Guidance for Industry

Fast Track Drug Development Programs — Designation, Development, and Application Review

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)

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I. INTRODUCTION

The fast track programs of the Food and Drug Administration (FDA) are designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs (fast track products). This document provides guidance to industry on the regulations, policies, and procedures related to the Agency's fast track programs. The guidance also clarifies the criteria and processes for designating fast track products.

Revision 1 of this guidance revised the *Fast Track* guidance that published September 1998. The revision clarified that a drug can be said to address an unmet medical need if the only available treatments for the condition are approved under the accelerated approval regulations (21 CFR. 314.500 and 601.40), either on the basis of an effect on a surrogate endpoint or with restrictions on distribution. Minor editorial changes were also made at that time to make this guidance consistent with the Agency's good guidance practices (GGP) regulation (21 CFR 10.115). Revision 2 of this guidance updates the Paperwork Reduction Act information included on the title page and in a new section VI.

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

[1] This guidance was developed by the Center for Drug Evaluation and Research (CDER) and the Center for Bioloics Evaluation and Research (CBER) in the Food and Drug Administration.

II. BACKGROUND

Section 112 of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) (P.L. 105-115) (Appendix 1) amended the Federal Food, Drug, and Cosmetic Act (the Act) by adding new section 506 (21 U.S.C. 356). The Modernization Act directed FDA to issue guidance describing its policies and procedures pertaining to fast track products. Section 506 authorizes FDA to take actions appropriate to facilitate the development and expedite the review of an application for such a product. These actions are not limited to those specified in the fast track provision but also encompass existing FDA programs to facilitate development and review of products for serious and life-threatening conditions. Such programs include (a) the procedures described in the 1988 interim rule "Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses" (21 CFR 312.80 through 312.88 (Subpart E)), in which FDA formalized certain procedures to facilitate the development of promising therapies (Appendix 2), and (b) the priority review procedures of the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research (CDER) (Appendix 3).[2]

Under the Subpart E regulations for investigational new drugs (Appendix 2), drug development is considered a continuum from early preclinical and clinical studies through submission of a marketing application. The regulations emphasize the critical nature of close early communication between the Agency and a sponsor, outline procedures such as pre-IND and end of phase 1 meetings as methods to improve the efficiency of preclinical and clinical development, and focus on efforts by the Agency and the sponsor to reach early agreement on the design of the major clinical efficacy studies that will be needed to support approval.

CBER and CDER have longstanding policies that describe criteria for review priority classification of marketing applications. Products regulated by CBER are eligible for priority review if they provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening disease (see Appendix 3). Products regulated by CDER are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease; eligibility is not limited to drugs for a serious or life-threatening disease (see Appendix 3). A fast track product would ordinarily meet either Center's criteria for priority review. Note, however, that an NDA or BLA sponsor need not seek fast track designation to be eligible for priority review.

The Modernization Act specifically permits FDA to:

1. Approve a marketing application under section 505(c) of the Act or section 351 of the Public Health Service Act "upon a determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit." This, in effect, codifies in statute FDA's Accelerated Approval Rule (Appendix 4), made final in 1992, which allows expedited marketing of certain new drugs or biological products intended to treat serious or life-threatening illnesses and that appear

[2] CBER and CDER describe their priority review procedures in SOPP 8405, Complete Review and Issuance of Action Letters (June 11, 1998) and MaPP 6020.3, Priority Review Policy (April 22, 1996), respectively.

to provide meaningful therapeutic benefits to patients compared with existing treatments. Under this rule, "FDA may grant marketing approval for a new drug [or biological] product on the basis of adequate and well-controlled trials establishing that the drug [or biological] product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity." Where an accelerated approval is based upon a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity, postmarketing studies are ordinarily required "to verify and describe the drug's clinical benefit and to resolve remaining uncertainty as to the relation of the surrogate endpoint upon which approval was based to clinical benefit, or the observed clinical benefit to ultimate outcome" (57 FR 58942, December 11, 1992).

2. Accept for review portions of a marketing application prior to receipt of the complete application.

Fast track programs should be distinguished from expanded access programs for investigational drugs such as the treatment investigational new drug (IND) regulations (52 FR 19466, May 22, 1987; codified as 21 CFR 312.34). Fast track 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. Expanded access programs such as the treatment IND are intended to facilitate access to investigational drugs ***prior*** to approval for patients with serious and life-threatening conditions and without therapeutic alternatives.

III. CRITERIA FOR QUALIFYING FOR A FAST TRACK DRUG DEVELOPMENT PROGRAM

Section 506(a)(1) of the Act states that a drug designated as a fast track product is intended for the treatment of a serious or life-threatening condition and demonstrates the potential to address unmet medical needs for the condition. The fast track classification thus does not apply to a product alone, but applies to a combination of the product and specific indication for which it is being studied. The indication, for the purposes of this document, includes both the condition for which the drug is intended (e.g., heart failure) and the anticipated or established benefits of use (e.g., improved exercise tolerance, decreased hospitalization, increased survival). It is therefore the development program for a specific drug for a specific indication that will receive fast track designation. Such a program is referred to in this document as a fast track drug development program and the criteria involved in designation are represented in Figure 1. These criteria are more fully described below.

A. Serious or Life-Threatening Condition

This section of the document provides specific guidance regarding how the Agency intends to determine whether a condition is serious and whether a drug is intended to treat a serious condition. All conditions meeting the definition of life-threatening as set forth at 21 CFR 312.81(a) would also be serious conditions. Because the benefits of fast track designation apply

to products for serious conditions as well as to products for life-threatening conditions, distinction between the two categories of conditions with regard to eligibility for fast track programs is unnecessary. Therefore, in the following discussion, all references to serious conditions will include life-threatening conditions.

1. Whether a condition is serious

As discussed in the preamble to the proposed accelerated approval rule (57 FR 13234, April 15, 1992), determination of the seriousness of a condition:

> ... is a matter of judgment, but generally is 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. Thus, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes [such as] ... inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression, psychoses, and many other diseases.

For a condition to be serious, the condition should be 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, providing it is persistent or recurrent.

2. Whether the drug is intended to treat a serious condition

For a product to be in a fast track drug development program, it must not only be used in patients with a serious condition, it must be intended to treat a serious aspect of that condition. Thus, in making a fast track determination, FDA will assess whether the development program is designed to demonstrate an effect on a serious aspect of the condition. The following examples illustrate FDA's approach:

a. A therapeutic product directed at some aspect of a serious condition would be considered to treat a serious condition if it were being evaluated for effects on a serious manifestation(s) or serious symptom(s) of the condition.

b. A diagnostic product would be considered to treat a serious condition if it were being evaluated directly for its impact on a serious aspect of the condition or if it were being evaluated for its ability to improve diagnosis or detection of the condition and scientific data provided a strong basis for a presumption that the improvements in diagnosis or detection of the condition would lead to improved outcome.

c. A preventive product would be considered to treat a serious condition if (1) it were being evaluated for its ability to prevent a serious manifestation(s) of the

condition, or (2) it were being studied for its ability to prevent the condition and it was scientifically reasonable to assume that prevention of the condition would prevent its serious consequences.

d. A product intended to ameliorate or prevent a side effect of therapy of a condition would be considered to treat a serious condition if the side effect were serious (e.g., serious infections in patients receiving immunosuppressive therapy).

e. A product intended and being studied for its ability to treat a condition while avoiding the side effects of currently accepted treatments of the condition might be considered to treat a serious condition if such side effects were serious (e.g., a less myelosuppressive treatment for a tumor or an anti-inflammatory drug that does not cause gastrointestinal bleeding). The potential for a new drug to avoid the serious sequelae of existing drugs would qualify that drug development program for fast track designation only in limited circumstances. Many therapies, even those intended to treat nonserious conditions, are associated with rare, serious, adverse reactions, and new therapies, despite initial hopes, often are associated with their own set of serious reactions. Nonetheless, some adverse reactions are significant public health problems, and the development of therapies that do not cause such serious reactions would merit close attention. The Agency may designate the development of such a therapy as a fast track drug development program when (1) currently accepted therapy is widely used despite an unavoidable serious risk, (2) serious outcomes are a significant public health issue, and (3) the new therapy shows significant potential to have a substantially improved overall safety profile with at least similar efficacy.

Many conditions not generally considered to be serious have rare or distant serious sequelae (e.g., urinary tract infections or duodenal ulcers). Product development programs for such conditions could be designated as fast track if the sponsor specifically designs the development program to demonstrate an effect on those serious sequelae. Conversely, some conditions that are generally considered to be serious have nonserious manifestations requiring symptomatic therapy (e.g., insomnia associated with schizophrenia, skin discoloration from Addison's disease, alopecia with lupus, subcutaneous nodules from rheumatoid arthritis). The Agency will not generally designate as fast track a development program for a product whose effect has been measured in terms of nonserious manifestations unless the product's effect on those manifestations is reasonably likely to predict benefit on a serious manifestation.

B. Demonstrating the Potential to Address Unmet Medical Needs

Section 506(a) of the Act further requires that the drug demonstrate the potential to address unmet medical needs. Thus, in designating a fast track drug development program, the Agency will determine whether the drug has a potential to address unmet medical needs and whether the development program is designed to evaluate this potential.

1. Evaluation of whether the drug development plan addresses unmet medical needs

An unmet medical need is a medical need that is not addressed adequately by an existing therapy.

a. Where there is no available therapy for the condition

If no therapy exists for a serious condition, there is an obvious unmet medical need and a new treatment effective in that condition would meet this aspect of the criteria for fast track designation.

b. Where there is available therapy for the condition

When therapies exist for a condition, the developmental program for the new agent would address unmet medical needs if it evaluated any of the following:

i. Improved effect(s) on serious outcomes of the condition that are affected by alternate therapies (e.g., superiority of the new drug used alone or in combination with other therapies in an active controlled trial assessing an endpoint reflecting serious morbidity).

ii. Effect(s) on serious outcomes of the condition not known to be affected by the alternatives (e.g., progressive disability in multiple sclerosis when the alternative treatments have shown an effect on exacerbations but have not shown an effect on progressive disability).

iii. Ability to provide benefit(s) in patients who are unable to tolerate or are unresponsive to alternative agents (e.g., an antipsychotic agent that is effective in people failing standard therapy), or an ability to be used effectively in combination with other critical agents that cannot be combined with available therapy.

iv. Ability to provide benefit(s) similar to those of alternatives while avoiding serious toxicity that is present in existing therapies, or avoiding less serious toxicity that is common and causes discontinuation of treatment of a serious disease.

v. Ability to provide benefit(s) similar to those of alternatives but with improvement in some factor, such as compliance or convenience, that is shown to lead to improved effects on serious outcomes.

c. Where the only available therapy is approved under the accelerated approval regulations (either on the basis of an effect on a surrogate endpoint or for restricted distribution)

A drug can be said to address an unmet medical need if the only available treatment(s) for the condition are approved under the accelerated approval

regulations (21 CFR 314.500 and 601.40), either on the basis of an effect on a surrogate endpoint or with restrictions on distribution.

FDA recognizes that, as a general matter, it is preferable to have more than one treatment approved under the accelerated approval provisions because of the uncertainty inherent in an approval under these provisions. For example, post-approval studies of a drug product may fail to establish a relationship of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. In these circumstances, it is important to continue to expedite the development and review of important new therapies for serious and life-threatening illnesses under the accelerated approval provisions. Therefore, if the only therapies that exist for a condition are approved under the accelerated approval regulations on the basis of a surrogate endpoint or are approved with restrictions on distribution necessary to ensure the safe use of the drug, FDA may designate a product as fast track notwithstanding the availability of other therapies approved under the accelerated approval regulations.

2. Demonstration of the drug's potential

The type of information needed to demonstrate the potential of a drug to address unmet medical needs will depend on the stage of drug development. Data that become available during clinical development should support the drug's potential to address unmet medical needs and the development plan should be designed to assess this potential. The Agency will rely on summaries of available data to determine whether the potential to address unmet medical needs has been demonstrated.

Before human studies begin, the potential for a drug to address unmet medical needs will be based on pharmacologic and animal model data. At this stage, there may be little evidence of effectiveness of the drug in humans and the potential will be largely theoretical. For later fast track designation, but still prior to the completion of the principal controlled trials, available clinical data should begin to confirm or be consistent with the potential to address unmet medical needs. Still later in the development of a drug, the Agency will normally consider whether the clinical data from controlled and uncontrolled trials, as summarized by the sponsor, support the potential of the drug to address unmet medical needs. At this later stage in development, when an alternate therapy is available, the Agency's determination will also be based on whether the new therapy has been evaluated by comparison with the existing therapy, usually by direct comparison in clinical trials. As noted above, if the only existing therapy is approved under the accelerated approval regulations, the relevant comparisons are to conventionally approved drugs (i.e., drugs approved under 21 CFR 314.105, 314.125, or 601.2), or drugs approved without restrictions, if there are any in either category. Evidence that a new therapy was less safe than a drug approved under the accelerated approval regulations could, however, be relevant.

IV. PROCESS FOR DESIGNATING A DRUG FOR THE FAST TRACK DRUG DEVELOPMENT PROGRAM

The general procedures applicable to the submission and review of fast track designation requests are described below.

A. Timing of Submission

A sponsor may submit a request for fast track designation at the time of original submission of its IND, or at any time thereafter prior to receiving marketing approval of its BLA or NDA. Note that the IND and potential fast track designation may be discussed prior to an IND submission in a pre-IND meeting, but a decision on designation would await submission of the IND. Although benefits associated with fast track designation may occur throughout the drug development process, from the early IND submission to evaluation of a marketing application, as a practical matter, requests should ordinarily occur no later than the sponsor's pre-BLA/NDA meeting with the Agency, as many of the benefits of fast track designation will no longer be applicable after that time.

B. Where to Send a Fast Track Designation Submission

A request for fast track designation should be submitted as an amendment to the sponsor's IND in triplicate with Form FDA 1571 attached or, if the request is simultaneous with submission of the original IND, should accompany the IND. The request for fast track designation should identify the sponsor's contact person, including the person's address, telephone number, and fax number. The IND or amendment should be submitted to the attention of the appropriate division in CBER or CDER and should clearly identify the submission as a "Request for Fast Track Designation." In the unusual situation where a request is made after the filing of a BLA or NDA, the request should be submitted to the BLA or NDA with a Form FDA 356h.

C. Content of a Fast Track Designation Submission

1. In general

The submission in support of a request for fast track designation should establish that the criteria necessary for designation are met: (1) that the drug is intended to treat a serious or life threatening condition (see section III.A. above), and (2) that the drug has the potential to address unmet medical needs and this potential is being evaluated in the planned drug development program (see section III.B. above). The sponsor should identify the serious condition and the unmet medical needs, provide a plausible basis for the assertion that the drug has the potential to address such unmet medical needs, and include in the development plan (at a level of detail appropriate to the stage of development) trials designed to evaluate this potential.

2. Discussion and supporting documentation

To facilitate FDA review, a submission for fast track designation should contain all discussion and supporting documentation necessary to permit a reviewer to assess whether the criteria for

fast track designation are met without having to refer to information located elsewhere, yet should also not be voluminous. The amount of discussion and supporting documentation that shows that the criteria are met will vary. For example, little explanation or supporting documentation may be needed to establish that studying the drug in the treatment of a fatal condition with no approved treatment would qualify if the endpoint were mortality. More extensive explanation and supporting documentation would likely be submitted to show that for a nonfatal condition, serious or life-threatening aspects of the condition will be studied. Where acceptable therapy for the condition already exists, still more extensive discussion and supporting documentation would probably be submitted to establish that the new therapy has the potential to fill a medical need not met by existing therapy.

Any data or published reports that support assertions made in the discussion section of the fast track submission and that have not previously been submitted to the sponsor's IND should be included in the submission. Supporting data already contained in the sponsor's IND generally need only be summarized in the fast track submission with reference to its location in the IND. For assertions made in the submission that are consistent with accepted medical knowledge, the sponsor does not need to include references to clinical data or other external sources. If a sponsor references a large number of sources, a list of those references should be included.

D. FDA Response

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

1. 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 (1) state that fast track designation is granted for development of the product for use in treating the specific serious or life-threatening condition, (2) point out that the sponsor should design and perform studies that can show whether the product fulfills unmet medical needs, and (3) alert the sponsor that the drug development program is expected to continue to meet the criteria for fast track designation (see section IV.E. below).

2. Non-designation letter

A nondesignation letter would reflect a determination that the request was incomplete or that the drug development program failed to meet the criteria for fast track designation. The nondesignation letter will explain the reasons for the Agency's decision. FDA will respond to a subsequent request for fast track designation after a nondesignation determination within 60 calendar days of receiving the subsequent request.

E. Continued Designation as a Fast Track Drug Development Program

It is foreseeable that, for certain products in fast track drug development programs, it will become apparent over the course of drug development that the development programs do not

continue to meet the criteria for fast track designation. A product in a fast track development program may not continue to meet the criteria if the drug no longer (1) demonstrates a potential to address unmet medical needs, or (2) is being studied in a manner that would show the product is able to treat a serious or life-threatening condition and fulfills unmet medical needs. It may no longer demonstrate a potential to address unmet needs, for example, if a new product were approved under a conventional approval that addressed the same needs, or if emerging clinical data failed to show that the product in a fast track development program had the anticipated advantage over existing 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/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 in plans.

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 classified as a fast track drug development program.

V. PROGRAMS FOR EXPEDITING DEVELOPMENT AND REVIEW

It is important to distinguish between fast track designation itself and the specific programs that are available to a sponsor or applicant of a product in a fast track drug development program under section 506(a) of the Act. A sponsor or applicant may apply for fast track designation at any time in the development process from the original submission of an IND until the BLA or NDA is approved by the Agency (see section IV.A.). A product that is in a fast track drug development program would be eligible for consideration for some or all of the programs outlined below.

It is also important to recognize that, with the exception of the submission of portions of a BLA/NDA before submission of the entire application, the programs described below have been established in regulations under authority separate from section 506 of the Act. Therefore, products that are not in fast track drug development programs may also be able to take advantage of these programs.

A. Meetings

Appropriately timed meetings between the regulated industry and FDA are a critical aspect of efficient drug development. Sponsors of products in fast track drug development programs should be in regular contact with the appropriate reviewing division to ensure that the evidence necessary to support marketing approval will be developed and presented in a format conducive to an efficient review. Specifically, the following are strongly recommended:

1. ***Pre-IND consultation*** so that (1) appropriate preclinical studies can be performed to demonstrate the potential to address unmet medical needs and to support introduction of

the product into human trials, (2) phase 1 studies can be optimally designed to support further product development, (3) overall development strategy can be considered, and (4) issues regarding the potential for fast track designation may be discussed.

2. ***An end of phase 1 meeting*** because, as discussed in 21 CFR 312.82 (see Appendix 3), the first phase 2 controlled trials in life-threatening or severely debilitating illnesses may provide sufficient data on safety and effectiveness to support approval, with later development of more extensive safety data, dose response information, and other information in postmarketing studies. It is critical that early trials with mortality/major morbidity endpoints be discussed before implementation to reach agreement on study design, including the statistical plan.

3. ***An end of phase 2 meeting*** to ensure that agreement between FDA and the sponsor has been reached on the design of the principal controlled trials intended to provide evidence of safety and efficacy. As noted in the paragraph above (section A.2.), for some fast track drug development programs, a meeting with much the same purpose will occur at the end of early clinical testing and may be referred to as *end of phase 1/2 meeting*. Note that the standard of evidence applicable to principal controlled trials is set forth at 21 CFR 314.126 (see also the FDA guidance document, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*).

4. ***A pre-BLA/NDA meeting*** to discuss and achieve agreement on critical issues including:

   - Whether preliminary evidence of effectiveness was seen in the principal controlled trials intended to provide evidence of effectiveness
   - Structure, content, and timing of submission of the BLA or NDA
   - Structure and content of any electronic submissions
   - Structure, content, and timing of submission of portions of an application for marketing approval, if such submission is appropriate
   - Readiness for, and proposed timing of, preapproval inspections
   - Potential for, and proposed timing of, advisory committee presentation if applicable

5. ***A meeting*** may be scheduled to discuss labeling issues as early in the review process as appropriate

B. Written Correspondence

In addition to meeting minutes,[3] the FDA should provide the sponsor with the following:

[3] Meeting minutes are part of the CBER and CDER procedures described in CBER SOPP 8101.1, Scheduling Meetings with Regulated Industry and CDER MaPP 4512.1, Formal Meetings Between CDER and External Constituents.

- Timely comments on the design of the proposed principal controlled clinical trials that are to provide the basis for the Agency's determination of the safety and effectiveness of the product.

- End of phase 1 and/or end of phase 2 letters commenting on the adequacy of phase 2/3 development plans

In addition to the usual information contained in premeeting packages described in the guidance for industry on *Formal Meetings with Sponsors and Applicants for PDUFA Products*, the sponsor should provide the following to FDA:

- Responses to FDA questions about any clinical trials that are to form the basis for the Agency's determination of the safety and effectiveness of the product
- At the earliest possible time, protocols of any clinical trials that are not being carried out under an IND (i.e., foreign studies) and that will form the basis for the Agency's determination of the safety and effectiveness of the product
- In meeting packages for meetings held after initial fast track designation, a discussion of how accumulated data and study plans continue to demonstrate that the product and the development plan meet the criteria for fast track designation
- If submission of portions of an incomplete application is sought, a written request for this kind of submission and a proposed schedule for submission (see V.C.2. below)
- As soon as possible, if there are plans to study a surrogate endpoint suitable for review under the accelerated approval provisions, a discussion of and support for the proposed endpoint

C. Review Programs

Sponsors of products in fast track drug development programs may be considered for one or more of the following procedures regarding marketing applications.

1. Priority review of BLAs and NDAs

Because fast track products are intended to treat serious or life-threatening conditions and must demonstrate the potential to address unmet medical needs for such conditions, a BLA or NDA for a product in a fast track drug development program ordinarily will be eligible for priority review (see CBER and CDER procedures in Appendix 3).

2. Submission of portions of an application

a. BLAs and NDAs

Section 506(c) of the Act provides that FDA may consider for review portions of a marketing application before the complete BLA or NDA is submitted. Filing may only occur if the

applicant provides a schedule for submission of information necessary to make the application complete and pays any fees that may be required under section 736 of the Act (i.e., user fees).

After the sponsor submits to the IND a preliminary evaluation of data from the clinical trials, the Agency may consider accepting portions of an application if (1) the clinical trials that would form the basis for the Agency's determination of the safety and effectiveness of the product and that would support drug labeling are nearing completion or have been completed, (2) the Agency agrees that the product continues to meet the criteria for fast track designation, and (3) the Agency agrees that preliminary evaluation of the clinical data supports a determination that the product may be effective.

A sponsor seeking to submit portions of an application should (1) provide a schedule for submission of the portions of the BLA or NDA and receive FDA agreement to accept portions of the application and agreement that the schedule is acceptable before making any submission under the schedule, and (2) pay any applicable user fee to the Agency at the time the first portion of the BLA or NDA is submitted. The pre-BLA/NDA meeting should be used to obtain preliminary Agency agreement on the proposal. At the meeting, the sponsor and the reviewing division should discuss the data that will be used to support effectiveness, the schedule for submission of each portion of the BLA or NDA, and 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/NDA meeting. If a sponsor seeks to submit portions of an application under these procedures after the pre-BLA/NDA meeting, the sponsor should request submission and submit 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 submitted as an amendment to the IND for the product in a fast track drug development program in triplicate with Form FDA 1571 attached. The amendment should be clearly identified a "Request for Submission of Portions of an Application." A sponsor may apply for fast track designation and submission of portions of a BLA or NDA at the same time. These requests should be submitted as one amendment to the IND.

FDA will respond to a request for submission of portions of an application by letter to the sponsor. Any changes in an agreement to accept portions of an application will also be in writing.

b. Portions of an application eligible for early submission

Generally, the Agency will accept for submission only a complete section of a BLA or NDA, such as the entire CMC section, toxicology section, or clinical section (Form FDA 356h may be a useful guide to items in a BLA or NDA). It is expected that a section submitted for review will be 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 (e.g., a CMC section lacking final consistency lot data and long term stability data; an acute toxicology section lacking

chronic toxicology data; or final study reports for some or all of the principal controlled trials without integrated summaries) if it determines that such a subsection would constitute a reviewable unit and would be useful in making the review process more efficient overall. The company should confirm that these subsections are final reports. The Agency and the sponsor should work together at the time of the pre-BLA/NDA meeting to clearly define the parameters of accepting an incomplete section and to determine whether FDA could conduct a meaningful review of the submission prior to receiving the missing information.

c. Submission of the user fee

Section 506(c)(1) of the Act requires a sponsor to pay any fee that may be required under section 736 of the Act before FDA may commence review of any portion of an application. The applicant should submit Form FDA 3397 with any applicable user fee and should follow the same procedures as those followed when a complete application is submitted.

d. Commencement of review

Acceptance of a portion of an application by the Agency does not necessarily mean that review will commence or proceed prior to the receipt of a complete application. Actual commencement and scheduling of review will depend on many factors, including staffing, workload, competing priorities, time line for completion of applications, and the perceived efficiency of commencing review before 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 has been submitted. Following notification that the application is complete, the Agency will make a filing determination within the usual time (see 21 CFR 314.101).[4]

3. Accelerated Approval

Applicants whose products are in fast track drug development programs may seek traditional approval based on data demonstrating an effect on clinically meaningful endpoints or well-established surrogate endpoints. Alternatively, they may seek approval under the accelerated approval regulations (Appendix 4). If an applicant seeks approval of a product in a fast track drug development program based on evidence of an effect on a less than well-established surrogate endpoint, FDA may grant accelerated approval based on a determination that the effect on the surrogate endpoint is reasonably likely to predict clinical benefit (21 CFR 314.510 and 601.41). Drug approval under the accelerated approval regulations may also be based on demonstrated clinical effects that are not the desired ultimate benefit but are reasonably likely to predict such benefit (e.g., improved exercise tolerance in refractory heart failure might be considered reasonably likely to predict ultimate benefit) (21 CFR 314.510 and 601.41).

[4] See also CBER SOPP 8404, Refuse to File Guidance for Product License Applications and Establishment License Applications.

Section 506(b) essentially codifies in statute FDA's accelerated approval regulations. A surrogate endpoint was defined in the preamble to the accelerated approval rule (57 FR 13234 at 13235, April 15, 1992) as "a laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy." Although some surrogate endpoints are recognized as well-established and have long been a basis for approval (e.g., change in blood pressure or cholesterol), the accelerated approval rule allows reliance in specific circumstances on a "surrogate endpoint that, while 'reasonably likely' to predict clinical benefit, is not so well-established as the surrogates ordinarily used as bases of approval in the past" (57 FR 58942 at 58944, December 11, 1992). To meet the statutory standard for approval, which requires the submission of "substantial evidence" to demonstrate effectiveness, "there must be evidence from adequate and well-controlled studies showing that the drug will have [its claimed] effect... That effect will, in this case, be an effect on a surrogate endpoint...." (57 FR 58943-44).

With respect to approval based on clinical endpoints other than survival or irreversible morbidity, the preamble to the final accelerated approval rule pointed out that such approval would usually be considered (like other approvals based on a clinical finding) under traditional procedures (i.e., not under accelerated approval). Approval based on clinical endpoints other than survival or irreversible morbidity would "be considered under the accelerated approval regulations only when it is essential to determine effects on survival or irreversible morbidity in order to confirm the favorable risk/benefit judgment that led to approval" (57 FR 58946). The following examples illustrate types of clinical endpoints that could be a basis for approval with a requirement for further studies under the provisions of the Modernization Act and the accelerated approval rule:

- Clinical endpoints measuring short-term benefit in a chronic condition where short-term benefit per se does not outweigh risk and where durability of benefit is uncertain but expected.

- Clinical endpoints measuring lesser symptoms or signs of a serious disease (e.g., weight loss, appearance) when the resulting benefits do not per se outweigh risks but are expected to lead to a favorable effect on ultimate outcome, which would outweigh risks.

- Clinical endpoints measuring substantial benefits otherwise suitable for ordinary approval but where there exists a significant but limited concern that the treatment may adversely affect ultimate outcome. Where such concerns are minimal, ordinary approval would be used. Where the concerns are substantial, data regarding ultimate outcome would be required preapproval. Between these extremes, accelerated approval may be considered.

D. Dispute Resolution

An FDA determination under the fast track program may be appealed to the reviewing division. If the sponsor is not satisfied with the response provided by the FDA component, the sponsor may elect to pursue the Agency's procedures for internal review or dispute resolution (see 21 CFR 10.75, 312.48, and 314.103).

VI. 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 60-160 hours per response, including the time to review instructions, search existing data resources, 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 Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

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 0910-0389 (expires 08/31/2008).

APPENDIX 1: SECTION 112 OF THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997

SEC. 112. EXPEDITING STUDY AND APPROVAL OF FAST TRACK DRUGS.

(a) IN GENERAL- Chapter V (21 U.S.C. 351 et seq.), as amended by section 125, is amended by inserting before section 508 the following:

`SEC. 506. FAST TRACK PRODUCTS.

`(a) DESIGNATION OF DRUG AS A FAST TRACK PRODUCT-

`(1) IN GENERAL- The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition. (In this section, such a drug is referred to as a `fast track product'.)

`(2) REQUEST FOR DESIGNATION- The sponsor of a new drug may request the Secretary to designate the drug as a fast track product. A request for the designation may be made concurrently with, or at any time after, submission of an application for the investigation of the drug under section 505(i) or section 351(a)(3) of the Public Health Service Act.

`(3) DESIGNATION- Within 60 calendar days after the receipt of a request under paragraph (2), the Secretary shall determine whether the drug that is the subject of the request meets the criteria described in paragraph (1). If the Secretary finds that the drug meets the criteria, the Secretary shall designate the drug as a fast track product and shall take such actions as are appropriate to expedite the development and review of the application for approval of such product.

‘(b) APPROVAL OF APPLICATION FOR A FAST TRACK PRODUCT-

`(1) IN GENERAL- The Secretary may approve an application for approval of a fast track product under section 505(c) or section 351 of the Public Health Service Act upon a determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit.

`(2) LIMITATION- Approval of a fast track product under this subsection may be subject to the requirements--

`(A) that the sponsor conduct appropriate post-approval studies to validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint; and

`(B) that the sponsor submit copies of all promotional materials related to the fast track product during the preapproval review period and, following approval and for such period thereafter as the Secretary determines to be appropriate, at least 30 days prior to dissemination of the materials.

`(3) EXPEDITED WITHDRAWAL OF APPROVAL- The Secretary may withdraw approval of a fast track product using expedited procedures (as prescribed by the Secretary in regulations which shall include an opportunity for an informal hearing) if--

`(A) the sponsor fails to conduct any required post-approval study of the fast track drug with due diligence;

`(B) a post-approval study of the fast track product fails to verify clinical benefit of the product;

`(C) other evidence demonstrates that the fast track product is not safe or effective under the conditions of use; or

`(D) the sponsor disseminates false or misleading promotional materials with respect to the product.

'(c) REVIEW OF INCOMPLETE APPLICATIONS FOR APPROVAL OF A FAST TRACK PRODUCT-

`(1) IN GENERAL- If the Secretary determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective, the Secretary shall evaluate for filing, and may commence review of portions of, an application for the approval of the product before the sponsor submits a complete application. The Secretary shall commence such review only if the applicant--

`(A) provides a schedule for submission of information necessary to make the application complete; and

`(B) pays any fee that may be required under section 736.

`(2) EXCEPTION- Any time period for review of human drug applications that has been agreed to by the Secretary and that has been set forth in goals identified in letters of the Secretary (relating to the use of fees collected under section 736 to expedite the drug development process and the review of human drug applications) shall not apply to an application submitted under paragraph (1) until the date on which the application is complete.

'(d) AWARENESS EFFORTS- The Secretary shall--

`(1) develop and disseminate to physicians, patient organizations, pharmaceutical and biotechnology companies, and other appropriate persons a description of the provisions of this section applicable to fast track products; and

`(2) establish a program to encourage the development of surrogate endpoints that are reasonably likely to predict clinical benefit for serious or life-threatening conditions for which there exist significant unmet medical needs.'.

(b) GUIDANCE- Within 1 year after the date of enactment of this Act, the Secretary of Health and Human Services shall issue guidance for fast track products (as defined in section 506(a)(1) of the Federal Food, Drug, and Cosmetic Act) that describes the policies and procedures that pertain to section 506 of such Act.

APPENDIX 2: PROCEDURES FOR DRUGS INTENDED TO TREAT LIFE-THREATENING AND SEVERELY DEBILITATING ILLNESSES

21 CFR Parts 312 and 314
Investigational New Drug, Antibiotic and Biological Drug Product Regulations;
Procedures for Drugs Intended to Treat Life-Threatening
and Severely Debilitating Illnesses; Interim Rule
(53 Federal Register 41516, October 21, 1998)

(Attachment provided separately)

APPENDIX 3: PRIORITY REVIEW POLICIES

Center for Biologics Evaluation and Research
Manual of Standard Operating Procedures and Policies
SOPP 8405, Complete Review and Issuance of Action Letters, June 11, 1998

Center for Drug Evaluation and Research
Manual of Policies and Procedures
MaPP 6020.3, Priority Review Policy, April 22, 1996

(Attachment provided separately)

APPENDIX 4: ACCELERATED APPROVAL OF NEW DRUGS AND BIOLOGICAL PRODUCTS FOR SERIOUS OR LIFE-THREATENING ILLNESSES

21 CFR 314 and 601
New Drug, Antibiotic, and Biological Drug Product Regulations;
Accelerated Approval; Final Rule
(57 Federal Register 58942, December 11, 1992)

(Attachment provided separately)