Guidance for Industry

Expedited Programs for Serious Conditions—Drugs and Biologics

DRAFT GUIDANCE

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

June 2013
Procedural

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Expedited Programs for Serious Conditions—Drugs and Biologics

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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). This guidance for industry provides a single resource for information on FDA's policies and procedures for these four programs as well as threshold criteria generally applicable to concluding that a drug is a candidate for these expedited development and review programs.

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

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

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

[2] For the purposes of this guidance, all references to "drugs" or "drug products" include both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

[3] Section III.A.1 explains that all references to serious conditions include life-threatening conditions.

[4] We update and issue guidances periodically. We recommend you check the FDA Web site to ensure that you have the most up-to-date version of a guidance. The guidances referenced in this document are available on the Drugs guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and the Biologics guidance page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

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

III. CONCEPTS FOR EXPEDITED PROGRAMS

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

A. Serious Condition

1. Whether a Condition Is Serious

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

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

---

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

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

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

[8] 21 CFR part 312, subpart I.

72 such factors as survival, day-to-day functioning, or the likelihood that the disease, if left
73 untreated, will progress from a less severe condition to a more serious one."[9]
74
75 This definition is derived from and consistent with the descriptions of the term in the preamble to
76 the accelerated approval proposed rule and the fast track guidance.
77
78 Note: For the purposes of this guidance, FDA considers the term *condition* to include a
79 disease or illness. All conditions meeting the definition of life-threatening as set forth at
80 21 CFR 312.81(a) would also be serious conditions.
81
82 *2. Whether the Drug Is Intended to Treat a Serious Condition*
83
84 As referenced in Section IV, as a general matter, the statutory and regulatory eligibility criteria
85 for expedited programs require that a drug be intended to treat a serious condition. To satisfy
86 this criterion, a drug must be intended to have an effect on a serious aspect of a condition, such
87 as a direct effect on a serious manifestation or symptom of a condition, or other intended effects,
88 including:
89
90 • A diagnostic product intended to improve diagnosis or detection of a serious condition in
91 a way that would lead to improved outcomes
92
93 • A product intended to improve or prevent a serious treatment-related side effect (e.g.,
94 serious infections in patients receiving immunosuppressive therapy)
95
96 • A product intended to avoid a serious adverse effect associated with available therapy for
97 a serious condition (e.g., less cardiotoxicity than available cancer therapy)
98
99 **B. Available Therapy**
100
101 For purposes of this guidance, FDA generally considers *available therapy* (and the terms *existing*
102 *treatment* and *existing therapy*) as a therapy that:
103
104 • Is approved or licensed in the United States for the same indication being considered for
105 the new drug and
106
107 • Is relevant to current U.S. standard of care (SOC) for the indication
108
109 *Approval or Licensure*: Only in rare cases will a treatment that is not approved for the indicated
110 use or is not FDA-regulated (e.g., surgery) be considered available therapy. In those cases, FDA
111 may consider an unapproved or unlicensed therapy to constitute "available therapy" if the safety
112 and effectiveness of the use is supported by compelling evidence, including evidence in the
113 published literature (e.g., certain established oncologic treatments).

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

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

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

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

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

141

142 **C. Unmet Medical Need**

143

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

149

150 *1. Where There Is No Available Therapy*

151

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

153

154

155

156 *2. Where There Is Available Therapy*
157
158 When available therapy exists for a condition, a new treatment generally would be considered to
159 address an unmet medical need if the treatment:
160
161 • Has an effect on a serious outcome of the condition that is not known to be influenced by
162 available therapy (e.g., progressive disability when the available therapy has shown an
163 effect on symptoms but has not shown an effect on progressive disability)
164
165 • Has an improved effect on a serious outcome(s) of the condition compared to available
166 therapy (e.g., superiority of the new drug used alone or in combination with available
167 therapy in an active- or historically-controlled trial assessing an endpoint reflecting
168 mortality or serious morbidity)
169
170 • Has a benefit for patients who are unable to tolerate available therapy or whose disease
171 has failed to respond to available therapy, or the treatment can be used effectively with
172 other critical agents that cannot be combined with available therapy
173
174 • Provides efficacy similar to those of available therapy, while (1) avoiding serious toxicity
175 that occurs with available therapy, (2) avoiding less serious toxicity that is common and
176 causes discontinuation of treatment of a serious condition, or (3) reducing the potential
177 for harmful drug interactions
178
179 • Provides similar safety and efficacy as available therapy but with another documented
180 benefit, such as improved compliance, that is expected to lead to an improvement in
181 serious outcomes
182
183 • Addresses an emerging or anticipated public health need, such as a drug shortage
184
185 In some disease settings, a drug that is not shown to provide a direct efficacy or safety advantage
186 over available therapy may nonetheless provide an advantage that would be of sufficient public
187 health benefit to qualify as meeting an unmet medical need. For example, in a condition for
188 which there are approved therapies that have a modest response rate or significant heterogeneity
189 in response, a drug with a novel mechanism of action (but comparable safety and effectiveness)
190 could have the potential to provide an advantage over available therapy. In such a case, the
191 novel mechanism of action should have a well-understood relationship to the disease
192 pathophysiology. In addition, there should be a reasonable basis for concluding that a significant
193 number of patients may respond differently to the new drug compared to available therapy. For
194 example, mechanistic diversity, even without a documented efficacy or safety advantage, could
195 be advantageous in disease settings in which drugs become less effective or ineffective over
196 time. For example, infectious disease drugs or targeted cancer therapies with novel mechanisms
197 of action, although appearing to have comparable efficacy across the disease population, could
198 benefit patients who no longer respond to available therapy. Accordingly, FDA intends to
199 consider a range of potential advantages over available therapy beyond those shown in head-to-
200 head comparisons.

201 *3. Where the Only Available Therapy Was Approved Under the Accelerated*
202 *Approval Program Based on a Surrogate or Clinical Endpoint and Clinical*
203 *Benefit Has Not Yet Been Verified*
204
205 As discussed in Section VII, FDA recognizes, as a general matter, that it is preferable to have
206 more than one treatment approved under the accelerated approval provisions because of the
207 possibility that clinical benefit may not be verified in post-approval confirmatory trials. FDA
208 may therefore consider products as addressing unmet medical need notwithstanding the
209 availability of therapies with accelerated approval.

210 **IV. OVERVIEW OF EXPEDITED PROGRAMS**

211 The table provides an overview of the four expedited programs. Additional details on the specific programs
212 are found in the sections that follow.
213

Comparison of FDA's Expedited Programs for Serious Conditions

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

Comparison of FDA's Expedited Programs for Serious Conditions

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

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

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

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

[d] See footnote b above.

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

V. FAST TRACK DESIGNATION

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

A. Qualifying Criteria for Fast Track Designation

1. Serious Condition

See Section III.A.

2. Demonstrating the Potential to Address Unmet Medical Need

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

B. Features of Fast Track Designation

1. Actions to Expedite Development and Review

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

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

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

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

256 reviewing portions of a marketing application before the sponsor submits the complete
257 application (see Appendix 2).[10]
258
259 # VI. BREAKTHROUGH THERAPY DESIGNATION
260
261 Section 506(a) of the FD&C Act provides for designation of a drug as a breakthrough therapy "if
262 the drug is intended, alone or in combination with 1 or more other drugs, to treat a *serious or*
263 *life-threatening disease or condition* and *preliminary clinical evidence* indicates that the drug
264 may demonstrate substantial improvement over *existing therapies* on 1 or more *clinically*
265 *significant endpoints*, such as substantial treatment effects observed early in clinical
266 development." This section describes the qualifying criteria (italicized terms) and the features
267 (e.g., benefits) of breakthrough therapy designation. Appendix 1 describes the breakthrough
268 therapy designation process.
269
270 ## A. Qualifying Criteria for Breakthrough Therapy Designation
271
272 ### *1. Serious Condition*
273
274 See Section III.A.
275
276 ### *2. Existing (or Available) Therapies*
277
278 See Section III.B.
279
280 ### *3. Preliminary Clinical Evidence*
281
282 Unlike the information that could support fast track designation, which could include theoretical
283 rationale, mechanistic rationale (based on nonclinical data), or evidence of nonclinical activity,
284 breakthrough therapy designation requires preliminary clinical evidence of a treatment effect that
285 would represent substantial improvement over available therapies for the treatment of a serious
286 condition. Assessment of the treatment effect for the purposes of breakthrough therapy
287 designation will be based on preliminary clinical evidence, which could include early clinical
288 evidence of both clinical benefit and an effect on a mechanistic biomarker (generally derived
289 from Phase 1 and 2 trials). Nonclinical information could support the clinical evidence of drug
290 activity. In all cases, preliminary clinical evidence demonstrating that the drug may represent a
291 substantial improvement over available therapy should involve a sufficient number of patients to
292 be considered credible. However, FDA recognizes that the data cannot be expected to be
293 definitive at the time of designation.
294
295 Ideally, preliminary clinical evidence would be derived from a study that compares the
296 investigational drug to an available therapy (or placebo, if there is no available therapy) in
297 clinical testing and shows superiority, or from a study that compares the new treatment plus SOC
298 to the SOC alone. FDA encourages sponsors to obtain some preliminary comparative data of

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

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

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

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

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

Approaches to demonstrating preliminary clinical evidence of substantial improvement include:

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

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

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

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

340 - The new drug reverses disease progression, in contrast to available therapies that only
341 provide symptomatic improvement.
342 - The new drug has an important safety advantage that relates to serious adverse events
343 compared to available therapies and has similar efficacy.
344
345 *Clinically Significant Endpoint*: For purposes of breakthrough therapy designation, FDA
346 considers *clinically significant endpoint* generally to refer to an endpoint that measures an effect
347 on irreversible morbidity or mortality (IMM) or on symptoms that represent serious
348 consequences of the disease. It can also refer to findings that suggest an effect on IMM or
349 serious symptoms, including:
350
351 - An effect on an established surrogate endpoint
352
353 - An effect on a surrogate endpoint or intermediate clinical endpoint (see Section VII.B.2)
354 considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval
355 standard)
356
357 - An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an
358 acceptable surrogate endpoint, but strongly suggests the potential for a clinically
359 meaningful effect on the underlying disease
360
361 - A significantly improved safety profile compared to available therapy (e.g., less dose-
362 limiting toxicity for an oncology agent), with evidence of similar efficacy
363
364 In a breakthrough therapy designation request, the sponsor should provide justification for why
365 the endpoint, biomarker, or other findings should be considered clinically significant.
366
367 **B. Features of Breakthrough Therapy Designation**
368
369 *1. All Fast Track Designation Features*
370
371 Section 902 of FDASIA instructs FDA to take actions appropriate to expedite the development
372 and review of a breakthrough therapy. Because a drug that qualifies for breakthrough therapy
373 designation would also meet the standard for fast track designation, FDA has determined that it
374 would be appropriate for the features of fast track designation to be available to a drug
375 designated as a breakthrough therapy (see Section V.B).
376
377 *2. Intensive Guidance on an Efficient Drug Development Program, Beginning as*
378 *Early as Phase 1*
379
380 As discussed previously, breakthrough therapy designation will usually mean that the effect of
381 the drug will be large compared to available therapies. In such cases, the development program
382 for the breakthrough therapy could be considerably shorter than for other drugs intended to treat
383 the disease being studied. However, FDA notes that a compressed drug development program
384 still must generate adequate data to demonstrate that the drug is safe and effective in order to

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

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

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

3. Organizational Commitment Involving Senior Managers

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

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

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

427 **VII. ACCELERATED APPROVAL**
428
429 The accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that
430 FDA may grant accelerated approval to:
431
432 a product for a *serious or life-threatening condition* . . . upon a determination that the
433 product has an effect on a *surrogate endpoint* that is *reasonably likely to predict clinical*
434 *benefit*, or an effect on a *clinical endpoint that can be measured earlier than an effect on*
435 *irreversible morbidity or mortality*, that is reasonably likely to predict an effect on
436 irreversible morbidity or mortality or other clinical benefit, taking into account the
437 severity, rarity, or prevalence of the condition and the *availability or lack of alternative*
438 *treatments*.
439
440 Accelerated approval is usually contingent on a sponsor's agreement to conduct additional post-
441 approval studies to verify and describe the drug's clinical benefit (see Sections VII.D.2 and
442 VII.D.3).[13]
443
444 This section describes the qualifying criteria, relevant terms (italicized terms), and the conditions
445 of accelerated approval. The FDASIA provisions facilitate somewhat broader use of accelerated
446 approval to expedite patient access to important treatments for serious conditions. FDA believes
447 the new provisions provide additional flexibility concerning the implications of available therapy
448 on eligibility for accelerated approval (see Section VII.A.2). They also provide clarification
449 concerning the use of clinical endpoints (herein referred to as intermediate clinical endpoints) as
450 a basis for accelerated approval (see Section VII.B.2). Finally, the new provisions make clear
451 that FDA has the authority to consider pharmacologic or other evidence developed using
452 biomarkers or other scientific methods or tools, in conjunction with other data, in determining
453 whether an endpoint is reasonably likely to predict clinical benefit (see Section VII.C.1).[14]
454
455 The accelerated approval pathway is most often useful in settings in which the disease course is
456 long and an extended period of time is required to measure the intended clinical benefit of a
457 drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. For
458 example, accelerated approval has been used extensively in drug development for a variety of
459 cancers and human immunodeficiency virus (HIV) disease—diseases in which the goal of
460 therapy is generally to improve survival or decrease morbidity and the duration of the typical
461 disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival
462 benefit.
463
464 Accelerated approval is generally less useful in more acute disease settings in which therapy is
465 intended to provide a more near-term clinical benefit. In such settings, even if there are

[13] FDCA 506(c)(2)(A).
[14] FDCA 506(c)(1)(B). FDA regulations provide that the agency may consider "epidemiologic, therapeutic, pathophysiologic or other evidence" in determining whether an endpoint is reasonably likely to predict clinical benefit. FDASIA provides that FDA may consider "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."

466 potentially predictive surrogate endpoints or intermediate clinical endpoints, there may be little
467 or no time advantage for studies evaluating a surrogate or intermediate endpoint compared to
468 studies evaluating the intended clinical benefit.
469
470 FDA encourages sponsors to communicate with the Agency early in development concerning the
471 potential eligibility of the drug for accelerated approval, proposed surrogate or intermediate
472 clinical endpoints, clinical trial designs, and study planning and conduct of confirmatory trials.
473
474 **A. Qualifying Criteria for Accelerated Approval**
475
476 At the time a product is given accelerated approval, there generally will be uncertainty about
477 whether a surrogate endpoint or intermediate clinical endpoint predicts the drug's ultimate
478 anticipated clinical benefit. The principal risk of this approach is the possibility that patients will
479 be exposed to a drug that will ultimately not be shown to provide an actual clinical benefit. In
480 addition, there may be fewer, smaller, or shorter clinical trials than is typical for a drug with
481 traditional approval, which for example could mean there is less information about the
482 occurrence of rare adverse events. For these reasons, accelerated approval is limited to a drug
483 intended to treat a serious condition which appears to provide some meaningful advantage over
484 available therapy.
485
486 *1. Serious Condition*
487
488 See Section III.A.
489
490 *2. Meaningful Advantage Over Available Therapy*
491
492 The accelerated approval regulations state that accelerated approval is available only for drugs
493 that provide a meaningful therapeutic benefit over existing treatments.[15] The accelerated
494 approval provision of section 901 of FDASIA (amending section 506 of the FD&C Act) requires
495 FDA to "tak[e] into account . . . the availability or lack of alternative treatments."
496
497 Amended section 506(c) may reasonably be interpreted as providing additional flexibility as
498 compared to the regulations. Specifically, section 506(c) broadens use of the accelerated
499 approval pathway to cases in which the advantage of a new drug over available therapy may not
500 be a direct therapeutic advantage, but is a clinically important improvement from a patient and
501 public health perspective. The discussion of unmet medical need in Section III.C.2 provides
502 examples of situations in which a drug could be shown to provide a meaningful advantage over
503 available therapy, including some in which there may not be a demonstrated direct therapeutic
504 advantage. Section III.B describes what constitutes available therapy for purposes of
505 determining whether a drug provides a meaningful advantage.
506
507

[15] 21 CFR 314.500 and 601.40.

508 **B. Accelerated Approval Endpoints**
509
510 There are two types of endpoints that can be used as a basis for accelerated approval: (1) a
511 surrogate endpoint that is considered reasonably likely to predict clinical benefit; and (2) a
512 clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that
513 is reasonably likely to predict an effect on IMM or other clinical benefit (also see Section
514 VII.D.2). For purposes of this guidance, these categories of endpoints are referred to as
515 surrogate endpoints and intermediate clinical endpoints, respectively.
516
517 A clinical endpoint is a characteristic or variable that directly measures a therapeutic effect of a
518 drug—an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved
519 mobility), or survives.
520
521 A clinical benefit is a positive therapeutic effect that is clinically meaningful in the context of a
522 given disease. The clinical benefit must be weighed against a treatment's risks to determine
523 whether there is an overall benefit for patients (i.e., a positive benefit-risk profile).
524
525 *1. Surrogate Endpoints*
526
527 For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory
528 measurement, radiographic image, physical sign, or other measure that is thought to predict
529 clinical benefit, but is not itself a measure of clinical benefit. Depending on the strength of the
530 evidence supporting the ability of a marker to predict clinical benefit, the marker may be a
531 surrogate endpoint that is known to predict clinical benefit (a validated surrogate endpoint, which
532 could be used for traditional approval), a surrogate endpoint that is reasonably likely to predict a
533 drug's intended clinical benefit (which could be used for accelerated approval), or a marker for
534 which there is insufficient evidence to support reliance on the marker as either kind of surrogate
535 endpoint (and thus cannot be used to support traditional or accelerated approval of a marketing
536 application).
537
538 HIV viral load, as evidenced by a laboratory measure of HIV in plasma, has been shown to
539 correlate with morbidity and mortality associated with HIV disease, but is not a direct measure of
540 clinical benefit. Prolonged suppression of viral load is known to reliably predict an effect on
541 survival.
542
543 *2. Intermediate Clinical Endpoints (clinical endpoints that can be measured earlier*
544 *than an effect on irreversible morbidity or mortality)*
545
546 For purposes of accelerated approval, an intermediate clinical endpoint is a measurement of a
547 therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug,
548 such as an effect on IMM.
549
550 A threshold question is whether the demonstrated therapeutic effect alone would be a basis for
551 traditional approval. For example, traditional approval would be appropriate where the effect is
552 modest, but a sufficiently meaningful benefit within the context of the disease to provide a

553 favorable risk-benefit profile. If the therapeutic effect is not a clinical benefit and a basis for
554 traditional approval, accelerated approval could be an option if there is a basis for concluding
555 that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a drug.
556 FDA has limited experience with accelerated approvals based on intermediate clinical endpoints.
557 However, we believe intermediate clinical endpoints generally would be used to support
558 accelerated approval in the following types of situations:
559
560 - The study results for a clinical endpoint demonstrate a therapeutic effect that would not
561 support traditional approval because:
562
563 - The effect is not a clinical benefit
564
565 - The effect is only a modest benefit within the context of the disease that alone
566 would not justify the risks associated with the drug, but there is an evidentiary
567 basis to conclude that the effect is reasonably likely to predict an effect on IMM
568 or other clinical benefit that would be a basis for traditional approval
569
570 - A clinical endpoint demonstrates a relatively short-term clinical benefit in a chronic
571 disease setting in which it is essential to confirm longer-term durability of the clinical
572 benefit for traditional approval but the short-term benefit is reasonably likely to predict
573 long-term benefit
574
575 - A clinical endpoint demonstrates a clinical benefit that is reasonably likely to predict an
576 effect on IMM in a disease setting in which it is essential to confirm the effect on IMM,
577 (e.g., because available therapy has established effects on IMM)
578
579 FDA expects that most demonstrations of clinical benefit would be a basis for traditional
580 approval. Sponsors considering a development program for accelerated approval based on an
581 intermediate clinical endpoint should discuss their development program with the appropriate
582 review division early in drug development.
583
584 **C. Evidentiary Criteria for Accelerated Approval**
585
586 Drugs granted accelerated approval must meet the same statutory standards for safety and
587 effectiveness as those granted traditional approval.[16] For effectiveness, the standard is
588 substantial evidence based on adequate and well-controlled clinical investigations.[17] For safety,
589 the standard is having sufficient information to determine whether the drug is safe for use under
590 conditions prescribed, recommended, or suggested in the proposed labeling.[18] Under accelerated
591 approval, FDA can rely on a particular kind of evidence, such as a drug's effect on a surrogate
592 endpoint, as a basis for approval (and ensure that remaining doubts about the relationship of the

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

593 effect on the surrogate to clinical benefit are resolved by additional post-approval studies).[19] An
594 application for accelerated approval should also include evidence that a surrogate or intermediate
595 clinical endpoint is reasonably likely to predict the intended clinical benefit of a drug.
596
597 *1. Whether an Endpoint Is "Reasonably Likely to Predict" Clinical Benefit*
598
599 Whether an endpoint is reasonably likely to predict clinical benefit is a function of the biological
600 plausibility of the relationship between the disease, endpoint, and the desired effect, and the
601 empirical evidence to support that relationship. The empirical evidence may include
602 "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed
603 using biomarkers, for example, or other scientific methods or tools."[20] Evidence of
604 pharmacologic activity alone is not sufficient, however.[21] Clinical data should be provided to
605 support the assertion that a relationship of the surrogate or intermediate clinical endpoint to the
606 outcome is reasonably likely, and should be relevant to the relationship between the specific
607 endpoint to be used and the specific intended clinical benefit of the drug.
608
609 Whether a drug effect on a given endpoint is reasonably likely to predict clinical benefit is a
610 matter of judgment. FDA considers all relevant evidence and weighs the uncertainty against the
611 severity of the disease to be treated and the lack of available therapy. On a case-by-case basis,
612 FDA will make informed judgments using both internal and external expertise. This guidance
613 provides an overview of some of the important factors to consider in identifying and assessing
614 the predictive potential of surrogate or intermediate clinical endpoints. However, this guidance
615 does not address clinical evidence requirements because they are not readily generalizable.
616
617 a. Understanding of the disease process
618
619 Surrogate endpoints are often thought to be a measure of, for example:

620 • The underlying cause of the disease (e.g., elevated uric acid and gout, elevated blood
621 pressure and hypertensive cardiovascular disease, low thyroxin levels and
622 hypothyroidism)
623
624 • An effect that predicts the ultimate outcome (e.g., tumor shrinkage could be expected to
625 delay symptomatic progression and improve survival, diuresis could be expected to
626 improve symptoms of heart failure)
627
628 • The state of the pathophysiologic pathway leading to the clinical outcome (e.g.,
629 replacement of a missing enzyme or clotting factor)
630

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

631 In such cases, the extent to which the pathophysiology of a disease is understood is an important
632 factor in determining whether an endpoint is reasonably likely to predict clinical benefit. If the
633 disease process is complex, has multiple pathophysiologic or causal pathways, and is poorly
634 understood, it may be difficult to identify a surrogate endpoint. For example, for some
635 reasonably well-understood enzyme deficiencies, replacement of the deficient enzyme reliably
636 predicts clinical benefit. In contrast, other enzyme deficiencies may involve a defect for which
637 the pathophysiologic or causal pathways are not well understood and where enzyme replacement
638 alone will not reasonably predict the disease course or treatment results.
639
640 Some effects on well-established, disease-related markers may have little or no ability to predict
641 clinical benefit. For example, fever occurs with most infectious diseases but lowering a patient's
642 body temperature with a non-steroidal anti-inflammatory drug does not predict the drug's effect
643 on the disease (although it could be a pertinent biomarker for an antibiotic). Similarly, in
644 prostate cancer, increased levels of prostate-specific antigen (PSA) are the result of advancing
645 tumor burden. Therefore, PSA is correlated with the progression of prostate cancer and risks of
646 mortality. However, PSA is not the mechanism through which the disease causes morbidity; so,
647 the effect of a drug on lowering PSA cannot necessarily be relied upon to predict the drug's
648 clinical benefit.
649
650 b. Understanding of the relationship between the drug's effect and the
651 disease process
652
653 The extent to which a drug's effect on the surrogate endpoint is known to predict an effect on the
654 disease is critical. Sometimes this relationship can be assessed epidemiologically but it is most
655 persuasively established by knowing that a drug that affects the surrogate also affects a clinical
656 outcome. Thus, lowering blood pressure has been shown repeatedly to reduce the incidence of
657 stroke and cardiovascular disease in people with hypertension. Similarly, killing infecting
658 bacteria or viruses leads to cure of infectious disease and shrinking a tumor for a sustained period
659 can lead to improved survival in patients with some cancers. These surrogate endpoint responses
660 are thus understood to have positive effects on the disease process.
661
662 Following are examples of factors to consider in identifying and assessing a surrogate endpoint:

663 • Whether there is reliable and consistent epidemiologic evidence supporting the
664 relationship between the endpoint and the intended clinical benefit[22]
665
666 • How precisely the epidemiologic relationship between the endpoint and clinical outcome
667 is defined. (The more precise the relationship, the stronger the basis for concluding that
668 an effect on the endpoint would have a reasonably well-defined effect on the clinical
669 outcome)
670

---

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

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

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

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

D. Conditions of Accelerated Approval

1. Promotional Materials

Unless otherwise informed by the Agency, an applicant must submit to the Agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval.[23] After 120 days following marketing approval, unless otherwise informed by the Agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.[24]

2. Confirmatory Trials

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

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

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

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

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

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

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

3. Withdrawal of Accelerated Approval

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

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

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

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

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

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

VIII. PRIORITY REVIEW DESIGNATION

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

A. Qualifying Criteria for Priority Review Designation

1. Serious Condition

See Section III.A.

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

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

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition

- Elimination or substantial reduction of a treatment-limiting drug reaction

- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes

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

791 • Evidence of safety and effectiveness in a new subpopulation
792
793 Although such evidence can come from clinical trials comparing a marketed product with the
794 investigational drug, a priority review designation can be based on other scientifically valid
795 information. Generally, if there is an available therapy (see Section III.B), sponsors should
796 compare their investigational drug to the available therapy in clinical testing with an attempt to
797 show superiority related to either safety or effectiveness. Alternatively, sponsors could show the
798 ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond
799 to, available therapy or show that the drug can be used effectively with other critical agents that
800 cannot be combined with available therapy. Although such showings would usually be based on
801 randomized trials, other types of controls could also be persuasive, for example, historical
802 controls.[32]
803
804 **B. Features of Priority Review Designation**
805
806 A priority review designation means FDA's goal is to take action on the marketing application
807 within 6 months (compared to 10 months under standard review).
808
809 **IX. GENERAL CONSIDERATIONS**
810
811 Communication with the Agency is a critical aspect of expedited programs. FDA will strive to
812 provide a timely response to a sponsor's inquiry regarding an expedited development program.
813 It is equally critical that the sponsor respond promptly to FDA's inquiries. This applies to formal
814 meetings and related inquiries, written correspondence, and other interactions. In addition to the
815 many types of formal meetings[33] and correspondence the Agency offers to sponsors, additional
816 considerations for sponsors of expedited programs are highlighted in this section.
817
818 **A. Manufacturing and Product Quality Considerations**
819
820 The sponsor of a product that receives an expedited drug development designation will probably
821 need to pursue a more rapid manufacturing development program to accommodate the
822 accelerated pace of the clinical program. The sponsor's product quality team and CMC teams
823 should initiate early communication with FDA to ensure that the manufacturing development
824 programs and timing of submissions meet the Agency's expectations for licensure or marketing
825 approval.[34]
826

[32] Sponsors contemplating the use of historical controls should consult the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001, ICH) for more detailed discussions.
[33] See the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applications*.
Also see the *CDER 21st Century Review Process Desk Reference Guide* accessible at
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf.
[34] See the guidance for industry *IND Meetings for Human Drugs and Biologics Chemistry, Manufacturing, and Controls Information*.

827 When sponsors receive an expedited drug development designation, they should be prepared to
828 propose a commercial manufacturing program that will ensure availability of quality product at
829 the time of approval. The proposal should consider estimated market demand and the
830 commercial manufacturing development plan, especially with regard to manufacturing facilities,
831 lifecycle process validation (including scale-up and comparability), methods validation, stability
832 studies, and potency studies if applicable. The proposal should also include a timeline for
833 development of the manufacturing capabilities with goals aligned with the clinical development
834 program. The applicant should ensure that the manufacturing process is sufficiently developed
835 in order to support the CMC section. After the initial discussion following designation, frequent
836 communication during development will generally facilitate meeting manufacturing development
837 and product quality goals.
838
839 The sponsors of such products should allow for an earlier submission of the CMC section
840 (including product quality information) for timely review, and, critically, for inspection planning.
841 Coordination with the sponsor and contract manufacturers may be necessary to ensure facilities
842 (e.g., the manufacturing process and equipment) are ready for inspection (e.g., during review of
843 the clinical section of the application). A comprehensive meeting with FDA's product quality
844 review and evaluation offices in advance of submission may facilitate quality assessment of
845 products designated for expedited programs.
846

847 **B. Nonclinical Considerations**

848
849 To ensure timely submission and review of nonclinical data, sponsors should initiate early
850 communication with FDA for their nonclinical study programs. Considerations, such as study
851 protocol modifications, sequence and scheduling of studies, and the need for specific studies
852 (e.g., long-term toxicity), may be important in the context of expedited drug development. FDA
853 will provide guidance to sponsors on the development of appropriate and timely nonclinical data
854 needed to support an application for marketing approval or licensure.
855

856 **C. Clinical Inspection Considerations**

857
858 Sponsors should anticipate the Agency's need to inspect clinical trials, including, if applicable,
859 the analytical component of bioavailability or bioequivalence studies. Inspections should be
860 scheduled early in the application review process so inspection results are available to inform the
861 review division and to allow time for the sponsor to address significant inspection findings. To
862 select sites for clinical inspections, it is important for reviewers to have timely access to adequate
863 and accurate data in BLA, NDA, or supplement submissions. Sponsors should initiate early
864 communication with FDA about information required for inspection planning and conduct.

865 **APPENDIX 1: PROCESSES FOR FAST TRACK, BREAKTHROUGH THERAPY, AND**
866 **PRIORITY REVIEW DESIGNATIONS**
867
868 This appendix describes general processes applicable to the submission and review of fast track,
869 breakthrough therapy, and priority review designations.
870
871 **A. Process for Fast Track Designation**
872
873 *1. When to Send a Designation Submission*
874
875 Sponsors may submit fast track designation requests when the IND is first submitted or at any
876 time thereafter before receiving marketing approval of its BLA or NDA. The IND and potential
877 fast track designation may be discussed before an IND submission in a pre-IND meeting, but a
878 decision on designation would await submission of the IND. As a practical matter, requests
879 should ordinarily occur no later than the sponsor's pre-BLA or pre-NDA meeting with the
880 Agency because many of the features of fast track designation will not apply after that time.
881
882 *2. Where to Send a Designation Submission*
883
884 The IND or amendment should be sent to the attention of the appropriate review division or
885 office in CBER or CDER.
886
887 *3. Content of a Designation Submission*
888
889 Fast track designation requests should contain the following information (in most cases, this
890 information could be captured in approximately 10 to 20 pages):
891
892 - If the fast track designation request is submitted to the sponsor's IND as an amendment,
893 the cover letter should indicate the submission as a **REQUEST FOR FAST TRACK**
894 **DESIGNATION** in bold, uppercase letters. If the request is submitted with an initial
895 IND, the cover letter should indicate the submission as both an **INITIAL**
896 **INVESTIGATIONAL NEW DRUG SUBMISSION** and **REQUEST FOR FAST**
897 **TRACK DESIGNATION** in bold, uppercase letters.
898
899 - In the cover letter of the submission include the name of the sponsor's contact person,
900 including the person's address, email address, telephone number, and fax number.
901
902 - If applicable, the IND application number should be noted.
903
904 - If available, include, for drug products, the proprietary name and active ingredient and,
905 for biological products, the proper name and trade name.
906
907 - The division or office to which the IND is being submitted or in which it is active.
908
909 - The proposed indication(s).

910 • A concise summary of information that supports the fast track designation request for the
911 indication being studied, including:
912
913 o The basis for considering the drug to be one intended to treat a serious condition
914
915 o The basis for considering the drug to have the potential to address an unmet
916 medical need and an explanation of how this potential is being evaluated in the
917 planned drug development program (e.g., a description of the trials intended to
918 evaluate this potential)
919
920 • If applicable, include a list of documents previously submitted to the IND that are
921 considered relevant to the designation request, with reference to submission dates. Paper
922 submissions can be resubmitted to FDA as appendices to the designation request.
923
924 *4. FDA Response*
925
926 FDA will respond to fast track designation requests within 60 calendar days of receipt of the
927 request.
928
929 a. Designation letter
930
931 If the Agency determines that the criteria for designation as a fast track drug development
932 program have been met, the designation letter will:
933
934 • State that fast track designation is granted for development of the product for use in
935 treating the specific serious condition
936
937 • Point out that the sponsor should design and perform studies that can show whether the
938 product fulfills an unmet medical need
939
940 • Alert the sponsor to the need for the drug development program to continue to meet the
941 criteria for fast track designation
942
943 b. Nondesignation letter
944
945 If the Agency determines that a fast track designation request was incomplete or that the drug
946 development program failed to meet the criteria for fast track designation, the Agency will send a
947 nondesignation letter to the sponsor. The nondesignation letter will state that fast track
948 designation is not granted and explain the reasons for the Agency's decision.
949
950 *5. Continued Fast Track Designation*
951
952 Over the course of drug development, it is foreseeable that certain products in fast track drug
953 development programs will not continue to meet the criteria for fast track designation. A drug
954 product in a fast track development program may not continue to meet the criteria if the drug: (1)

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

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

B. Process for Breakthrough Therapy Designation

1. When to Send a Designation Submission

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

2. Where to Send a Designation Submission

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

3. Content of a Designation Submission

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

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

998 • If the breakthrough therapy designation request is submitted to the sponsor's IND as an
999 amendment, the cover letter should indicate the submission as a **REQUEST FOR**
1000 **BREAKTHROUGH THERAPY DESIGNATION** in bold, uppercase letters. If the
1001 request is submitted with an initial IND, the cover letter should indicate the submission as
1002 both an **INITIAL INVESTIGATIONAL NEW DRUG SUBMISSION** and
1003 **REQUEST FOR BREAKTHROUGH THERAPY DESIGNATION** in bold,
1004 uppercase letters.
1005
1006 • In the cover letter of the submission, the name of the sponsor's contact person, including
1007 the person's address, email address, telephone number, and fax number.
1008
1009 • If applicable, the IND application number should be noted.
1010
1011 • If available, include, for drug products, the proprietary name and active ingredient and,
1012 for biological products, the proper name and trade name.
1013
1014 • The division or office to which the IND is being submitted or in which it is active.
1015
1016 • The proposed indication(s).
1017
1018 • A concise summary of information that supports the sponsor's breakthrough therapy
1019 designation request for the indication being studied, including:
1020
1021 o The basis for considering the drug to be one intended to treat a serious condition
1022
1023 o The preliminary clinical evidence that the drug may demonstrate substantial
1024 improvement over available therapies. A sponsor should describe the preliminary
1025 clinical evidence, including, for example, justification for the clinical study
1026 endpoint used and a brief description of statistical analyses
1027
1028 • If applicable, include a list of documents previously submitted to the IND considered
1029 relevant to the designation request, with reference to submission dates. Paper
1030 submissions can be resubmitted to FDA as appendices to the designation request.
1031
1032 *4. FDA Response*
1033
1034 FDA will respond to breakthrough therapy designation requests within 60 calendar days of
1035 receipt of the request.

1036 a. Designation letter
1037
1038 If the Agency determines that the criteria for designation as a breakthrough therapy development
1039 program have been met, the designation letter will:
1040

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

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

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

b. Nondesignation letter

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

5. Continued Designation as a Breakthrough Therapy Development Program

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

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

C. Process for Priority Review Designation

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

1085 *1. When to Send a Designation Submission*
1086
1087 Sponsors may request priority review designation when they submit an original BLA, NDA, or
1088 efficacy supplement. The Agency does not anticipate that priority review designation requests
1089 will be made after the filing of a BLA, NDA, or efficacy supplement.
1090
1091 *2. Where to Send a Designation Submission*
1092
1093 Priority review designation requests may be submitted with the original BLA, NDA, or efficacy
1094 supplement.
1095
1096 *3. Content of a Designation Submission*
1097
1098 Priority review designation requests should contain the following information:
1099
1100 • The cover letter included with the request should be clearly identified as a **REQUEST**
1101 **FOR PRIORITY REVIEW DESIGNATION** in bold, uppercase letters.
1102
1103 • In the cover letter of the submission include the name of the sponsor's contact person,
1104 including the person's address, email address, telephone number, and fax number.
1105
1106 • If available, include, for drug products, the proprietary name and active ingredient and,
1107 for biological products, the proper name and trade name.
1108
1109 • The proposed indication(s).
1110
1111 • A concise summary of information that supports the priority review designation request,
1112 including:
1113
1114 o The basis for considering the drug to be intended to treat a serious condition
1115
1116 o The basis for the assertion that the drug would be a significant improvement in the
1117 safety or effectiveness of the treatment, diagnosis, or prevention of a serious
1118 condition
1119
1120 *4. FDA Response*
1121
1122 The Agency will inform the applicant in writing of a priority review designation by Day 60 of
1123 the review. The division will inform the applicant in writing of a standard review designation by
1124 Day 74 of the review. Applications that are not filed do not receive a review designation.
1125
1126 *5. Continued Priority Review Designation*
1127
1128 After priority review designation is assigned, the timeline will not change during the first review
1129 cycle, even if a redetermination of review status is made because of approval of other drugs,

1130 availability of new data, or submission of a request for dispute resolution by the applicant. In
1131 addition, applications filed over protest are assigned a standard review. If the application is
1132 resubmitted after FDA's refuse-to-file decision or if the application is withdrawn before FDA's
1133 action and then resubmitted, FDA will make its determination of review designation based on the
1134 resubmitted application.

1135 **APPENDIX 2: PROCESSES FOR ROLLING REVIEW**
1136
1137 This appendix describes general processes applicable to the submission and review of portions of
1138 an application, a feature of fast track designation (see Section V.B.2).
1139
1140 **A. Agreement on Proposal**
1141
1142 Sponsors obtain preliminary Agency agreement on the proposal at the pre-BLA or pre-NDA
1143 meeting. At the meeting, the sponsor and the review division should discuss: (1) the data that
1144 will be used to support effectiveness, (2) the schedule for submission of each portion of the
1145 BLA or NDA, and (3) a description of portions of the application to be submitted separately.
1146 A request to submit portions of an application ordinarily should be included in the
1147 information package for the pre-BLA or pre-NDA meeting. If a sponsor seeks to submit
1148 portions of an application to the IND after the pre-BLA or pre-NDA meeting, the sponsor
1149 should make such a request and provide a proposed schedule for submission of portions of an
1150 application to the IND as soon as possible.
1151
1152 A request for submission of portions of an application should be sent as an amendment to the
1153 IND for the product in a fast track drug development program; attach Form FDA 1571. The
1154 amendment should be clearly identified as a "**REQUEST FOR SUBMISSION OF**
1155 **PORTIONS OF AN APPLICATION**" in bold uppercase letters. A sponsor may apply for
1156 fast track designation and submission of portions of a BLA or NDA at the same time. In such
1157 cases, sponsors should submit requests as one amendment to the IND. FDA responds to
1158 sponsors' requests for submission of portions of an application by letter. FDA also responds
1159 to changes to an agreement to accept portions of an application by letter.
1160
1161 **B. Portions of an Application Eligible for Early Submission**
1162
1163 Generally, the Agency accepts for submission a complete section of a BLA or NDA only,
1164 such as the entire CMC section, toxicology section, or clinical section.[36] A section of a BLA
1165 or NDA should be submitted for review in a form adequate to have been included in a
1166 complete BLA or NDA submission. Drafts should not be included in a submission; if final
1167 reports need to be updated, the applicant should submit a formal amendment to the BLA or
1168 NDA with the revised information. Occasionally, the Agency may, in its discretion, accept
1169 less than a complete section if the Agency determines that such a subsection would constitute
1170 a reviewable unit and be useful in making the review process more efficient (e.g., less than a
1171 complete section could be a CMC section lacking final consistency lot data and long term
1172 stability data, an acute toxicology section lacking chronic toxicology data, final study reports
1173 for some or all of the principal controlled trials without integrated summaries). The sponsor
1174 should confirm these subsections are final reports.
1175
1176 At the pre-BLA or pre-NDA meeting, the Agency and the sponsor should work together to
1177 clearly define the parameters of accepting an incomplete section and to determine whether

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

1178 FDA could conduct a meaningful review of the submission before receiving the missing
1179 information.
1180

1181 ### C. Submission of User Fees
1182

1183 A sponsor is required to pay applicable fees as stated in section 736 of the FD&C Act before
1184 FDA may commence review of any portion of an application. The applicant should submit Form
1185 FDA 3397 with applicable user fees and follow the same procedures as those followed when a
1186 complete application is submitted.
1187

1188 ### D. Commencement of Review
1189

1190 If FDA accepts a portion of an application, this does not necessarily mean that review will
1191 commence or proceed before we receive the complete application. Actual commencement and
1192 scheduling of review depends on many factors, including staffing, workload, competing
1193 priorities, timeline for completion of applications, and the perceived efficiency of commencing
1194 review before receipt of the complete submission.
1195

1196 ### E. Calculation of Review Time
1197

1198 The review clock will not begin until the applicant informs the Agency that a complete BLA or
1199 NDA was submitted.[37] After the Agency is notified of the complete application, we will make a
1200 filing determination within the usual time.[38]
1201

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

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