM will usually be considered under traditional approval procedures. Approvals based on such clinical endpoints will be considered under the accelerated approval pathway only when it is essential to determine effects on IMM or other clinical benefit in order to confirm the predicted clinical benefit that led to approval. Although FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, FDA believes intermediate clinical endpoints generally could be used to support accelerated approval in situations such as:

- A study demonstrates a relatively short-term clinical benefit in a chronic disease setting in which assessing durability of the clinical benefit is essential for traditional approval, but the short-term benefit is considered 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).

[19] See the draft guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment.* When final, this guidance will represent FDA's current thinking on this topic.

Examples of cases in which FDA has used an intermediate clinical endpoint to support accelerated approval include the following:

- A treatment for multiple sclerosis was approved based on a large therapeutic effect on relapse rate through approximately 13 months of treatment, but where there was uncertainty about the durability of the observed effect. Under accelerated approval, the sponsor was required to continue the existing trials into the postmarketing period to confirm durability of the observed effect at 2 years.

- A treatment for preterm labor was approved based on a demonstration of delay in delivery. Under accelerated approval, the sponsor was required to conduct postmarketing studies to demonstrate improved long-term postnatal outcomes.

FDA will not grant accelerated approval to products that meet standards 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.[20] For effectiveness, the standard is substantial evidence based on adequate and well-controlled clinical investigations.[21] 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.[22] 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. FDA carefully evaluates such evidence to ensure that any remaining doubts about the relationship of the effect on the surrogate to clinical benefit are resolved by additional postapproval studies or trials.[23] An application for accelerated approval should also include 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. The empirical evidence may include ". . . epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."[24] Evidence of pharmacologic activity alone is not sufficient, however.[25] Clinical data should be provided to support a conclusion that a relationship of an effect on the

[20] Section 505(d) of the FD&C Act.
[21] Section 505(d)(5) of the FD&C Act.
[22] Section 505(d)(1) of the FD&C Act.
[23] 57 FR 58942 at 58948.
[24] Section 506(c)(1)(B) of the FD&C Act.
[25] 57 FR 58942.

surrogate endpoint or intermediate clinical endpoint to an effect on the clinical outcome is reasonably likely.

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, as needed. This guidance provides an overview of some of the important factors to consider in identifying and assessing the predictive potential of surrogate endpoints or intermediate clinical endpoints. 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 or IMM because such evidence is case-specific and is not readily generalizable.

1. Understanding of the Disease Process

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

- The underlying cause of the disease (e.g., elevated uric acid and gout, elevated blood pressure and hypertensive cardiovascular disease, low thyroxine levels and hypothyroidism, high ammonia levels and urea cycle disorders)

- 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, effects on serum creatinine or glomerular filtration rate (if not transient or reversible) are accepted surrogates for predicting effects on chronic renal disease and delaying the occurrence of end-stage renal disease)

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

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 determine whether an effect on a surrogate endpoint represents a meaningful effect on the causal pathway. 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 as measured by blood levels, but not tissue levels, will not reasonably predict the disease course or treatment results.

Some effects on well-established, disease-related biomarkers[26] may have little or no ability to predict clinical benefit or their ability to predict benefit may vary depending on the disease or the

[26] FDA's CDER has established the Biomarker Qualification Program to support work with external scientists and clinicians in developing biomarkers. The Biomarker Qualification Program offers a formal process to guide submitters as they develop biomarkers and rigorously evaluate them for use in the regulatory process. Details on 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 non-steroidal anti-inflammatory drug does not predict the drug's effect on the disease. However, a fall in a patient's body temperature in response to an antibiotic may be an indication of an effect on the disease. Similarly, in prostate cancer, increased levels of prostate-specific antigen (PSA) may be the result of advancing tumor burden. Therefore, PSA may be correlated with the progression of prostate cancer and the risks of mortality. However, the relationship between increasing PSA and disease progression and morbidity is not uniform. Thus the ability of a drug to lower PSA levels cannot necessarily be relied upon to predict the drug's clinical benefit.

2. 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 either because the effect is on the causal pathway or correlates with clinical outcomes is critical. Sometimes this relationship can be assessed epidemiologically but it is most persuasively established by knowing that a drug that affects the surrogate endpoint also affects a clinical outcome. Thus, 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. Similarly, killing infecting bacteria or viruses leads to curing 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.

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

- Whether there is reliable and consistent epidemiologic evidence supporting the relationship between the endpoint and the intended clinical benefit.[27]

- How precisely the epidemiologic relationship between the endpoint and clinical outcome is defined. For example, the extent to which an abnormal endpoint corresponds to a worse clinical outcome, as is the case for blood pressure and low-density lipoprotein (LDL) cholesterol. (The stronger the correlation between the abnormality and clinical outcome, the stronger the basis for concluding that an effect on the endpoint would have a reasonably well-defined effect on the clinical outcome.)

- Whether 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.

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program are available at http://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm284076.htm.

[27] Note, however, that 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.

Particularly in rare diseases, there may be limited information in the literature, lack of in-depth epidemiological or historical data, and little or no experience with other drugs to inform the interpretation of surrogate endpoints or intermediate clinical endpoints. FDA may consult with external experts on surrogate endpoints and intermediate clinical endpoints where there is a lack of historical data for a given disease.[28]

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.[29] 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.[30]

2. Confirmatory Trials

For drugs granted accelerated approval, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on IMM or other clinical benefit. These trials must be completed with due diligence.[31]

FDA has interpreted the due diligence requirement to mean that the postmarketing trial(s) intended to verify the clinical benefit must be conducted promptly to facilitate determination, as soon as possible, of whether clinical benefit has been verified. The protocol for a postmarketing trial should be developed as early as possible, and timelines for the trial should be specified; for example, timelines for enrollment and trial completion should be stipulated. There should be agreement between FDA and the sponsor on the design and conduct of the confirmatory trial(s).

If it is clear during development that a product is intended to be approved under accelerated approval on the basis of a surrogate endpoint or an intermediate clinical endpoint, confirmatory trial(s) should be underway at the time the marketing application is submitted. If it is not clear until shortly before or after submission of a marketing application that a surrogate endpoint or an intermediate clinical endpoint will be the proposed basis for accelerated approval, there should be agreement on the design and conduct of such trial(s) before approval.

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[28] See, for example, section 569(a)(2), (b), and (c) of the FD&C Act, *Consultation With External Experts on Rare Diseases, Targeted Therapies and Genetic Targeting of Treatments*, which describes general consideration for consultation with external experts, topics for consultation, and classification as special Government employees.
[29] 21 CFR 314.550 and 601.45.
[30] 21 CFR 314.550 and 601.45.
[31] Section 506(c)(3)(A) of the FD&C Act and §§ 314.510 and 601.41. Where confirmatory trials verify clinical benefit, FDA generally will terminate the requirement (21 CFR 312.560 and 601.46).

Generally, the confirmatory trial would evaluate a clinical endpoint that directly measures clinical benefit. For example, the confirmatory trial population would ordinarily be 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 in the same disease population. In these cases, a confirmatory trial may be conducted in a different but related population that is capable of verifying the predicted clinical benefit. This is often the case in oncology, where after accelerated approval of a drug for late-stage disease is granted, the confirmatory trial is conducted in an earlier stage of the same cancer.

There are also cases in which additional evaluation (longer duration) of the same surrogate endpoint that was used to support accelerated approval (rather than a clinical endpoint) in the same population could be persuasive evidence of clinical benefit. For example, in the case of HIV treatment, an effect on viral load of relatively short duration (24 weeks) was considered reasonably likely to predict clinical benefit supporting accelerated approval. An effect of longer (1 year) 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 for traditional approval.[32]

When it is possible to use a later effect in a trial to verify the effect seen earlier in the same trial that supported accelerated approval, the same clinical trial(s) can be used to support accelerated approval and verify and describe the clinical benefit. In this 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 randomized trial(s) to obtain data on the clinical endpoint that will be the basis for verifying the clinical benefit. When the same trial is used to support accelerated approval and verify clinical benefit, the data to verify the clinical benefit may be, in some cases, 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,[33] for example:

- A trial required to verify the predicted clinical benefit of the product fails to verify such benefit.
- Other evidence demonstrates that 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.

[32] Although an effect on viral load changes of short duration had been used in the past as a surrogate endpoint to support accelerated approval, FDA now considers this endpoint acceptable, in some circumstances, to grant traditional approval based on years of experience with this endpoint.

[33] See section 506(c)(3) of the FD&C Act and §§ 314.530(a) and 601.43(a). Part 314, subpart E and part 601, subpart H describe additional grounds for withdrawal.

- 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 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 request withdrawal of approval under § 314.150(d) or notify the applicant of FDA's proposal to withdraw approval in a notice of opportunity for hearing (NOOH). The NOOH generally will state the proposed grounds for withdrawal of approval.[34] 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.[35] An applicant may also request the Agency to withdraw approval of an application approved under accelerated approval.[36]

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, specific statutory provisions 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 and the features of priority review designation. Appendix 1 describes the process for priority review designation.

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 at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis 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

[34] 21 CFR 314.530(b) and 601.43(b).
[35] 21 CFR 314.530(c)(1) and 601.43(c)(1).
[36] 21 CFR 314.150(c) and 601.5(a).

- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- 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 relating to either safety or effectiveness. Alternatively, sponsors could show the drug's 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.[37]

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 of receipt (compared with 10 months under standard review). The PDUFA review clock for applications filed by FDA under the Program is described in section IV.

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 a sponsor respond promptly to FDA's inquiries.[38] This applies to formal meetings and related inquiries, written correspondence, and other interactions. In addition to the many types of formal meetings[39] 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 may need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program. The sponsor's product quality and CMC teams should initiate early

[37] Sponsors contemplating the use of historical controls should consult ICH E10 for more-detailed discussions.
[38] For example, FDA may request updates on a breakthrough therapy designation program in order to provide the sponsor with guidance on drug development.
[39] See the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants*.
Also see the *CDER 21st Century Review Process Desk Reference Guide* accessible at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm.

communication with FDA to ensure that the manufacturing development programs and timing of submissions meet the Agency's expectations for licensure or marketing approval.[40]

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. The proposal should also consider manufacturing facilities and a lifecycle approach to process validation. Additionally, the proposal should include a timeline for development of the manufacturing capabilities with goals aligned with the clinical development program. After the initial discussion following designation, frequent communication during development will generally facilitate meeting manufacturing development goals and product quality goals.

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 activities.[41] Coordination with the sponsor and contract manufacturers may be necessary to ensure that manufacturing facilities and equipment are ready for inspection during review of the clinical section of the application. A comprehensive meeting with FDA's product quality review groups in advance of submission may facilitate the quality assessment of products designated for expedited programs.

Although sponsors must ensure the availability of quality product at the time of approval, FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components (e.g., stability updates, validation strategies, inspection planning, manufacturing scale-up). The level of flexibility will be determined on a case-by-case basis after consideration of factors such as the following: (1) product characteristics, (2) seriousness of the condition and medical need, (3) manufacturing processes, (4) the robustness of the sponsor's quality system, and (5) the strength of the sponsor's risk-based quality assessment. FDA's consideration of the sponsor's proposal for an integrated postmarketing plan will also take into account whether elements of the plan may be appropriately executed as a postmarketing commitment or requirement. For example, FDA will consider impacts on clinical performance, such as safety and immunogenicity. Sponsors should meet with the Agency to discuss their proposed plan as soon as possible and no later than the pre-NDA or pre-BLA meeting.

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

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

[41] For products designated as fast track or breakthrough therapy, this can be accomplished through rolling review (see 2. Submission of Portions of an Application (Rolling Review), 3. Submission of Portions of an Application (Rolling Review), and Appendix 2: Processes for Rolling review). For products submitted under an NDA without such a designation, flexibility is permitted in § 314.50(d)(1)(iv). For BLAs without such a designation, there is flexibility also to allow an early submission of the CMC section when resources permit.

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. Sponsors should be prepared for inspections to be scheduled by the Agency 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.

D. Companion Diagnostics

Development programs utilizing one or more of the expedited programs described in this guidance may involve an in vitro companion diagnostic device. Sponsors using one of the expedited programs for a product that involves an in vitro companion diagnostic device should consult FDA's guidance on the topic.[42]

X. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The time required to complete this information collection is estimated to average 30 hours per response to prepare a priority review designation request and 70 hours per response to prepare a breakthrough therapy designation request, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy
10903 New Hampshire Avenue, Bldg. 51, rm. 6360
Silver Spring, MD 20993-0002

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR 202.1, certain parts of part 314, part 601, and sections 506(b)(1), 735, and 736 of the FD&C Act have been approved under OMB control numbers 0910-0686, 0910-0001, 0910-0338, and 0910-0297. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0765. The current expiration date is available at https://www.reginfo.gov (search ICR and enter OMB control number).

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 request fast track designation when the IND is first submitted or at any time thereafter before receiving marketing approval of their 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, FDA should ordinarily receive a fast track designation request 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. If a sponsor's drug development program is granted fast track designation for one indication and has subsequently obtained data to support fast track designation for another indication, the sponsor should submit a separate request.

2. Where to Send a Designation Submission

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

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, identification of the submission in the cover letter as a **REQUEST FOR FAST TRACK DESIGNATION** in bold, uppercase letters. If the request is submitted with an initial IND, identification of the submission in the cover letter 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, the name of the sponsor's contact person and the contact person's address, email address, telephone number, and fax number.

- If applicable, the IND application number.

- If available, for drug products, the proprietary name and active ingredient and for biological products, the proper name and proprietary 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 following:
    - 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, a list of documents previously submitted to the IND that is 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 meets 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 Designation as a Fast Track Development Program

Over the course of drug development, it can be expected that some products granted fast track designation 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 meets 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 when the IND is first submitted or at any time thereafter, 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."[43] FDA therefore expects that in most cases breakthrough therapy designation requests would be submitted as an amendment to the IND. Ideally, FDA should receive a breakthrough therapy designation request before initiation of the clinical trial(s) intended to serve as the primary basis for demonstration of efficacy if most of the benefits of 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 anticipates that breakthrough therapy designation requests will rarely be made after the submission of an original BLA or NDA or a supplement. If a sponsor's drug development program is granted breakthrough therapy designation for one indication and has subsequently obtained preliminary clinical evidence to support breakthrough therapy designation for another indication, the sponsor should submit a separate request.

If a sponsor has not requested breakthrough therapy designation, FDA may suggest that the sponsor consider submitting a request if: (1) after reviewing available data and information, the Agency thinks the drug development program may meet the criteria for breakthrough therapy designation and (2) the remaining drug development program and review can benefit from the designation. However, the Agency still needs to review the submitted request (including preliminary clinical evidence) to determine if it meets the criteria for breakthrough therapy designation. A suggestion by the Agency that a sponsor consider submitting a request for

[43] Section 506(a)(1) of the FD&C Act.

breakthrough therapy designation is advisory and should not be interpreted as guaranteeing breakthrough therapy designation once a request is submitted and reviewed.

2. Where to Send a Designation Submission

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

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):

- If the breakthrough therapy designation request is submitted to the sponsor's IND as an amendment, identification of the submission in the cover letter as a **REQUEST FOR BREAKTHROUGH THERAPY DESIGNATION** in bold, uppercase letters. If the request is submitted with an initial IND, identification of the submission in the cover letter 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 and the contact person's address, email address, telephone number, and fax number.

- If applicable, the IND application number.

- If available, for drug products, the proprietary name and active ingredient and for biological products, the proper name and proprietary 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 breakthrough therapy designation request for the indication being studied, including the following:

    - 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.[44] FDA does not expect the sponsor to submit primary data (data sets); but, the sponsor should describe the preliminary clinical evidence, including, for example, a brief description of available therapies (if there are any) and their effectiveness; justification for the comparator selected

[44] If the designation is being submitted with the IND, examples of information that could be submitted to support a designation request include data from foreign clinical trials not conducted under IND, a different formulation or route of administration, a use in an unrelated indication, or the published literature.

for the clinical studies, the study design, the population studied, and the endpoint used; and a brief description of the study results and statistical analyses (including, for example, subgroup analysis).

- If applicable, a list of documents previously submitted to the IND that is 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 that the drug development program 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. Where appropriate, the letter may also include advice to the sponsor regarding subsequent development, including what would be needed in a new breakthrough therapy designation request.

5. Continued Designation as a Breakthrough Therapy Development Program

Over the course of drug development, it can be expected that some products granted breakthrough therapy designation will no longer be considered a breakthrough therapy. For example, a drug 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. Consistent with FDA's commitment to communicate frequently, and in an interactive manner, with sponsors of drugs designated as breakthrough therapies, FDA will notify the sponsor of its intent to rescind and will offer the sponsor an opportunity to justify its product's continued designation. FDA recognizes that sponsors of products that have had their breakthrough therapy designation rescinded because available data no longer support the designation may still have sufficient evidence after completion of the drug development program to support marketing approval.

C. Process for Priority Review Designation

FDA determines whether an application qualifies for priority review (versus standard review) for every application, not just when priority review is 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 to the attention of the appropriate review division or office in CDER or CBER.

3. Content of a Designation Submission

Priority review designation requests should contain the following information:

- Identification of the submission in the cover letter as a **REQUEST FOR PRIORITY REVIEW DESIGNATION** in bold, uppercase letters.

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

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

- The proposed indication(s).

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

    - 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, prevention, or diagnosis of a serious condition

4. FDA Response

FDA 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 formal 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 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.) and breakthrough therapy designation (see section V1.B.3.).

A. Agreement on Proposal

Sponsors obtain preliminary Agency agreement on the proposal at the pre-BLA or pre-NDA meeting or earlier for products with breakthrough therapy designation (e.g., end-of-phase 2 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; attach Form FDA 1571. The amendment should be clearly identified as a **REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION** in bold, uppercase letters. 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.[45] 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, a 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

[45] 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 the complete application is submitted. Actual commencement and scheduling of review depends on many factors, including staffing, workload, competing priorities, timeline for completing the application, 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.[46] After the Agency is notified of the complete application, we will make a filing determination within the usual time.[47]

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[46] 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.

[47] See § 314.101, CDER MAPP 6025.4, *Good Review Practice: Refuse to File*, available on the Internet at http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm370948.htm 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.