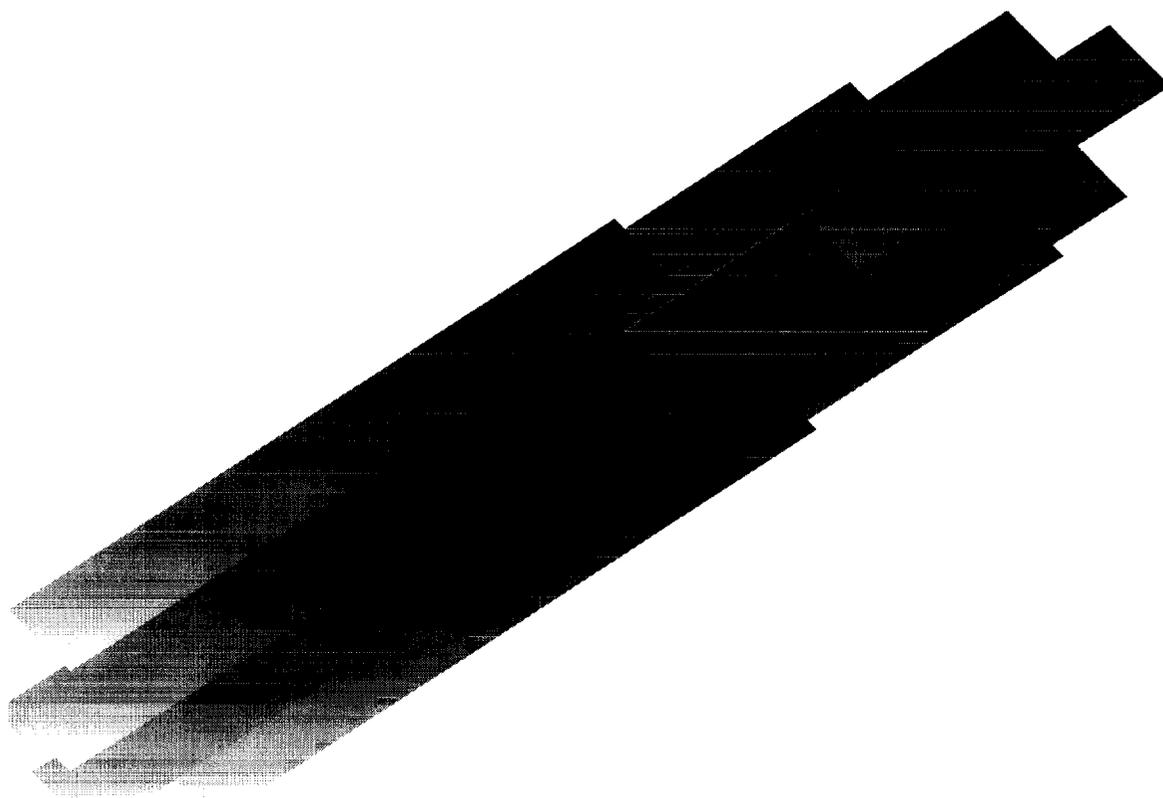


Guidance for Industry

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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Procedural #**

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Comments and suggestions regarding this document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the guidance. All comments should be identified with the docket number provided at the beginning of the notice. Submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

After the comment period closes, comments should be provided in writing to the Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; or Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Rockville, MD 20852-1448.

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GUIDANCE FOR INDUSTRY¹

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

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 FDA's fast track programs and, in doing so, is intended to meet the requirement of section 112(b) of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) (P.L. 105-115) (Appendix 1). Section 112 of the Modernization Act amends the Federal Food, Drug, and Cosmetic Act (the Act) by adding new section 506 (21 U.S.C. 356) and directs 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 (CBER) (SOPP 8405, *Complete Review and Issuance of Action Letters* (June 11, 1998)) and the Center for Drug Evaluation and Research (CDER) (MAPP 6020.3, *Priority Review Policy* (April 22, 1996)) (Appendix 3).

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 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

¹ This guidance has been prepared by the Fast Track Working Group comprising individuals in the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the policies and procedures that pertain to fast track products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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 (CBER SOPP 8405) (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 (CDER MAPP 6020.3) (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 to provide meaningful therapeutic benefits to patients compared with existing treatments.² 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."³ Where an accelerated approval is based upon a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity, post-marketing 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,

² See 21 CFR Part 314, Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) and 21 CFR Part 601, Subpart E (Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses).

³ 21 CFR 314.510 and 601.41. The accelerated approval regulations give FDA flexibility with respect to the types of endpoints that can be relied on to support marketing approval, but do not affect the quantity or quality of evidence needed to demonstrate substantial evidence of effectiveness. Any endpoint considered appropriate to be relied on to support approval, whether a surrogate endpoint or a clinical endpoint, must be supported by substantial evidence of effectiveness. Section 506 of the Act, in incorporating the language of the accelerated approval regulations, affirms FDA's authority to base marketing approval on data other than clinical efficacy data directly establishing an effect on the ultimate clinical outcome (57 FR 58942 at 58946, December 11, 1992).

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 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.

In this guidance, the Agency will discuss the regulations, policies, and procedures related to facilitating development and expediting review of promising therapies for serious and life-threatening conditions for which there is an unmet medical need. This guidance will seek to clarify the criteria and processes for designation of fast track products and to present a coherent, integrated description of the diverse activities and policies that can facilitate development and expedite review of drugs that demonstrate the potential to advance the treatment of serious and life-threatening illnesses.

II. CRITERIA FOR QUALIFICATION AS 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).⁴ 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

⁴ The specific benefit being studied, and what is to be shown about that benefit, could affect fast track designation. For example, an anti-fungal agent under development to treat a life-threatening, systemic fungal infection not adequately treated by existing therapy would be eligible for fast track, but if the same anti-fungal were being developed to treat only a non-serious, superficial fungal infection or a systemic infection that was treatable with existing therapy, and without an attempt to show that it fills an unmet need, the anti-fungal agent would not be eligible for fast track. If both development programs were occurring simultaneously, only the development program for the life-threatening infection would receive fast track designation.

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 that is directed at some aspect of a serious condition would be considered to treat a serious condition if it is 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 is being evaluated directly for its impact on a serious aspect of the condition or if it is being evaluated for its ability to improve diagnosis or detection of the condition and scientific data provide a strong basis for a presumption that the improvements in diagnosis or detection of the condition will lead to improved outcome.
- c. A preventive product would be considered to treat a serious condition if (i)

it is being evaluated for its ability to prevent a serious manifestation(s) of the condition, or (ii) it is being studied for its ability to prevent the condition and it is scientifically reasonable to assume that prevention of the condition would prevent its serious consequences.

- d. A product that is 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 is serious (e.g., serious infections in patients receiving immunosuppressive therapy).
- e. A product that is intended, and is being studied for its ability, to treat a condition while avoiding the side effects of currently accepted treatments of the condition may be considered to treat a serious condition if such side effects are 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 non-serious 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 (i) currently accepted therapy is widely used despite an unavoidable serious risk, (ii) serious outcomes are a significant public health issue, and (iii) 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 non-serious 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 non-serious 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.⁵

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.

III. PROCESS FOR THE DESIGNATION OF A DRUG AS A PRODUCT IN A 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

⁵ Although improved convenience alone could be considered an improvement in therapy, a product will generally qualify as being in a fast track drug development program only if it is reasonable to believe or is demonstrated that greater convenience will lead to better compliance and better compliance will lead to a favorable effect on serious outcomes, and only if the potential effect on serious outcomes is being assessed in clinical trials.

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 have a cover letter that clearly identifies 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, i.e., (i) that the drug is intended to treat a serious or life threatening condition (see section II.A. above), and (ii) 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 II.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 needed 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 needed to show 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. It will usually be necessary to submit more extensive explanation and supporting documentation to show that for a non-fatal 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 may be

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

2. Non-designation letter

A non-designation 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 non-designation letter will explain the reasons for the Agency's decision. FDA will respond to a subsequent request for fast track designation after a non-designation 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 (i) demonstrates a potential to address unmet medical needs, or (ii) 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 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.

IV. 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 III.A.). A product designated as being 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,⁶ the programs described below have been established in regulations under authority separate from section 506 of the Act. Therefore, products that are not in drug development programs that have been designated as fast track 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:

⁶ Current FDA regulations do not provide for Agency review of portions of a BLA or NDA prior to the submission of the complete application, except a complete Chemistry, Manufacturing, and Controls (CMC) section can be submitted to an NDA 90 to 120 days before the anticipated submission of the remainder of the NDA under 21 CFR 314.50(d)(1)(iv).

1. Pre-IND consultation so that (i) 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, (ii) phase 1 studies can be optimally designed to support further product development, (iii) overall development strategy can be considered, and (iv) 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 post marketing 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."⁷ 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* (May, 1998)).
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.

⁷ Functionally, the end of phase 1/2 meeting is an end of phase 2 meeting that occurs at the end of phase 1.

B. Written Correspondence

1. In addition to meeting minutes, described in CBER SOPP 8101.1 (*Scheduling Meetings with Regulated Industry*) and CDER MAPP 4512.1 (*Formal Meetings Between CDER and External Constituents* (March 7, 1996)), the following should be provided to the sponsor by FDA:
 - 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.

2. In addition to the usual information contained in premeeting packages described in CBER SOPP 8101.1 and CDER MAPP 4512.1, 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 IV.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 (CBER SOPP 8405, CDER

MAPP 6020.3) (see Appendix 3).

2. Submission of portions of an application

a. Submitting portions of a BLA/NDA

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 (i) 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, (ii) the Agency agrees that the product continues to meet the criteria for fast track designation, and (iii) 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 (i) 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 (ii) 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 cover letter to the amendment should clearly identify the amendment as "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 and CBER SOPP 8404, *Refuse to File Guidance for Product License Applications and Establishment License Applications* (June 11, 1998)).

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).

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..."⁸ That effect will, in this case, be an effect

⁸ Under current law, as amended by section 115(a) of the Modernization Act, the Agency may, in some circumstances, consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence ... to constitute substantial evidence." See the FDA guidance document, *Providing Clinical Evidence of Effectiveness*

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:

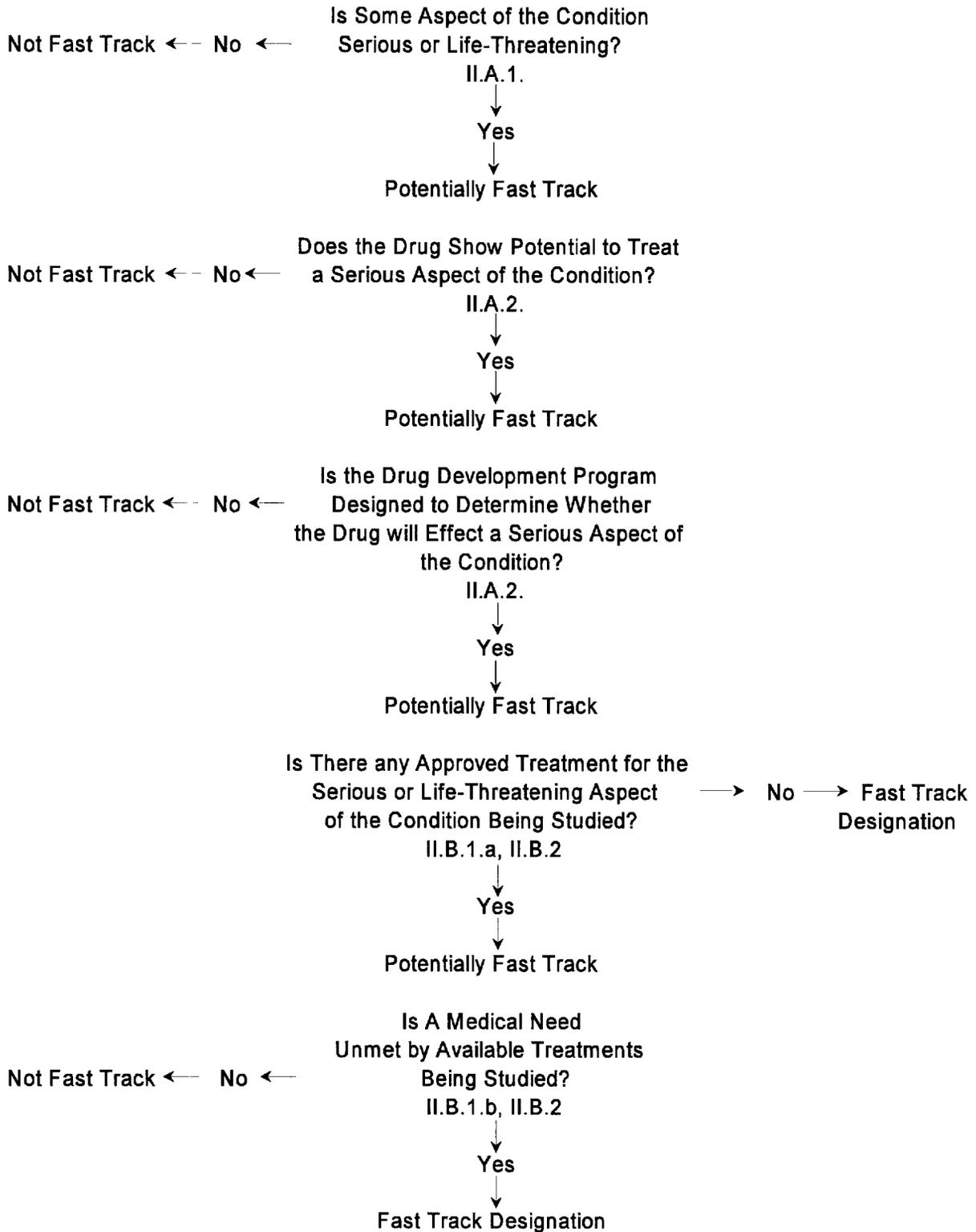
- Clinical endpoints measuring short-term benefit in a chronic condition where short-term benefit per se does not outweigh risk and where durability of benefit is uncertain but expected.
- Clinical endpoints measuring lesser symptoms or signs of a serious disease (e.g., weight loss, appearance) when 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 effect ultimate outcome. Where such concerns are minimal, ordinary approval would be used. Where the concerns are substantial, data regarding ultimate outcome would be required pre-approval. 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).

Figure 1

Scheme for Determining Fast Track



APPENDIX 1.

**Excerpt from the Food and Drug Administration Modernization Act of 1997
(P.L. 105-115)**

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)

(please insert)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 312 and 314

[Docket No. 88N-0359]

Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses

AGENCY: Food and Drug Administration.

ACTION: Interim rule; opportunity for public comment.

SUMMARY: The Food and Drug Administration (FDA) is issuing interim regulatory procedures designed to speed the availability of new therapies to desperately ill patients, while preserving appropriate guarantees for safety and effectiveness. These procedures are intended to facilitate the development, evaluation, and marketing of such products, especially where no satisfactory alternative therapies exist. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedures apply to products intended to treat acquired immunodeficiency syndrome (AIDS), some cancers, and other life-threatening or severely-debilitating illnesses. FDA is issuing these procedures as an interim rule with opportunity for public comment.

DATES: Interim rule effective October 21, 1988; comments by December 20, 1988.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305) Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Steven H. Unger, Center for Drug Evaluation and Research (HFD-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8049,

or

Steven F. Falter, Center for Biologics Evaluation and Research (HFB-130), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892, 301-295-8046.

SUPPLEMENTARY INFORMATION:

Expediting the availability of promising new therapies has been a major priority of FDA over the past several years. In the Federal Register of May 22, 1987 (52 FR 19466), FDA issued new regulations designed to increase the availability to desperately ill patients of promising investigational new drug (IND) and biological products before general marketing begins. This rulemaking initiative, known as the treatment IND program, was endorsed by the President's Task Force on Regulatory Relief, chaired by Vice President George Bush. The final rule has received broad support from the medical and patient communities. The significance and utility of the treatment IND program has also been recognized and endorsed by the President's Commission on the Human Immunodeficiency Virus (HIV) Epidemic.

The treatment IND regulations became effective on June 22, 1987. Since that time, seven promising experimental therapies have been made available to patients stricken with AIDS, cancer, Parkinson's disease, and other serious conditions. In February 1988, the American Medical Association and FDA cosponsored a major national conference intended to educate physicians and health care organizations about the treatment IND program. FDA has also publicized specific treatment IND approval actions in both medical and lay journals (Refs. 1 through 8).

The treatment IND program is part of FDA's comprehensive efforts to facilitate the development and availability of significant new therapies. For example, through its implementation of the Orphan Drug Act, enacted in 1983, FDA has given special emphasis to potential new therapies for rare diseases or conditions. Since 1983, FDA has granted orphan drug designation to over 200 products, many of which are for life-threatening illnesses. (Orphan drug designation provides the commercial sponsor with certain economic incentives to encourage drug development, including tax credits for the cost of clinical development and exclusive marketing rights for the designated indication upon marketing approval.) FDA has approved for marketing 27 such orphan products, including therapies to treat such life-threatening illnesses as leukemia and AIDS.

FDA has also instituted a number of management improvements designed to expedite the evaluation of AIDS-related products in particular. These include establishment of a top "1-AA" priority for the review of all AIDS products, and

the creation of two new divisions—one for drugs and one for biologicals—to give special focus to the review of such products. FDA's actions have led to the approval in record time of the first drug, zidovudine (formerly called AZT), to treat the AIDS virus, as well as approval for human testing of the first potential AIDS vaccines.

Building on these achievements, on August 3, 1988, Vice President Bush, in his capacity as chairman of the Presidential Task Force on Regulatory Relief, requested FDA to develop procedures for expediting the marketing of new therapies intended to treat AIDS and other life-threatening illnesses. This charge recognized the urgency felt by desperately ill patients and their families. The charge was directed to FDA as the Federal agency that regulates the transfer of the fruits of biomedical research to the marketplace.

The procedures contained in this notice respond to the Vice President's charge. In developing these procedures, FDA met informally with representatives of AIDS interest groups as well as with representatives of consumer, health professional, academic, orphan drug, and industry organizations. FDA also met informally with leadership of the National Institutes of Health.

As described further below, FDA is issuing these new procedures as an interim rule, effective immediately, with an opportunity for public comment. Highlights of the interim rule are summarized below, followed by a section-by-section description of the new procedures.

I. Highlights of the Regulations

New procedures are being codified as part of FDA's IND regulations, by adding a new Subpart E consisting of §§ 312.80 through 312.88, and by adding a conforming amendment to FDA's new drug application (NDA) regulations, new paragraph (c) of § 314.25. The purpose of these new procedures (§ 312.80) is to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening or severely-debilitating illnesses, especially where no satisfactory alternative therapies exist. The procedures themselves focus on the entire drug development and evaluation process—from early preclinical and clinical testing, through FDA evaluation of controlled clinical trials and marketing applications, to postmarketing surveillance—in order to treat the entire process as a coherent whole and thereby significantly increase its overall efficiency.

The scope of the new procedures (§ 312.81) will apply to new drugs, antibiotics, and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating illnesses. Within the context of these procedures, the term "life-threatening" is defined to include diseases where the likelihood of death is high unless the course of the disease is interrupted (e.g., AIDS and cancer), as well as diseases or conditions with potentially fatal outcomes where the end point of clinical trial analysis is survival (e.g., increased survival in persons who have had a stroke or heart attack). The term "severely-debilitating" refers to diseases or conditions that cause major irreversible morbidity (e.g., blindness or neurological degeneration).

A key component of the procedures is early consultation between FDA and drug sponsors (§ 312.82) to seek agreement on the design of necessary preclinical and clinical studies needed to gain marketing approval. Such consultation is intended to improve the efficiency of the process by preventing false starts and wasted effort that could otherwise result from studies that are flawed in design. Most important, at the end of early (phase 1) clinical testing, FDA and the sponsor will seek to reach agreement on the proper design of phase 2 controlled clinical trials, with the goal that such research will be adequate to provide sufficient data on the product's safety and effectiveness to support a decision on its approvability for marketing. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members.

If the preliminary analysis of test results appears promising, FDA may ask the sponsor (§ 312.83) to submit a treatment protocol to be reviewed under the treatment IND regulations. Such a treatment protocol, if submitted and granted, would serve as a bridge between the completion of early stages of clinical trials and final marketing approval.

Once phase 2 testing and analysis is completed by the sponsor and a marketing application is submitted, FDA will evaluate the data utilizing a medical risk-benefit analysis (§ 312.84). As part of this evaluation, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy. In making decisions on whether to grant marketing approval

for products that have been the subject of an end-of-phase 1 meeting under this rule, FDA will usually seek the advice of outside expert scientific consultants or advisory committees.

As a conforming amendment, a new paragraph (c) is being added to § 314.125 of FDA's NDA regulations. This paragraph is designed to make clear that FDA's evaluation of marketing applications for drugs to treat life-threatening and severely-debilitating diseases will incorporate the criteria being added to § 312.84. These criteria include the adoption of a medical risk-benefit analysis when assessing the safety and effectiveness of these drugs.

Finally, when approval or licensing of a product is being granted, FDA may seek agreement from the sponsor (§ 312.85) to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, and use of the drug over a longer period of time.

These procedures are modeled after the highly successful development, evaluation, and approval of zidovudine, the first drug approved to treat the AIDS virus. Close consultation between FDA, the sponsor, and the National Institutes of Health resulted in efficient preclinical animal testing (2 to 4 weeks in duration), focused phase 1 clinical testing, and a well-designed and conducted multicenter phase 2 clinical trial that provided dramatic evidence of increased survival in patients with advanced cases of AIDS. Given such evidence, FDA approved a treatment protocol in 5 days, and marketing approval in 107 days. Concurrent with approval, the sponsor agreed to conduct phase 4 research studying the effects of zidovudine in patients at an earlier stage of the disease. In total, the drug development and evaluation process, which takes an average of 8 years from initial human testing under an IND to final marketing approval, took only 2 years for zidovudine. Although the total development time will vary with different drugs, FDA believes that the approach contained in these new procedures has great potential for increasing significantly the efficiency of the drug development and evaluation process for the drugs affected.

Moreover, to the extent that the Commissioner determines that clinical trials to treat life-threatening or

severely-debilitating diseases are already underway and are consistent with the requirements of these rules, upon his own initiative and in cooperation with the drug sponsor, he may recommend that a marketing application be submitted under the new procedures.

In conjunction with these procedures, FDA may, in certain circumstances, undertake focused regulatory research (§ 312.86) addressing critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. The FDA Commissioner and other agency officials will also actively monitor (§ 312.87) the progress of the conduct and evaluation of clinical trials for products covered by these procedures, and will be involved in facilitating their appropriate progress.

The final provision of these procedures (§ 312.88) references applicable safeguards inherent in existing FDA regulations to ensure patient safety during clinical testing and the safety of products following marketing approval. These safeguards include FDA requirements regarding informed consent and institutional review boards. These safeguards further include the review of animal studies prior to initial human testing, and the monitoring of adverse drug experiences during the IND, marketing application, and postmarketing phases.

FDA believes that this program, taken as a whole, establishes a new and innovative approach to stimulating the development of particularly important drugs, while at the same time building on past practices that have proven to be successful.

II. Effective Date and Opportunity for Public Comment

For the reasons described below, FDA is issuing these procedures as an interim rule, with an opportunity for public comment. Because of the urgency associated with life-threatening illnesses, the agency intends to begin implementation of these procedures immediately, but will consider modifications to them based on issues raised during the comment period and experience gained under the interim rule.

The program established in this interim rule is intended to bring about a significant improvement in the efficiency of the development, evaluation, and marketing of new therapies for life-threatening and severely-debilitating illnesses, while preserving appropriate quarantees for safety and effectiveness. Although the program is important, it

builds upon managerial and regulatory options available under existing practices and procedures. The opportunity for early consultation with sponsors on the design of clinical trials, for example, is permissible under the existing investigational new drug review provisions of FDA's regulations. Because the new program represents a fundamental commitment to expediting the development of innovative products, it is appropriate to identify and describe the components of that program and to codify them for ready reference by affected persons. Moreover, the amendment to Part 314, requiring consideration of risk-benefit criteria in decisions to approve or disapprove these drugs, is consistent with the flexibility granted to the Agency under the statute in determining whether substantial evidence of safety and effectiveness has been demonstrated.

To the extent that the elements of the program announced today are regarded as new rules, they are within the exception to the Administrative Procedure Act notice-and-comment requirement for general statements of policy and rules of agency organization, procedure, and practice (5 U.S.C. 553(b)(A)). Moreover, if the new program is regarded as substantive rulemaking, the Commissioner hereby finds good cause for not providing notice and an opportunity to comment prior to its effectiveness. The importance of developing new therapies for life-threatening diseases has been highlighted in recent years by the AIDS crisis. In addition, the sustained search by drug researchers for treatments for many other diseases, including Alzheimer's disease and cancer, merits immediate attention. FDA believes that, as promising new therapies for these diseases are identified, they must be developed by sponsors and evaluated by the agency as expeditiously as possible. It would therefore be contrary to the public interest to delay the implementation of this program pending the time necessary to engage in the APA's notice-and-comment procedures, and such delay would also be unnecessary because the program derives from existing regulations that have already been the subject of notice and an opportunity for comment (5 U.S.C. 553(b)(B); 21 CFR 10.40(e)).

FDA believes, however, that it should invite and consider public comment on its practices and procedures for reviewing investigational new drug, new drug approval, and biologics license applications, including those described in this notice.

III. Contents of the Program

A. Purpose

The drug development process is generally thought of, in simplified terms, as consisting of three phases of human testing to determine if a drug is safe and effective: Phase 1 with 10 to 50 patients to study how the drug is tolerated, metabolized, and excreted; phase 2 with 50 to 200 patients in which the safety and efficacy of the drug are first evaluated in controlled trials; and phase 3 with 200 to 1,000 or more patients to confirm and expand upon the safety and efficacy data obtained from the first two phases. (For purposes of this discussion, the word "drug" is meant to include new drugs, antibiotic drugs, and biological products.)

A recent study of new drug development has documented the percentage of drugs whose development is discontinued after each of these phases. Of the 174 new chemical entities that entered phase 1 testing under U.S. IND's between 1976 and 1978, 70 percent successfully completed phase 1 and moved on to phase 2, while 33 percent successfully completed phase 2 and moved on to phase 3. At this point the dropout rate slowed considerably, as 27 percent successfully completed phase 3 and were submitted to FDA in the form of a marketing application, and 20 percent actually received marketing approval from the agency (Ref. 9).

The three phases describe the usual process of drug development, but they are not statutory requirements. The basis for marketing approval is the adequacy of the data available; progression through the particular phases is simply the usual means the sponsor uses to collect the data needed for approval. The statute itself focuses on the standard of evidence needed for approval, as derived from adequate and well-controlled clinical investigations, with no mention of phases 1, 2, and 3. FDA believes that if sufficient attention is paid to the quality and amount of data obtained in phase 2, it should be possible to identify early those drugs that represent safe and effective treatments for life-threatening and severely-debilitating diseases—and to develop the evidence needed for their marketing—in the course of carrying out the first controlled trials.

This program is based on that premise. For drugs intended to treat life-threatening and severely debilitating illnesses, it should be possible to reduce the total premarket drug development time by designing and conducting phase 2 controlled trails that are capable of providing necessary data on the drug's safety and effectiveness. FDA would

analyze data from such studies utilizing medical risk-benefit considerations appropriate for drugs intended to treat life-threatening or severely-debilitating illnesses. The treatment IND, as appropriate, could continue to serve as a bridge between phase 2 trials and the point of marketing approval. Drug sponsors might also conduct postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. The FDA Commissioner and other agency officials would actively monitor the process to ensure that such products are developed by the sponsor and analyzed by the agency as expeditiously as possible.

Section 312.80 of the rule summarizes the program's purpose: to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening or severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated in FDA's new drug application regulations (§ 314.105(c)), while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. In promulgating this interim rule, FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. The procedures contained in this rule reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedures outlined in this notice should be interpreted consistent with this statement of purpose.

B. Scope

Section 312.81 of the rule outlines the scope of this rule. The rule applies to new drug, antibiotic, and biological products being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

A "life-threatening" disease is defined as one in which the likelihood of death is high unless the course of the disease is interrupted (e.g., progression from asymptomatic HIV infection to

symptomatic HIV infection, or further progression to a later stage of AIDS; metastatic cancer; amyotrophic lateral sclerosis). This use of the term "life-threatening" plainly includes any disease whose progression is likely to lead to death, especially in a short period of time (e.g., 6 months to 1 year). This section also applies to any condition in which a study is to be carried out to determine whether the treatment has a beneficial effect on survival (e.g., increased survival after a stroke or heart attack).

The term "severely-debilitating" is defined as a disease or condition that leads to major irreversible morbidity (e.g., severe functional deficits in multiple sclerosis, Alzheimer's disease or progressive ankylosing spondylitis; prevention of blindness due to cytomegalovirus infection in AIDS patients).

With respect to "severely-debilitating" illnesses, the procedures contained in this rule are applicable to those instances where the studies proposed will examine the treatment's capacity to prevent or reverse what would otherwise be irreversible damage, such as putting ankylosing spondylitis into remission and stopping joint damage and deformity, or preventing blindness. It is in such studies that excellence in study design and an early answer to key questions on safety and effectiveness are especially critical. The agency notes that there are many other studies that examine symptomatic relief (e.g., pain of ankylosing spondylitis) rather than irreversible morbidity. While products being studied for symptomatic relief of a particular disease would likely qualify for treatment IND consideration under § 312.34(b)(2), they would not be covered by the procedures contained in this interim rule.

In all of the cases covered by these new procedures, when the end points of clinical study relate to survival or prevention of major disability, they are of such great importance that it is imperative that the first controlled clinical trials be designed and conducted as well as possible. If this is not done, preliminary reports of success from poorly designed studies might make it difficult ever to carry out the proper trials. FDA believes it is clearly in the public interest to assure in such situations, to the extent possible, that the first clinical trials be designed so that the true merit of the drug or biologic can be evaluated as promptly as possible. FDA will also expedite the designation of eligible orphan products to provide additional incentive for their development.

The agency recognizes that the scope of these procedures is subject to interpretation, and the examples given above are illustrative only. FDA intends to be flexible in its implementation of this program and, subject to available resources, provide early advice when it is sought. The agency encourages sponsors to consult with FDA on the program's applicability to particular products.

C. Elements of the Program

1. *Early consultation.* A key component to be addressed is early consultation, which is covered in § 312.82 of the rule. In 1987, FDA codified the practice that, upon request of a drug's sponsor, FDA medical staff will hold a conference with the sponsor at the end of phase 2 testing. (See § 312.47(b)(1).) The goal of this conference is to reach agreement on a plan of phase 3 testing that will provide the needed remaining evidence of the drug's safety and efficacy to gain marketing approval. If, however, the evidence obtained from well-planned and well-executed phase 2 research is sufficient under the statute for marketing approval, there may be no need for additional phase 3 premarket testing, and the drug can become available much more rapidly than usual.

This is most likely to occur for drugs to treat life-threatening illnesses where the relatively small amount of data available at this stage may nevertheless be sufficient for approval. For example, phase 2 research was sufficient for approval of zidovudine the only drug approved thus far to treat the AIDS virus. Zidovudine was developed and approved in record time, largely because further premarketing (phase 3) studies were not needed to support safety and effectiveness following completion of a highly successful well-controlled multicenter phase 2 study that demonstrated dramatic effects on survival.

There have been other circumstances, particularly in the oncology area, where early (phase 2) results were such that additional studies were not needed to conclude that the drug was effective and that its benefits outweighed its risks. For example, the licensing of alpha interferons to treat hairy cell leukemia was based on phase 2 trials that showed partial or complete remission of the disease in 75 to 90 percent of patients.

To build upon these successes, FDA is instituting a process for conferences to be held at the end of phase 1 (rather than waiting until the end of phase 2) with the sponsors of drugs and biologics intended to treat life-threatening and severely-debilitating illnesses, especially where there are no

satisfactory alternative therapies. The purpose of these conferences will be to review the product's phase 1 test results and phase 2 plans for clinical testing. If enough is known about the drug at that time, agreement would be reached on a phase 2 testing program (e.g., the design of the studies, the number of patients to be tested, the end points to be used, and the proposed mode of replication), that would be sufficient to establish the drug's safety and effectiveness. Where the data resulting from these phase 2 studies prove sufficient to allow a determination that, on the basis of risk-benefit considerations detailed further below, the drug is safe and effective, FDA will approve the drug without further preapproval studies. In this case, phase 2 thus obviates the need for further research in phase 3, if the phase 2 trials prove successful. Of course, when the results of phase 2 research do not provide evidence that fulfills the statutory criteria for approval, further preapproval studies will be necessary.

Because the end-of-phase 1 conference serves the same function (except earlier in the process) as an end-of-phase 2 conference would otherwise serve, FDA will apply the same procedures to both meetings, as codified in § 312.47(b)(1). This includes provision for documenting the agreements reached at the meeting. In order to provide the broadest possible expertise available, FDA may invite to the meeting one or more of its advisory committee members or other scientific consultants. The sponsor may, of course, also bring scientific consultants to the meeting.

With respect to study design, the agency recognizes that there has been some confusion about the role of placebo-controlled studies in patients with a life-threatening disease. FDA believes that a requirement for placebo-controlled studies is *not* appropriate in those situations where there is known to be an effective therapy, for the stage of disease or condition under investigation, that can improve survival or prevent irreversible morbidity. For example, in the case of symptomatic AIDS or advanced AIDS-related complex (ARC), where zidovudine is known to improve survival, it would not be appropriate to compare a new drug with placebo. Rather, the new drug should be compared with zidovudine. It would also be possible to compare the new drug plus zidovudine with zidovudine alone, but in neither case would it be necessary to deny patients therapy with zidovudine which is known to improve survival. In contrast, where no therapy has been shown to be effective, it is scientifically and ethically appropriate

to randomize patients to test drug and placebo. This was done with zidovudine and, by providing early and clear evidence of benefit in terms of improved survival, enabled FDA to confer the rapid approval that made the drug widely available to AIDS patients.

The Institute of Medicine, in its recent report entitled, "Confronting AIDS: Update 1988," emphasized the importance of controlled clinical trials as the "fastest, most efficient way to determine what treatments work" (Executive Summary at page 19; Report at page 139) (Ref. 10). As the report continues, "Conducting well-designed trials from the beginning will benefit more patients, sooner, than any other approach. Poorly designed trials, or administering drugs without controls and 'observing' the course of the disease, risk being inconclusive or drawing incorrect conclusions." (Report at page 139) (Ref. 10). FDA fully supports the early initiation of well-designed phase 2 controlled clinical trials as the most efficient mechanism of evaluating treatments for the desperately ill.

When planning phase 2 studies, it will be particularly important to make optimal use of pharmacokinetic/pharmacodynamic studies carried out in phase 1. Such phase 1 data are particularly useful in selecting the best dose(s) and dosing intervals for phase 2 testing. Therefore, FDA input should be helpful in the design of phase 1 studies also.

FDA can also make the drug development process more efficient by interacting with the drug sponsor, even before phase 1 testing begins, to help identify the animal studies necessary to assess the toxicity of the new drug and assure that clinical studies can be initiated with reasonable assurance of safety. In consulting with sponsors on animal studies, FDA takes into account the seriousness of the disease to be treated and the nature of the clinical studies planned. In this way, FDA involvement can facilitate the initiation of trials in human patients as early as the safety studies in animals permit, thereby reducing potential barriers to innovation at this early but important stage of new pharmaceutical development.

For example, using this process, some new AIDS drugs have been able to enter clinical testing after animal studies that were 4 weeks long or less in duration, and the preclinical animal studies completed before initial human use of zidovudine were 2 to 4 weeks long. By working closely with the sponsor, FDA can suggest the minimum amount of preclinical testing needed to go forward without compromising the safety of

clinical study participants. Unnecessary animal studies can be avoided, animal lives can be spared, and the sponsor can move the drug into clinical testing in the shortest possible time. Moreover, early FDA involvement can also shorten the time it takes the agency to review and IND submission and lessen the likelihood of FDA placing the application on clinical hold.

2. *Treatment IND's.* Section 312.63 of the rule outlines the role of the treatment IND in the context of this overall program. As codified in §§ 312.34 and 312.35, treatment IND's are intended to permit the wider use of promising experimental drugs for serious and immediately life-threatening illnesses in patients who lack satisfactory alternative therapy. Within the drug development process, treatment IND's can provide a bridge between the completion and initial analysis of promising phase 2 studies and the point of marketing approval. Thus, when early evidence from phase 2 indicates that a drug for a life-threatening or severely-debilitating illness is promising, FDA will actively work with the sponsor to evaluate the appropriateness of a treatment protocol. This approach was used during the development of zidovudine, and allowed wide availability of the drug to over 4,000 patients while the marketing application was being assembled by the sponsor and reviewed by FDA. In addition, FDA will continue to work actively to educate physicians and drug sponsors on how to utilize the treatment IND process most effectively.

3. *Risk-benefit analysis.* Section 312.84(a) of the rule provides that FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in § 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

While the statute uses the terms safety and effectiveness, rather than risks and benefits, the decision on whether to approve a drug inherently represents a medical risk-benefit judgment. The agency recognizes that safety and effectiveness are not absolute (i.e., not all drugs are free of risk or have unequivocal benefits), but must be assessed in light of what condition the drug treats. This is particularly true in the case of drugs to

treat life-threatening diseases, where drugs that are quite toxic may nevertheless be considered safe under the circumstances.

In carrying out the statutory mandate, FDA will consider the seriousness of the disease being treated in balancing risks and benefits. For example, as a class, oncologic drugs are highly toxic, but this is acceptable when they are used to treat illnesses for which they represent the only available method of treatment and when they can have a favorable influence on survival or on intractable symptoms. Moreover, dramatic responses (i.e., great benefit), especially on significant end points like survival or progression to an inevitably fatal stage of illness, make it easier to conclude that the benefits of treatment outweigh its risks, even if not all important questions about the drug are answered. Clearly, for a life-threatening illness, a relatively high level of known risk and some uncertainty about potential risk from the drug can be acceptable in exchange for the improved survival provided by effective drug treatment for a condition that, left untreated, would result in death. Similarly, for the same life-threatening illnesses, evidence of effectiveness must be weighed against risks of the drug and the knowledge that death would result in the absence of treatment.

Section 312.84(b) of the rule provides that the agency will usually seek the advice of outside expert consultants or advisory committees in reaching its conclusions. That section also provides that FDA will notify the members of the relevant standing advisory committee of the filing of a marketing application covered by this rule, and its availability for review.

In seeking to utilize phase 2 data for final decisionmaking, FDA would be trying to increase the likelihood that a safe and effective drug, especially one that affects mortality or major irreversible morbidity, would be shown safe and effective in the shortest possible time by assuring that the initial studies are adequate to do this—i.e., to provide evidence, even though derived from a limited data base, that would be sufficient to reach a benefit-risk judgment. FDA's goal is to be able to reach a scientifically defensible decision based on the results of well-designed phase 2 controlled clinical trials. If, on the basis of phase 2 testing, a therapy is found to effectively treat a life-threatening disease for which no other therapy exists, it would not be appropriate to continue premarketing research into phase 3. However, poorly

designed phase 2 studies serve to retard the drug development process.

If FDA concludes that the data presented are not sufficient for marketing approval, § 312.84(b) of the rule provides that FDA will issue a letter to the sponsor describing the deficiencies in that application, including why the results of the research design agreed to under § 312.82 of this rule, or in subsequent meetings, did not provide sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

To increase the likelihood that phase 2 testing can provide sufficient results, sponsors could need to plan phase 2 studies that are somewhat larger and more extensive than is currently the norm, including a mode for replication of key findings. Moreover, to avoid missing an effect by using too little drug, or to avoid studying a dose that proves toxic, it may be necessary to study several doses in the first formal trials, an approach that may require a larger study but can plainly save time, thereby enabling physicians to treat patients with life-threatening illnesses more rapidly. However, it should be appreciated that a drug has only minor or inconsistent therapeutic benefits, its positive effects may be missed in this stage of clinical testing, even if the drug ultimately proves to be beneficial following more extensive phase 3 trials.

The issue of replication requires careful consideration. The requirement in the statute for adequate and well-controlled "clinical investigations" (21 U.S.C. 355(d) (emphasis added)) has long been interpreted to mean that the effectiveness of a drug should be supported by more than one well-controlled clinical trial and carried out by independent investigators. This interpretation is also consistent with the general scientific demand for replicability to ensure reliability of study results. Therefore, as a general requirement, the clinical trials submitted in a marketing application—including trials on products covered by this rule—must include studies by more than one independent investigator, each of whom has studied a number of patients adequate to generate statistically reliable results.

When applying the statutory requirement of "adequate and well-controlled investigations" to a drug for a life-threatening or severely-debilitating disease, FDA will consider the quality of the data submitted, including the assurance of the data's consistency, reliability, and reproducibility. There

have been a few unusual instances in which a particularly persuasive multi-center study has been accepted in support of a claim of increased survival because the study was, due to its design and dramatic and reliable results, considered highly persuasive; therefore, replication was not required for ethical reasons. One such example was the approval of zidovudine to treat AIDS patients (discussed earlier in this preamble). A second example involved the approval of timolol for reduction of post-infarction mortality, where a major effect on mortality was demonstrated in a large multi-center study. The timolol study was very persuasive because of excellent design, minimal or no problems during execution of the study, and a high degree of statistical significance associated with the critical finding.

In both these instances, the sufficiency of a multi-center study for marketing approval was based on the research being well-designed and well-conducted, and a dramatic increase in survival of the patients using the drug. Under these circumstances, FDA believed it would be unethical to repeat the trial. FDA would consider applying the same principle to other such cases in which the outcome of a multi-center study demonstrated a consistently dramatic increase in survival among independently evaluable study sites and where repetition of the study would be unethical. However, the agency cautions that persuasively dramatic results are rare and that two entirely independent studies will generally be required. Sponsors should therefore plan in advance a strategy for replication of key findings through a second well-controlled study. Such replication need not delay approval where a sponsor carries out all necessary clinical studies concurrently.

Finally, § 312.84(d) of the rule provides that marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in 21 CFR Part 314 or Part 600, as well as those in this interim rule. FDA has also added a conforming amendment to § 314.125 of the new drug application regulations, noting that for drugs intended to treat life-threatening or severely-debilitating illnesses that are developed in accordance with §§ 312.80 through 312.88, the criteria contained in paragraphs (b)(3), (4), and (5) of § 314.125 shall be applied according to the considerations contained in § 312.84.

While FDA can contribute to the design of the controlled clinical trials, and actively urge that such trials be pursued, the agency has no direct

control over the pace at which trials are initiated and completed. Success of drug development depends on the willingness of the sponsor and clinical investigators to devote the necessary time and resources to complete the studies expeditiously.

4. Phase 4 studies. Section 312.85 of the rule describes the role of phase 4 studies in this program. If FDA approval is gained on the basis of limited, but sufficient, clinical trials, it will usually be important to conduct postmarketing (phase 4) clinical studies that will extend the knowledge about the drug's safety and efficacy and allow physicians to optimize its use. For example, in the case of zidovudine, early appearance of a dramatic improvement in survival of the treated patients was taken as clear evidence that, for the relatively advanced HIV-infected patients treated, the benefits clearly outweighed the risks. Although significant side effects of zidovudine were found, the clinically demonstrated benefit of prolonged survival clearly outweighed those risks.

This does not mean that all important questions were answered at the time of approval of zidovudine and that research into its use could end. It was critical to examine—after marketing—its use in earlier stages of the disease, where its toxicity might outweigh its benefit (i.e., in earlier stages of the disease, survival is much greater without treatment so that there is less improvement possible, but toxicity might be just as severe). It was also important to explore dosing regimens that might be less toxic and equally effective. In addition, as with any drug, it is important to consider whether there are long-term adverse effects that might "take away" the early gain. As with zidovudine, FDA has generally been able to obtain a voluntary agreement with drug sponsors about the need to do such followup studies and the nature of their design, because sponsors also recognize important gaps in the data base and believe they need to be filled. Section 312.85 of the rule codifies this practice.

5. Focused FDA regulatory research. The responsibility for conducting the preclinical and clinical testing needed to gain marketing approval clearly rests with the drug's sponsor. This rule does not alter that responsibility. Recognizing the lack of available therapy for certain life-threatening and severely-debilitating illnesses, § 312.86 of the rule provides that in certain circumstances FDA may, in its discretion, undertake research on critical rate-limiting aspects of the preclinical, chemical/manufacturing,

and clinical phases of drug development and evaluation. For example, FDA often needs specific information upon which critical regulatory decisions are made—e.g., manufacturing standards and assays for vaccine or biotechnology products. Recent examples include FDA potency testing of vaccines and development of assay methods for drug bioavailability. FDA is prepared to intensify this practice on a limited basis as a means of meeting a public health need in facilitating the development of therapies to treat life-threatening illnesses, rather than merely waiting passively.

6. *Active monitoring of conduct and evaluation of clinical trials.* Section 312.87 of the rule provides that the Commissioner and other agency officials will actively monitor the progress of the conduct and evaluation of clinical trials and be involved in stimulating their appropriate progress. Recognizing that people with life-threatening diseases face a catastrophic condition that requires special attention, it is imperative that the conduct of clinical trials and FDA's evaluation of them proceed as expeditiously as possible. FDA actions would include, for example, contacting the sponsor directly when clinical trials are not proceeding on schedule. FDA may also convene special meetings of its advisory committees, as necessary, rather than waiting for the next scheduled periodic meeting.

Finally, FDA, in conjunction with other Public Health Service agencies, will utilize, to the extent possible, clearinghouse mechanisms for informing physicians and patients of investigational therapies for life-threatening illnesses. Existing mechanisms of this type will be augmented, as appropriate.

7. *Safeguards for patient safety.* If successfully implemented, this program will expedite the availability and approval of new therapies for life-threatening and severely-debilitating illnesses while assuring that the products are shown safe and effective under the law. Section 312.88 of the rule references safeguards inherent in FDA regulations that ensure the safety of clinical testing and the safety of products following marketing approval. These include the requirements for informed consent (21 CFR Part 50) and institutional review boards (21 CFR Part 56). These safeguards further include the review of animal studies prior to initial human testing (§ 312.23); IND safety reports during the conduct of clinical trials and treatment IND protocols (§ 312.32); safety update reports during

the review of marketing applications (§ 314.50); and adverse drug reaction reports after products are approved for marketing (§ 314.80).

In addition to these regulatory safeguards designed to assure patient safety, FDA's practices and procedures provide additional safeguards to assure the quality and integrity of the drug development and review process. These include conducting on-site audits of key studies and/or clinical investigators to assure authenticity of the data submitted to FDA, and inspections of manufacturing facilities before marketing approval is granted to assure that manufacturers are able to produce properly formulated compounds.

D. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

E. Economic Impact

FDA has considered the economic impacts of this interim rule and concludes that additional costs resulting from this rule will be negligible, and to the limited extent that they may occur, they will likely be more than off-set by the societal benefits of this rule.

The compression of the drug development process set forth in this rule for life-threatening and severely-debilitating illnesses presents a trade-off for affected sponsors. They would be relieved of conducting the customary phase 2/phase 3 clinical studies if they participate in early study design consultation with FDA, conduct a sufficiently comprehensive phase 2 study, and stand ready to conduct any necessary phase 4 studies. Considering the probable time savings of this process, it is expected that the net cost of clinical development and regulatory review for a sponsor will remain constant or possibly decrease. Even if costs were to increase slightly, the societal benefits would more than likely compensate for any added costs since a considerable patient population would be receiving the life-saving benefits of the expedited therapy over an extended period of time that would not otherwise be realized.

Accordingly, FDA concludes that this interim rule is not a major rule as defined by Executive Order 12291, which would require a regulatory flexibility analysis. Furthermore, this rule is not expected to impose substantial impacts on a significant

number of small entities which would require a regulatory flexibility analysis under the requirements of the Regulatory Flexibility Act of 1980.

F. Paperwork Reduction Act of 1980

This interim rule does not contain new collection of information requirements. Section 312.88 does refer to regulations that contain collection of information requirements that were previously submitted for review to the Director of the Office of Management and Budget (OMB) under section 3504 of the Paperwork Reduction Act of 1980. Sections 312.23 and 312.32 were approved under OMB control number 0910-0014. Section 314.50 was approved under OMB control number 0910-0001. Section 314.80 was approved under OMB control number 0910-0230.

References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Young, Frank E., and Stuart L. Nightingale, "FDA's Newly Designated Treatment IND's," "Information on Treatment IND's as They Become Available to the Practitioner," *Journal of the American Medical Association*, 260:224-225, 247, 1988.
2. Young, Frank E., John A. Norris, Joseph A. Levitt, and Stuart L. Nightingale, "The FDA's New Procedures for the Use of Investigational Drugs in Treatment," *Journal of the American Medical Association*, 259:2267-2270, 1988.
3. "Drugs Hold Hope for Parkinson's Obsessive-Compulsive Patients," *FDA Consumer*, September 1988:31.
4. Young, Frank E., "Experimental Drugs for the Desperately Ill: A Progress Report," *FDA Consumer*, May 1988:2-3.
5. "Updates," *FDA Consumer*, February 1988:2-3.
6. Young, Frank E., "New Drug Development in the United States," *FDA Consumer*, November 1987:4-5.
7. "Updates," *FDA Consumer*, September 1987:5-8.
8. Young, Frank E., "Experimental Drugs for the Desperately Ill," *FDA Consumer*, June 1987:2-3.
9. Office of Planning and Evaluation Study 77, "The Outcome of Research on New Molecular Entities Commencing Clinical Research in the Years 1976-78," FDA, May 1988.
10. "Confronting AIDS: Update 1988," Institute of Medicine, 1988.

List of Subjects

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, Parts 312 and 314 are amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. Subparts E and F are redesignated as Subparts F and G, respectively, and new Subpart E is added consisting of §§ 312.80 through 312.88 to read as follows:

Subpart E—Drugs Intended To Treat Life-threatening and Severely-debilitating Illnesses

Sec.

- 312.80 Purpose.
- 312.81 Scope.
- 312.82 Early consultation.
- 312.83 Treatment protocols.
- 312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.
- 312.85 Phase 4 studies.
- 312.86 Focused FDA regulatory research.
- 312.87 Active monitoring of conduct and evaluation of clinical trials.
- 312.88 Safeguards for patient safety.

Authority: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 483 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262); 21 CFR 5.10, 5.11.

Subpart E—Drugs Intended To Treat Life Threatening and Severely-debilitating Illnesses**§ 312.80 Purpose.**

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated § 314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side

effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with that purpose.

§ 312.81 Scope.

This section applies to new drug, antibiotic, and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

(a) For purposes of this section, the term "life-threatening" means:

- (1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and
- (2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.

(b) For purposes of this section, the term "severely debilitating" means diseases or conditions that cause major irreversible morbidity.

(c) Sponsors are encouraged to consult with FDA on the applicability of these procedures to specific products.

§ 312.82 Early consultation.

For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings

(a) *Pre-investigational new drug (IND) meetings.* Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, and the best approach for presentation and formatting of data in the IND.

(b) *End-of-phase 1 meetings.* When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach

agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing. The procedures outlined in § 312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.

§ 312.83 Treatment protocols.

If the preliminary analysis of phase 2 test results appears promising, FDA may ask the sponsor to submit a treatment protocol to be reviewed under the procedures and criteria listed in §§ 312.34 and 312.35. Such a treatment protocol, if requested and granted, would normally remain in effect while the complete data necessary for a marketing application are being assembled by the sponsor and reviewed by FDA (unless grounds exist for clinical hold of ongoing protocols, as provided in § 312.42(b)(3)(ii)).

§ 312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.

(a) FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in § 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

(b) In making decisions on whether to grant marketing approval for products that have been the subject of an end-of-phase 1 meeting under § 312.82, FDA will usually seek the advice of outside expert scientific consultants or advisory committees. Upon the filing of such a marketing application under § 314.101 or Part 601 of this chapter, FDA will notify the members of the relevant standing advisory committee of the application's filing and its availability for review.

(c) If FDA concludes that the data presented are not sufficient for marketing approval, FDA will issue (for a drug) a not approvable letter pursuant to § 314.120 of this chapter, or (for a biologic) a deficiencies letter consistent with the biological product licensing procedures. Such letter, in describing the

deficiencies in the application, will address why the results of the research design agreed to under § 312.82, or in subsequent meetings, have not provided sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

(d) Marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in Part 314 or Part 600 of this chapter, as well as those in this subpart.

§ 312.85 Phase 4 studies.

Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

§ 312.86 Focused FDA regulatory research.

At the discretion of the agency, FDA may undertake focused regulatory research on critical rate-limiting aspects

of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. When initiated, FDA will undertake such research efforts as a means for meeting a public health need in facilitating the development of therapies to treat life-threatening or severely debilitating illnesses.

§ 312.87 Active monitoring of conduct and evaluation of clinical trials.

For drugs covered under this section, the Commissioner and other agency officials will monitor the progress of the conduct and evaluation of clinical trials and be involved in facilitating their appropriate progress.

§ 312.88 Safeguards for patient safety.

All of the safeguards incorporated within Parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. This includes the requirements for informed consent (Part 50 of this chapter) and institutional review boards (Part 56 of this chapter). These safeguards further include the review of animal studies prior to initial human testing (§ 312.23), and the monitoring of adverse drug experiences through the requirements of IND safety reports (§ 312.32), safety update reports during agency review of a marketing

application (§ 314.50 of this chapter), and postmarketing adverse reaction reporting (§ 314.80 of this chapter).

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

2. The authority citation for 21 CFR Part 314 continues to read as follows:

Authority: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049-1053 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); 21 CFR 5.10, 5.11.

3. Section 314.125 is amended by adding paragraph (c) to read as follows:

§ 314.125 Refusal to approve an application.

* * * * *

(c) For drugs intended to treat life-threatening or severely-debilitating illnesses that are developed in accordance with §§ 312.80 through 312.88 of this chapter, the criteria contained in paragraphs (b) (3), (4), and (5) of this section shall be applied according to the considerations contained in § 312.84 of this chapter.

Otis R. Bowen,

Secretary of Health and Human Services.

Dated: October 18, 1988.

[FR Doc. 88-24457 Filed 10-19-88; 10:18 am]

BILLING CODE 4160-01-M

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

(please insert)

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)

(please insert)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. 91N-0278]

RIN 0905-AD66

New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations under which the agency will accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provisions for any necessary continued study of the drugs' clinical benefits after approval or with restrictions on use, if necessary. These new procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic benefit compared to existing treatment. Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence from adequate and well-controlled studies of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under these procedures will have met the requisite standards for safety and effectiveness under the Federal Food, Drug, and Cosmetic Act (the act) or the Public Health Service Act (the PHS Act) and, thus, will have full approval for marketing.

EFFECTIVE DATE: January 11, 1993.

FOR FURTHER INFORMATION CONTACT: Marilyn L. Watson, Center for Drug Evaluation and Research (HFD-360), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-295-8038.

SUPPLEMENTARY INFORMATION:

I. Background

In the *Federal Register* of April 15, 1992 (57 FR 13234), FDA published proposed procedures under which the

agency would accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs. FDA provided 60 days for public comment, and, upon request, in the *Federal Register* of June 18, 1992 (57 FR 27202), extended the comment period for an additional 30 days until July 15, 1992. The final rule incorporates all of the provisions of the proposed rule and provides additional clarification regarding both timing and content of the submissions of promotional materials and regarding the nature of required postmarketing studies. The agency has added a new provision clarifying when certain postmarketing requirements of the rule will be terminated.

Highlights of the final rule are summarized below, followed by a summary and discussion of the comments.

II. Highlights of the Final Rule

This final rule establishes procedures under parts 314 and 601 (21 CFR parts 314 and 601) under which FDA will accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs. These procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic advantage over existing treatment. The preamble of the proposed rule (57 FR 13234) provides a description of other mechanisms available to facilitate access, speed development, and expedite review of therapeutic products (e.g., treatment investigational new drug applications (IND's), subpart E, parallel track). Where appropriate, these mechanisms can be utilized in concert with accelerated approval. The major provisions of the final rule are as follows:

A. Scope

The new procedures apply to certain new drug, antibiotic, and biological products used in the treatment of serious or life-threatening diseases, where the products provide meaningful therapeutic advantage over existing treatment (21 CFR 314.500 and 601.40).

B. Criteria for Approval

Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under this final rule will have met the requisite standards for safety and effectiveness under the act or the PHS Act and, thus, will have full approval for marketing (21 CFR 314.510, 314.520, 601.41, and 601.42). Ordinarily, products used to treat serious or life-threatening illnesses, for which approval is based on a surrogate endpoint that is recognized as validated by definitive studies, will be considered for approval under the traditional process rather than under accelerated approval.

C. Postmarketing Studies

Where a drug's approval under these provisions is based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity, the applicant will be required to conduct clinical studies necessary 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. The requirement for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval; it is expected that the studies will usually be underway at the time of approval. The proposed regulations have been revised to clarify that required postmarketing studies must also be adequate and well-controlled (21 CFR 314.510 and 601.41).

D. Restrictions on Use After Marketing

FDA may grant marketing approval of a drug or biological product shown to be effective where safe use can only be assured if distribution or use is restricted. Under this final rule, FDA may: (1) Restrict distribution to certain facilities or to physicians with special training or experience, or (2) condition distribution on the performance of

specified medical procedures. The restrictions on use will be tailored to the specific safety issue raised by the particular drug or biological product and agreed to by the applicant at the time of approval (21 CFR 314.520 and 601.42). FDA expects that the imposition of these restrictions on distribution will be rare.

E. Promotional Materials

The final rule requires submission of planned promotional materials, including promotional labeling and advertisements, both prior to approval (reflecting the initial campaign), and following approval, unless informed by the agency that such submission is no longer necessary, at least 30 days before the intended time of initial dissemination of the promotional labeling or initial publication of the advertisement (21 CFR 314.550 and 601.45).

F. Withdrawal of Approval

The final rule establishes an expedited procedure for the withdrawal of approval if: (1) Postmarketing clinical studies fail to verify clinical benefit; (2) the applicant fails to perform the required postmarketing study with due diligence; (3) use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug or biological product; (4) the applicant fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug or biological product is not shown to be safe or effective under its conditions of use (21 CFR 314.530 and 601.43).

G. Termination of Requirements

In response to comments, the final rule provides that the requirements set forth in §§ 314.520, 314.530, and 314.550 for new drugs and antibiotics and §§ 601.42, 601.43, and 601.45 for biological products ordinarily will terminate when FDA determines that the results of required postmarketing studies have demonstrated that the drug or biological product has clinical benefit, or, where restrictions on distribution or use have been imposed, when FDA determines that safe use of the drug or biological product can be ensured without such restrictions, e.g., through appropriate labeling. FDA will notify the applicant when these requirements no longer apply (21 CFR 314.560 and 601.46).

III. Effective Date

This regulation will become effective on January 11, 1993.

IV. Comments on the Proposed Rule

FDA received 54 comments on the proposed rule. The comments came from individuals, specific disease organizations, universities, pharmaceutical manufacturers, trade associations, health professionals, and professional societies. The comments reflect broad support and acceptance of the goal of expediting the approval of drugs intended for the treatment of serious and life-threatening illnesses. A number of comments asked that the proposal be finalized expeditiously without change. Many comments posed specific questions and raised important concerns.

A. General Comments

1. One comment suggested that the term "conditional approval" was less confusing and ambiguous than the term "accelerated approval." The comment also referred to the statement in the proposal that "Drugs * * * approved under this proposal will have met the requisite standards * * * under the (act)" and argued that because postmarketing conditions may be imposed, this statement can only be read to say that the requisite standards under the act can only be met by a lower standard of evidence in hand, combined with assurance that further evidence will be obtained.

Another comment expressed concern that the proposal appears to establish a standard for the evaluation of drug product effectiveness that is inconsistent with the substantial evidence requirement of section 505(d) of the act (21 U.S.C. 355(d)), which means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling * * *." The comment argued that, with few exceptions, the agency has consistently interpreted the "substantial evidence" requirement as an instruction that determinations of effectiveness be based on data unambiguously reflecting the clinical status of subjects evaluated under controlled conditions in bona fide clinical experiments. In the absence of compelling empirical evidence documenting that a drug-induced change in a surrogate measure reliably and consistently predicts improved

clinical outcome, a surrogate indicator is no more than a hypothetical construct. The comment asserted that the proposed rule's endorsement of the use of unvalidated surrogate endpoints, therefore, appears to represent a significant departure from traditional agency interpretations of "substantial evidence" within the meaning of the act because it allows belief rather than evidence to serve as the basis for a conclusion about the effectiveness of a new drug.

Three comments asserted that the new regulations are not needed to approve drugs intended to treat serious or life-threatening illnesses. Two comments cited FDA's approval, without new regulations, of didanosine (formerly called ddi) and zalcitabine (formerly called ddc) in combination with zidovudine (formerly called AZT) based on a surrogate marker, i.e., an increase in CD4 cell counts and the "subpart E" procedures at 21 CFR part 312, which address the need for expediting the development, evaluation, and marketing of new therapies intended to treat life-threatening or severely debilitating illnesses as examples of existing mechanisms for the expedited approval of important new drugs. One comment argued that the act requires that drugs be shown to be "safe" and "effective," and proof of effectiveness is not limited by the act to demonstration of an effect on "survival or irreversible morbidity," as the proposed rule seems to assume. The comment further argued that FDA has considerable statutory discretion to define what type of data constitutes proof of effectiveness, and demonstration of an effect on a surrogate marker is one type of such proof.

The agency believes that what the procedures are called is much less important than what the procedures are. The shorthand term selected by the agency reflects the intent of the rule, especially that part related to use of surrogate markers, which is to make drugs that provide meaningful improvement over existing therapies for serious illnesses widely available (through marketing) at the earliest time consistent with the law. The essence of the proposal is thus acceleration, not the imposition of conditions. Approval under these procedures is dependent on compliance with certain additional requirements, such as timely completion of studies to document the expected clinical benefit. The evidence available at the time of approval under this rule will meet the statutory standard, in that there must be evidence from adequate and well-controlled studies showing that the drug will have

that considerable risk is acceptable) and/or when the surrogate endpoint is well supported. In addition, it will be the sponsor's clear obligation to resolve any doubts as to clinical value by carrying out definitive studies.

FDA does not agree that it would be more appropriate to seek an amendment to the act than to adopt the proposed requirements. As discussed in the preamble to the proposed rule as well as elsewhere in this preamble to the final rule, existing provisions of the act and the PHS Act authorize promulgation of the requirements in the final regulations.

3. One comment expressed concern that because the proposed rule would establish conditions on a drug's approval, third-party payors may decline reimbursement because the so-called approval would have attributes of investigational status.

The agency expects that, because drugs approved under the accelerated approval process meet the statutory standards for safety and effectiveness, they would be eligible for reimbursement under State Medicaid programs or other third-party plans. Drug products granted accelerated approval will not be, under the law, investigational, as suggested by the comment.

4. One comment asked if all drugs considered for accelerated approval must be reviewed by an advisory committee. The comment stated that because advisory committees meet infrequently, waiting for the next meeting may slow down the approval process.

FDA is not required to consult with an advisory committee before approving an application under these accelerated approval regulations, or any other regulation. However, FDA intends to consult the appropriate committee in most instances. Advisory committee meetings can usually be scheduled to avoid significant delays in the review process. The agency will consider any request by an applicant for referral of the application to an advisory committee.

B. Scope

5. Four comments asked for further clarification of what diseases are covered by the rule. One comment stated that the terms "serious," and "life-threatening," are defined in the proposal by reference to 21 CFR 312.34, followed by a brief statement explaining the role of judgment and examples of diseases that are currently judged to be

serious. The comment asked that FDA also describe: (1) Diseases that are not currently included in the category of "serious," (2) examples of diseases that are currently judged "life-threatening," and (3) examples of diseases that are not currently included in the category "life-threatening."

One comment contended that the statement in the preamble that "seriousness of a disease 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" too narrowly limits diseases covered by the proposed rule (57 FR 13234 at 13235). The comment argued that some "less severe" diseases, even if treated, may progress to a more serious state, and that these diseases should also be covered by the rule. On the other hand, two comments argued that the language in the preamble that classifies diseases as "serious" was overly broad and subjective and far too large a number of illnesses could be eligible as being "serious."

FDA discussed the meaning of the terms "serious" and "life-threatening" in its final rules on "treatment IND's" (52 FR 19466 at 19467, May 22, 1987) and "subpart E" procedures (54 FR 41516 at 41518-41519, October 21, 1988). The use of these terms in this rule is the same as FDA defined and used the terms in those rulemakings. It would be virtually impossible to name every "serious" and "life-threatening" disease that would be within the scope of this rule. In FDA's experience with "treatment IND's" and drugs covered by the "subpart E" procedures there have not been problems in determining which diseases fall within the meaning of the terms "serious" and "life-threatening," and FDA would expect no problems under this accelerated approval program. The likelihood of progression to a serious condition with available treatments would also be considered in assessing whether the disease is within the scope of the final rule. The preamble to the proposed rule (57 FR 13234 at 13235) referred to chronic illnesses that are generally well managed by available therapy, but can have serious outcomes for certain populations or in some or all of their phases. Applicants are encouraged to consult with FDA's reviewing divisions early in the drug development process if they have questions about whether their specific product is within the scope of this rule.

The concerns expressed in these and other comments about considering too many illnesses eligible for consideration under the accelerated approval procedures may arise from the underlying fear that reliance on surrogate endpoints will become routine, the "normal" way drugs are brought to the market. This fear is groundless. The vast majority of drugs are directed at symptomatic or short-term conditions (pain, heart failure, acute infections, gastrointestinal complaints) whose response to drugs, if it occurs, is readily measured and where there is no need to consider or accept surrogate endpoints. Surrogates, with few exceptions, are of interest in the following situations: (1) Where the clinical benefit, if there is one, is likely to be well in the future; and (2) where the implications of the effect on the surrogate are great because the disease has no treatment at all or the drug seems to treat people with no alternative (e.g., because they cannot tolerate the usual effective treatment). In the first case, great care is needed, and would be given, as there would generally be no experience linking an effect on the surrogate to clinical success, and there have been conspicuous examples of lack of linkage (CAST, referred to above; drugs that increase cardiac output in patients with heart failure but that decrease survival; imperfect agreement of effects on coronary artery patency and effects on survival in patients with myocardial infarction; lack of beneficial effect on bone fracture rate despite favorable effects on bone density in patients with osteoporosis). FDA and outside experts will be aware of these examples as proposed surrogates are considered. The implications are especially great when considering prophylactic therapy, i.e., treatments to prevent chronic illness (coronary artery disease, cancer), in an essentially well population. In the second case, there will generally have been experience (with the standard therapy) to evaluate in considering linkage of the surrogate to benefit; this was, for example, the case with didanosine, where evidence from zidovudine studies of the relationship of an effect on CD4 lymphocytes and clinical outcome could be assessed. Similarly, there is considerable experience to show that durable complete responses in many cancers correspond to improved survival, so that an agent inducing them in refractory illness or in primary

disease that had previously been poorly responsive would generally be seen as reasonably likely to provide a clinical benefit.

6. One comment stated that epilepsy is a serious and life-threatening condition and asked that it be included within the scope of the proposal. The preamble cited, among other illnesses, depression and psychoses as examples of chronic illnesses that can have serious outcomes even if they are generally well managed. One comment asserted that neither depression nor psychosis is a disease, nor is either one serious or life-threatening. The comment stated that depression and psychosis are diagnoses. The comment urged the agency to remove them from the definition of life-threatening "illnesses" or "diseases."

With respect to epilepsy, FDA notes that in the "treatment IND" final rule (52 FR 19466 at 19467, May 22, 1987), the agency listed "certain forms of epilepsy" as an example of a disease or stage of disease that would normally be considered "serious." Certain forms of epilepsy may also be considered "serious" under the accelerated approval program. It is unlikely, however, that a surrogate endpoint would be utilized in such a case, as seizure frequency, a clinical endpoint, is readily measured.

FDA's reference to depression and psychoses was intended to give examples of conditions or diseases that can be serious for certain populations or in some or all of their phases. While drugs for the treatment of depression and psychosis would be examples of those that could be covered by the accelerated approval program, it is not the use of surrogate endpoints that would be expected; the symptoms and signs of these diseases are readily studied. On the other hand, some of these drugs have been quite toxic (e.g., clozapine for refractory psychoses) and might be considered for approval with restrictions to ensure safe use.

7. Two comments asked how FDA will decide that a drug is eligible for accelerated approval. One comment asserted that the decision should be an option for the applicant to consider, not a decision for FDA to make unilaterally. Pointing to a statement in the preamble (57 FR 13234 at 13235) that FDA reserves the right not to apply accelerated approval procedures when it believes in good faith that the drug's foreseeable use is reasonably likely to be outside the scope of "life-threatening diseases without meaningful therapeutic benefit over existing therapy," the comments argued that, if there are patients with life-threatening conditions

that can benefit from expedited approval, the needs of the patients should determine the procedures used to approve the drug. One comment contended that applicants of products considered candidates for accelerated approval may have their drug or biological product "forced" into the accelerated approval process and be forced to conduct a program of studies to substantiate that surrogate endpoints actually predict significant clinical benefits.

The medical reviewing divisions within FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) will determine the type of regulatory review that FDA may apply to an application. FDA encourages sponsors to meet with FDA early in the drug development process to discuss the applicability of the accelerated approval program to their product; however, FDA reserves the discretion to determine whether these procedures are applicable to a specific product.

With respect to the preamble statement cited by one comment, the comment misreads the preamble statement, which does not say that FDA will, in all cases, apply FDA's traditional approval mechanisms rather than this accelerated process for drugs where a majority of the drug's foreseeable uses are outside the scope of "life-threatening" diseases without meaningful therapeutic benefit over existing therapy. The statement merely informs applicants that FDA will consider the possible impact of widespread use of a drug for uses other than the one supporting accelerated approval; drugs approved under this program would often have only small safety data bases so that widespread off-label use might have serious implications. The agency does not believe that such a situation would regularly lead to exclusion from these provisions.

FDA does not agree that applicants seeking approval to market drug and biological products that would be candidates for accelerated approval will be forced to use the accelerated approval mechanism. It is true, however, that some proposed surrogate endpoints would not be considered acceptable bases for approval without assurance that the clinical studies to show clinical benefit will be conducted. A sponsor that wishes the application to be considered under the traditional approval process may request and receive such consideration.

The agency wishes to clarify the circumstances in which the accelerated

approval regulations will apply. Sections 314.500 and 601.40 describe aspects of the scope of these regulations. Moreover, these regulations are intended to apply to applications based on surrogate endpoints whose validity is not fully established, to applications based on clinical endpoints that leave unanswered major questions about the product's effect on ultimate outcome, and to applications for products whose safe and effective use requires limitations on distribution or use. In all other situations, accelerated approval requirements will not apply.

Where approval is based on a surrogate endpoint that is accepted as validated to predict or correlate with clinical benefit, the product will be considered under the traditional process, and the postmarketing requirements under accelerated approval will not apply. Approvals of products for serious or life-threatening illnesses based on clinical endpoints other than survival or irreversible morbidity will usually also be considered under traditional procedures. Approvals based on such clinical endpoints will 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. Applications for products for serious or life-threatening illnesses that provide a meaningful therapeutic benefit over existing therapy will receive a priority rating and expedited review, even when not considered under the accelerated approval procedures.

The agency also wishes to clarify that whenever an application is approved under § 314.510 or § 601.41, postmarketing studies confirming the product's clinical benefit will thus be required. Therefore, in order to eliminate potential confusion, the agency has amended §§ 314.510 and 601.41 to clarify these points.

FDA also recognizes that over time a particular surrogate, once acceptable as a basis for approval only under the accelerated approval regulations, could become recognized as validated by definitive studies (just as high blood pressure, for example, over time became validated as a surrogate with clinical significance). In such cases, a future application relying on such a surrogate would not require postmarketing studies confirming the surrogate's clinical benefit and the application would be considered under traditional procedures.

8. Two comments asked for clarification of the phrase "meaningful

therapeutic benefit over existing therapy" as used in the description of what drugs the accelerated approval program should apply to. Specifically, pointing to an example described in the preamble that a new therapy would be eligible for accelerated approval if there was "a clear improvement" over existing therapy in being more effective or better tolerated, one comment urged FDA to clarify the meaning of "clear improvement" to discourage applicants of "me-too" products from wasting the agency's time and resources by applying for accelerated approval of such products. The comment also asked that FDA specify that if a new drug is approved under the accelerated approval provisions because the drug exhibits a "clear improvement" over an existing drug that was also granted accelerated approval, then specific restrictions will be placed on the prior approved drug to limit its use only to patients who cannot tolerate the new drug, or whose physicians assess that a change to the new drug might involve significant risks to the patient that outweigh the benefits. One comment asked that the term "meaningful therapeutic benefit over existing therapy" be interpreted and consistently applied to both drugs and biological products.

FDA believes that the examples given to help clarify the phrase "meaningful therapeutic benefit over existing therapy" (ability to treat unresponsive or intolerant patients or improved response compared to available therapy) are readily understood illustrations of the intent of the requirement. A drug that is essentially the same as available treatment (what the comment refers to as a "me too" drug) will not have a credible claim to a meaningful therapeutic benefit over that existing treatment and this should be easily detected.

With respect to restricting use of a drug previously approved under accelerated approval procedures when a new drug granted accelerated approval is a clear improvement over the prior approved drug, this would rarely be appropriate. Although, in some instances, certain therapies are identified as "second-line," this requires essentially unequivocal evidence of an advantage of alternative therapy, not likely on the basis of a surrogate endpoint. Labeling for both drugs will be accurate, however, allowing physicians to prescribe both the newly approved drug and the prior drug properly.

9. One comment asked if a change in the route of administration would be

considered as a meaningful benefit and within the scope of the proposal.

A change in the route of administration may be a candidate for accelerated approval depending upon the particular evidence presented.

10. One comment asked if subpart E drugs currently under investigation will be considered for accelerated approval. The comment assumed that new drug applications (NDA's) and supplemental NDA's considered for accelerated approval will have the highest priority for review.

Subpart E drugs will be considered for accelerated approval if they satisfy both eligibility criteria for accelerated approval, i.e., if they are being developed for the treatment of serious or life-threatening illnesses and the products will provide meaningful therapeutic benefits to patients over existing treatment. As discussed above, applicants should consult with FDA early in the development process to determine the nature of the regulatory review. Early consultations are a critical part of subpart E procedures. Drugs being reviewed under accelerated approval procedures will receive high priority review. However, applications for drugs for acquired immunodeficiency syndrome (AIDS) and human immunodeficiency virus (HIV)-related conditions will receive the highest priority review.

C. Criteria for Approval

11. Two comments expressed concern that the proposal did not provide enough detail on what constitutes an appropriate surrogate endpoint. One comment recommended that FDA adopt specific criteria for what constitutes an appropriate surrogate endpoint. The comment suggested that such criteria should include: (1) The surrogate endpoint must be biologically plausible in that it must be consistent with what is known about the pathophysiology and pathogenesis of the disease; (2) the surrogate endpoint must be present or abnormal in a large percentage of people who have the disease; (3) the surrogate endpoint must be a good predictor of the disease progression and should correlate closely with the significant clinical endpoint; (4) there should be a correlation between the quantitative aspect of the surrogate endpoint and the progression of the disease (e.g., the more severe the disease, the more deviant the surrogate endpoint from normal); (5) the regression of the surrogate endpoint should be significantly associated with clinical improvement (e.g., those with the greatest improvement in the surrogate endpoint should also show the greatest clinical effects); conversely, the

lack of regression of the surrogate endpoint should be commonly associated with a lack of clinical improvement; and (6) the incidence of regression or improvement in the surrogate endpoint should be significantly greater in treated than untreated patients.

One comment asked if the use of microalbuminuria data is a surrogate for diabetic nephropathy and if all drugs relying on surrogate endpoints would be eligible for accelerated approval, e.g., an angiotensin receptor antagonist with potential utility for treatment of congestive heart failure. The comment also asked what would happen if postmarketing studies demonstrate beneficial changes of surrogate endpoints but not beneficial clinical endpoints. The comment also asked if FDA will consider publishing guidelines on which surrogate endpoints would be appropriate for the diseases that may be affected by the proposed rule. Another comment expressed the belief that there is no evidence that surrogate endpoints are necessarily good indicators of therapeutic benefit. The comment stated that a drug may have an effect on a surrogate endpoint, but will not make any clinical difference because the advanced stage of the patient's disease precludes any effective therapy or the surrogate marker is not synchronous with the patient's clinical condition.

Another comment asserted that the requirement to base an approval on a surrogate endpoint that is "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit other than survival or irreversible morbidity" is not restrictive enough to assure adequate consumer protection. Terms like "reasonably likely" and "or other evidence" allow drug manufacturers too much latitude for claiming that there is a correlation between surrogate endpoints affected by their drugs and clinical endpoints. The comment argued that until a correlation between a surrogate endpoint and a clinical endpoint has been established, a particular surrogate endpoint should only be used to approve subsequent drugs, without adequate clinical evidence, if there is a very strong effect of the drug on the surrogate marker or, if the effect is not sufficiently strong, there is an additional surrogate marker which corroborates the results of the first.

FDA intends to publish informal guidance concerning surrogate endpoints, but does not believe specific requirements for an appropriate surrogate should be specified by

regulation. Any given specifications may not be applicable to a particular case. For example, the thoughtful suggested criteria supplied by the comment would rarely, if ever, be applicable to the first effective drug for a disease, because criterion 5 requires that regression of the surrogate endpoint be associated quantitatively with clinical improvement. If there had never been effective treatment, this would never be known. Yet the surrogate could be persuasive on other grounds, such as a well-documented etiologic relation. In general, it is likely that one or another strongly supportive piece of evidence might outweigh gaps in other areas.

In developing informal guidance on surrogate endpoints, FDA will consider the suggestions in this comment. Interested persons will have an opportunity to comment on any guidance documents in this area developed by the agency. In some cases, new or revised drug class, or disease-specific, clinical guidelines may refer to surrogate endpoints. FDA is not prepared, at this time, to comment on the acceptability of an endpoint that it has not specifically considered, e.g., microalbuminuria.

The final regulations make it clear that not all drugs submitted for approval based on surrogate endpoint data are eligible for accelerated approval (§§ 314.500 and 601.40). The drug in question must be for a serious or life-threatening condition and must provide meaningful therapeutic benefit over existing therapy. In the case of an angiotensin receptor antagonist posed by the comment, there is existing documented life-prolonging treatment for congestive heart failure. An application for a new agent, to be eligible for accelerated approval, would have to show potential benefit over available therapy as well as identify a reasonable surrogate endpoint. This is problematic since no accepted surrogate endpoint for studies to treat congestive heart failure has been identified to date. For example, some drugs with favorable effects on hemodynamic measures in heart failure patients have been clinically ineffective.

The regulations are clear in requiring that, for drugs approved under these provisions based on surrogate endpoints, the postmarketing studies must show clinical benefit, not just the previously shown effect on the surrogate (§§ 314.510, 314.530, 601.41, and 601.43).

Surrogates, or proposed surrogates, are not always good, nor necessarily bad, indicators of therapeutic benefit and must be judged on a case-by-case basis. Even very good surrogates may

not be perfect: Blood pressure lowering has been a better predictor of effect on stroke than on coronary artery disease, cholesterol lowering has had a clearer effect on coronary artery disease than on survival. Moreover, a surrogate may be persuasive for a phase of disease with short expected survival but much less so in an earlier phase of the disease. Caution is always appropriate in evaluating surrogate endpoints and the particular therapeutic setting should always be considered. The agency believes that the evaluation of surrogate endpoint data and the safeguards built into these accelerated approval procedures will provide adequate consumer protection.

12. One comment expressed concern that if there is no accepted surrogate endpoint, an applicant's only option is to conduct a study using some clinical event as an endpoint, which may result in long, large studies that delay approval to the detriment of patients and sponsors. One comment suggested as an alternative that FDA permit approval of a drug based on a study using a clinical endpoint, but accept a less rigorous standard of statistical significance, e.g., 0.20 or 0.15 instead of 0.05. The comment further suggested that the sponsor could then complete postmarketing studies to establish statistical significance at conventional levels. The comment argued that this alternative is totally consistent with FDA's willingness to accept greater uncertainty in approving drugs for serious and life-threatening illnesses.

The intent of the rule is to allow FDA to utilize a particular kind of evidence, an effect on a surrogate endpoint, as a basis for approval, and, where appropriate, to ensure that remaining doubts about the relationship of the effect on the surrogate to clinical benefit are resolved by additional adequate and well-controlled studies with clinical endpoints. The rule is not intended to place into the market drugs with little evidence of usefulness. Although there is no statutory requirement for significance testing of any particular value, there are well-established conventions for assessing statistical significance to support the statutorily required conclusion that the well-controlled studies have demonstrated that a drug will have the effect it is represented to have. There is nothing about serious or life-threatening diseases that make them uniquely difficult to study. A meaningful effect on survival or morbidity where there is no effective therapy should be readily discerned. Such studies need be long and large only when the effect is small or difficult to detect. In that event,

proper assessment of benefit, and valid weighing of its relation to risk, is especially critical.

13. One comment asked that FDA clarify that one study could be the basis of approval and that one postmarketing study should be all that is needed to establish the link between the endpoint used for approval and some relevant clinical benefit.

FDA interprets the statute, and good science, as requiring at least two adequate and well-controlled studies to establish effectiveness. In some instances, drugs have been approved on the basis of a single well-controlled study; this has been done where the study was of excellent design, showed a high degree of statistical significance, involved multiple study centers, and showed some evidence of internal replicability, e.g., similar effects in major study subsets. FDA encourages applicants to discuss with FDA early in a drug's development the basis for the applicant's choice of a specific endpoint and, where applicable, the basis for its belief that a single study would be a sufficient basis for approval. With respect to postmarketing studies, FDA anticipates that the requirement will usually be met by studies already underway at the time of approval. As stated in the proposed rule, the requirement for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval of the same drug for the same claim.

14. One comment expressed concern that the preamble to the proposed rule implied that a sponsor of an AIDS drug might have to do a postmarketing study to establish an effect on survival after showing an effect on such endpoints as weight or incidence of opportunistic infection (57 FR 13234 at 13235-13236). The comment stated that FDA's own advisory committee indicated that it was pleased to see an effect from a nucleoside analogue on the incidence of opportunistic infections with AIDS patients but did not suggest that further work should be done to show an effect on mortality. The comment argued that in some cases direct correlation with clinical endpoints such as mortality is difficult to prove and urged FDA to be flexible on this issue to encourage sponsors to go through the accelerated approval process.

Ordinarily, an effect on a meaningful clinical endpoint, e.g., on rate of opportunistic infections in AIDS, is a sufficient basis for approval without need for followup studies. Other endpoints, however, might leave major questions unanswered. For example, a

modest effect on weight gain in AIDS without other demonstrated benefit, if considered an adequate basis for approval, while a clinical endpoint, might leave sufficient doubt as to the ultimate value of the effect so that further studies would be necessary. FDA intends to interpret this provision of the regulations with flexibility. This provision should also serve as a reminder, however, that for life-threatening diseases, the ultimate aim of therapy is improved survival as well as improved symptoms.

15. One comment asked FDA to clarify what a sponsor's obligation is to continue supplying medication on a compassionate basis if clinical efficacy is not demonstrated to FDA's satisfaction in postmarketing studies but individual patients appear to be benefiting from use of the drug.

Sponsors are not obligated to supply drugs on a "compassionate basis." Whether, if clinical studies did not show effectiveness, further availability of the drug would be appropriate under any mechanism would be determined case-by-case.

D. Promotional Materials

16. Three comments asserted that requiring advance submissions of promotional materials is both beyond FDA's statutory authority and is unnecessary. Although FDA stated in the proposal that it does not intend specifically to approve promotional materials, two comments contended that is the likely effect of advance submission. The comment cited section 502(n) of the act (21 U.S.C. 352(n)), which provides that no regulation promulgated under that provision shall require prior FDA approval of the content of any advertisement "except in extraordinary circumstances," and asserted that the "extraordinary circumstances" language would not apply to drugs approved under the accelerated approval program. One comment argued that submission of promotional material prior and subsequent to approval is unwarranted when dealing with treatments for serious or life-threatening illnesses where dissemination of the most current and timely information is important to the treating physician. One comment questioned why there would be any greater likelihood of misleading promotional claims for products approved under the proposed accelerated approval process than for drugs intended to treat serious or life-threatening diseases that are approved under the normal NDA procedures. The comment also expressed the hope that the proposed requirement for advance

submission of promotional materials was not based upon an assumption that promotional materials for drugs intended to treat serious diseases are more likely to be misleading than promotional materials for other types of drugs because any such assumption would be unfounded. One comment argued that if an advertisement or labeling is inaccurate, the product is misbranded and FDA could then obtain injunctive relief, seize the product, and/or initiate criminal proceedings. Another comment considered requiring advance submission of promotional materials unreasonable because companies are not required to do so now. One comment questioned the legal authority for requiring presubmission of promotional material following approval of a drug product, and the reason for the requirement.

The agency believes that the requirements for submission of promotional materials in the context of accelerated approval are authorized by statute. Subsections 505(d)(4) and (d)(5) of the act provide that, in determining whether to approve a drug as safe and effective, the agency may consider not only information such as data from clinical studies but also "any other information" relevant to safety and effectiveness under the proposed conditions of use. Such information would include information about how the drug would be promoted. In determining whether the drug's proposed labeling would be "false or misleading" under section 505(d)(7) of the act, the agency is similarly authorized to evaluate "all material facts" during the approval process, including the facts about promotion.

FDA is also authorized by section 505(k) of the act to require reporting of information subsequent to approval necessary to enable the agency to determine whether there may be grounds for withdrawing the approval. Among the grounds for withdrawal specified in section 505(e) of the act are that the evidence reveals the drug is not shown to be safe and effective under its conditions of use. In addition, drug approval may be withdrawn if information shows the labeling to be false or misleading. Information on how the drug will be promoted is again relevant to whether the drug's marketing approval should be withdrawn. Section 701(a) of the act (21 U.S.C. 371(a)) generally authorizes FDA to promulgate regulations for the efficient enforcement of the act.

For biological products, additional authority in section 351 of the PHS Act (42 U.S.C. 262) authorizes the promulgation of regulations designed to

ensure the continued safety, purity, and potency of the products. The content of promotional materials is important to the continued safe and effective use of biologicals.

Therefore, the provisions of the final rule requiring submission of promotional materials prior to approval under the accelerated approval procedures and subsequent to such approval are authorized by statutory provisions. FDA might also invoke the authority of section 502(n) of the act (21 U.S.C. 352(n)) to require prior approval of the content of any prescription drug advertisement in "extraordinary circumstances." Whether FDA could appropriately rely on section 502(n) of the act in promulgating §§ 314.550 and 601.45 need not be determined, however, because FDA is not relying upon section 502(n) of the act as legal authority for these (or any other) sections of the accelerated approval regulations.

The agency believes that advance submissions of promotional materials for accelerated approval products are warranted under the accelerated approval circumstances. The special circumstances under which drugs will be approved under these provisions and the possibility that promotional materials could adversely affect the sensitive risk/benefit balance justify review of promotional materials before and after approval. For example, if the promotional materials exaggerate the known benefits of the drug, wider and inappropriate use of the drug could be encouraged, with harmful results.

Similarly, high risk drugs that are approved based on postmarketing restrictions would not have been approved for use without those restrictions because the risk/benefit balance would not justify such approval. If promotional materials were to undermine the postmarketing restrictions, the health and safety of patients could be greatly jeopardized.

Although there is potential harm from any misleading promotion, and there is no reason to believe improper promotion is more likely in this setting than in others, the risk/benefit balance is especially sensitive in this setting. The relatively small data base available and the minimal published information available also can contribute to making the physician and patient populations particularly vulnerable under accelerated approval circumstances.

Reliance on court actions (such as seizures, injunctions, and criminal prosecutions) can be effective in ending false promotions, but can only be initiated after the fact, when harm has already occurred. Corrective efforts can

be helpful but are always somewhat delayed. Under the circumstances of accelerated approval, FDA believes that it is far preferable to avoid problems by reviewing the promotional materials in advance of drug approval and of dissemination of the materials.

17. Two comments supported the provision about submission of promotional materials. One comment urged the agency to require that specific patient information be included in promotional materials to indicate the fact that the drug's clinical benefit has not yet been established. For drugs approved under the restricted use provision, the comment recommended that the labeling specify in detail the exact restrictions placed on the drug. In both cases, the comment recommended that this patient information appear as boxed warnings.

Section 502(n) of the act and regulations at § 202.1(e)(2) (21 CFR 202.1(e)(1)) require prescription drug advertisements (promotional materials) to contain, among other things, a true statement of information in brief summary relating to side effects, contraindications, and effectiveness, which would include warnings, precautions, and limitations on use. The information in brief summary relating to side effects, contraindications, and effectiveness is required to be based solely on the approved labeling. Therefore, to the extent that a drug's labeling reflects the extent of clinical exposure and includes appropriate warnings, a drug's promotional material would also include this information.

FDA regulations governing prescription drug labeling (21 CFR 201.56 and 201.57) require that serious adverse reactions and potential safety hazards, as well as limitations in use imposed by them, be included in the "Warning" section of the labeling. In the case of approval based upon effect on a surrogate endpoint, the "Indications and Usage" section of the labeling would reflect the nature of the demonstrated effect. If the approval is based on use restrictions, the label would also specify the restrictions.

FDA may require boxed warnings if there are special problems associated with a drug, particularly those that may lead to death or serious injury (21 CFR 201.57(e)). The agency does not agree that information related to clinical benefit or use restrictions for accelerated approval drugs would necessarily always require a boxed warning.

As indicated by §§ 314.550 and 601.45 of the final rule, applicants will be required to submit promotional materials prior to approval and in advance of dissemination subsequent to

approval whether the product is a new drug, an antibiotic, or a biological product.

18. One comment contended that FDA review and approval of all promotional pieces before their use will indefinitely delay product marketing campaigns and other patient and physician educational activities, which are essential to market a product, thereby significantly diminishing the advantage of securing an early approval for the applicant. The comment further contended that the requirement to submit "all promotional materials * * * intended for dissemination or publication upon marketing approval" will be overly burdensome for FDA and will unnecessarily slow down the process for review of all materials, not just those for products subject to this proposed rule. The comment recommended that FDA only request for review the primary advertising pieces, such as the introductory letter to physicians, the main detail piece, and the main journal advertisement, but not the secondary materials, e.g., a letter to pharmacists, of the initial promotional campaign.

As previously discussed in this preamble, FDA will be reviewing an applicant's planned promotional materials both prior to approval of an application (reflecting the initial campaign) and subsequent to approval to ascertain whether the materials might adversely affect the drug's sensitive risk/benefit balance. Because all promotional materials, including those referred to by the comment as "secondary" materials, can have significant adverse effects if they are misleading, the agency does not agree that such materials should, as a matter of course, not be requested for review. Insofar as such materials may be directly derived from the introductory letter to physicians, or other materials characterized by the comment as "primary" materials, the additional time to review the derivative materials should not be extensive.

The agency does not agree with the comment's contention that the requirement to submit all promotional materials prior to and subsequent to approval will indefinitely delay marketing campaigns and educational activities or be overly burdensome to FDA reviewers. FDA is committed to rapid review and evaluation of all drugs considered for approval under this rule and will promptly review the promotional materials.

19. One comment suggested a passive, time-limited clearance system for review of advertising after the initial promotional campaign such as that used for review of IND's, which would allow

the sponsor to proceed to use promotional materials after an allotted timeframe, such as 30 days, unless otherwise notified by FDA.

As indicated by this comment and others, additional clarification regarding both timing and content of the submissions of promotional materials seems useful. Therefore, the agency is revising proposed §§ 314.550 and 601.45 to make it clear that, unless otherwise informed by the agency, applicants must submit during the preapproval review period copies of all promotional materials intended for dissemination or publication within the first 120 days following marketing approval. The initial promotional campaign, sometimes referred to as the "launch campaign," often has a significant effect on the climate of use for a new product. As discussed elsewhere in this preamble, the risk/benefit balance of accelerated approval products is especially sensitive, and inappropriate promotion may adversely affect the balance with resulting harm.

There may be some instances in which promotional materials that had not been completed and submitted by the applicant prior to approval would be beneficial in fostering safe and effective use of the product during the first 120 days. Under revised §§ 314.550 and 601.45, FDA would have the discretion to consider such materials at a later time. An applicant who requested permission to include additional materials among those disseminated within the first 120 days following product approval would be notified of FDA's determination. If FDA agreed that dissemination of such materials was acceptable, the materials could then be disseminated or published upon notification.

For promotional materials intended for dissemination subsequent to the initial 120 days under §§ 314.550 and 601.45 FDA would review the submitted materials within 30 days of receipt. This 30-day period is meant to be time-limited, so that the applicant will be assured of no unnecessary delay. It will be important for the applicant to identify the materials being submitted appropriately, so that it is clear that the materials are subject to the 30-day review period. The agency intends to review all such materials promptly, and to notify the applicant of any identified problems as soon as possible. The agency expects that, if the agency notifies the applicant of significant objections to the proposed materials, no materials will be disseminated or published until the agency's objections are resolved. The applicant should plan to allow sufficient time after receiving

FDA's comments for resolving differences and incorporating requested changes in the submitted materials prior to dissemination or publication.

When FDA removes the requirement for advance submission of promotional material, the agency will continue to offer a prompt review of all voluntarily submitted promotional material.

E. Postmarketing Restrictions

FDA received many comments on the proposed requirement to limit distribution to certain facilities or physicians with special training or experience, or condition distribution on the performance of specified medical procedures if such restrictions are needed to counterbalance the drug's known safety concerns.

20. Several comments questioned FDA's authority to impose restrictions on distribution or use after an approved drug is marketed. Two comments disagreed with the statutory provisions cited by FDA in the proposed rule as its authority to impose restrictions on distribution or use stating that they refer only to FDA's general authority to ensure that drugs are not misbranded, which is an entirely separate issue. Another comment argued that section 503(b) of the act (21 U.S.C. 353(b)) contemplates that the issues warranting a restriction as to distribution are not factors in whether a drug product is "safe" for purposes of approval, but rather only whether the product must be limited to prescription status. Two comments said that, in the absence of specific statutory authority, the courts clearly have refused to permit FDA to impose restrictions on distribution and cited *American Pharmaceutical Association (APhA) v. Weinberger*, 377 F. Supp. 824, 829 n. 9 (D.D.C. 1974), *aff'd sub nom. APhA v. Mathews*, 530 F.2d 1054 (D.C. Cir 1976), a case concerning conditions placed on the approval of the drug methadone.

Some comments asserted that placing restrictions on the distribution of an approved drug to only certain facilities or physicians, or restricting use to certain medical procedures interferes with the practices of medicine and pharmacy, which the comments contended FDA does not have the authority to regulate.

The agency believes that the restrictions to ensure safe use contemplated for approvals under §§ 314.520 and 601.42 are authorized by statute. As discussed in the preamble to the proposed rule (57 FR 13234 at 13237), sections 501, 502, 503, 505, and 701 of the act provide broad authority for FDA to issue regulations to help

assure the safety and effectiveness of new drugs.

The agency does not agree with the comments' contention that the misbranding provisions of the act are irrelevant. Section 502(a) of the act prohibits false or misleading labeling of drugs, including (under section 201(n) of the act) failure to reveal material facts relating to potential consequences under customary conditions of use. Section 502(f) of the act requires drugs to have adequate directions for use and adequate warnings against unsafe use, such as methods of administration, that may be necessary to protect users. In addition, section 502(j) of the act prohibits use of drugs that are dangerous to health when used in the manner suggested in their labeling. Each of these misbranding provisions is intended, at least in significant part, to protect consumers against the marketing of drugs that would not be safe under certain conditions of use. Section 701(a) of the act authorizes FDA to issue regulations for the efficient enforcement of the act. The restrictions on use contemplated by §§ 314.520 and 601.42 help to ensure that products that would be misbranded under section 502 of the act are not marketed.

The restrictions on use imposed under section 503 of the act, which relate to prescription use limitations, primarily concern whether a drug is safe for use except under the supervision of a licensed practitioner. While the agency agrees that the restrictions imposed under §§ 314.520 and 601.42 concerning distribution to certain facilities or physicians with special training or experience would be in addition to ordinary prescription limitation, FDA believes these restrictions are consistent with the spirit of section 503 of the act, as well as the other provisions of the act referred to, in ensuring safe use.

New drugs may be approved under section 505(d) of the act only if they are safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. In addition, for approval, a drug's labeling must not be false or misleading based on a fair evaluation of all material facts, which would include details about the conditions of use. For biological products, section 351(d) of the PHS Act also authorizes the imposition of restrictions through regulations "designed to insure the continued safety, purity, and potency" of the products.

The agency disagrees with the comments' implication that the courts' rulings in *American Pharmaceutical Association (APhA) v. Weinberger* mean

there is no statutory authority to impose restrictions on distribution for accelerated approval drugs. The situation considered in that case is readily distinguishable from the situation addressed in §§ 314.520 and 601.42 of the accelerated approval regulations. The APhA case concerned a regulation that withdrew approval of NDA's for methadone, but permitted distribution to certain maintenance treatment programs and certain hospital and community pharmacies. Because methadone is a controlled substance within the provisions of the Controlled Substances Act, which is implemented by the Drug Enforcement Administration with the Justice Department, the district court concluded that the question of permissible distribution of the drug was within the jurisdiction of the Justice Department, not FDA. The Court of Appeals determined that the type of misuse associated with methadone, i.e., misuse by persons who have no intent to try to use drugs for medical purposes, differed from safety issues contemplated for control under section 505 of the act. In contrast, the restrictions contemplated under §§ 314.520 and 601.42 are precisely those deemed necessary to ensure that section 505 criteria have been met, i.e., restrictions to ensure that the drug will be safe under its approved conditions of use. It is clearly FDA's responsibility to implement the statutory provisions regarding new drug approval.

Nor does FDA agree that the provisions placing restrictions on distribution to certain facilities or physicians, or conditioned on the performance of certain medical procedures, impermissibly interfere with the practice of medicine and pharmacy. There is no legal support for the theory that FDA may only approve sponsors' drugs without restriction because physicians or pharmacists may wish to prescribe or dispense drugs in a certain way. The restrictions under these provisions would be imposed on the sponsor only as necessary for safe use under the extraordinary circumstances of the particular drug and use. Without such restrictions, the drugs would not meet the statutory criteria, could not be approved for distribution, and would not be available for prescribing or dispensing. The agency, as a matter of longstanding policy, does not wish to interfere with the appropriate practice of medicine or pharmacy. In this instance, the agency believes that rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases,

approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing.

21. One comment asserted that postmarketing restrictions on distribution to certain facilities or physicians with certain training or experience should be limited to rare occasions in cases of extreme hazard to patient safety in which toxicity of a particular drug may require it, but should not be applied because of insufficient efficacy data. Some comments argued that safety issues in the context of drug use should be addressed through patient management and effective product labeling, not through restricted distribution. In support of this argument, the comments cited the labeling of oncologic drugs, which provides physicians with adequate warnings and recommendations for their use without limiting distribution.

FDA agrees with these comments in part and intends to impose restrictions on distribution or use under this rule only in those rare instances in which the agency believes carefully worded labeling for a product granted accelerated approval will not assure the product's safe use. As stated in the preamble to the proposed rule (57 FR 13234 at 13237), FDA believes that the safe use of most prescription drugs will continue to be assured through traditional patient management by health professionals and through necessary safety warnings in the drug's labeling.

22. Two comments asked who will determine if restricted distribution should occur and what facilities or physicians with special training or experience will participate. Several comments expressed concern that restricted distribution and/or conditional use may not include all health care professionals who should participate in safe and effective patient care. Two organizations representing pharmacists asked that FDA develop functional and objective criteria that clearly establish the activities of pharmacists, physicians, and others in the care of patients receiving a drug under restricted distribution. The comments asserted that any health care professional that met these criteria should be allowed to participate in distribution of the drug and care of the patient. One comment recommended that any postmarketing restrictions on distribution or use of a drug approved under the accelerated approval process be developed by appropriate FDA advisory committees or panels expanded to include physicians and pharmacists with expertise in the

therapeutic area being considered and in relevant drug distribution systems. Where appointment of pharmacists to these committees or panels is not feasible, the comment recommended that FDA use pharmacists in a consultant capacity. Another comment argued that current systems for drug distribution incorporate "checks and balances" such that prescribers and pharmacists work together to assure safe use of a drug by a patient. Two comments would oppose any restricted distribution system that allows manufacturers exclusively to deliver prescription drugs directly to patients. One comment asked whether FDA or the applicant would monitor the criteria for restricted distribution sites or physicians.

The medical reviewing divisions within FDA's CDER and CBER will determine if restricted distribution or use should be imposed. FDA will usually seek the advice of outside expert consultants or advisory committees before making this determination, and will, of course, consult with the applicant.

The agency does not agree that FDA should develop criteria that clearly establish the activities of health care professionals in the care of patients receiving a drug approved under this rule and for which restricted distribution has been imposed. Any postmarketing restrictions required under this rule will impose an obligation on the applicant to ensure that the drug or biological product is distributed only to the specified facilities or physicians. FDA will seek the advice of outside consultants with expertise in distribution systems or advisory committees when necessary in determining the need for or type of restricted distribution. The limitations on distribution or use imposed under this rule, including specific distribution systems to be used and the applicant's plan for monitoring compliance with the limitations, will have been agreed to by the applicant at the time of approval. The burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed. As appropriate, FDA may monitor the sponsor's compliance with the specified terms of the approval and with the sponsor's obligations.

23. One comment recommended that proposed § 314.520 be modified to include therapeutic outcomes monitoring as a third example of a permissible postmarketing restriction. The comment defined therapeutic outcomes monitoring as the systematic and continual monitoring of the clinical and psychosocial effects of drug therapy

on a patient which achieves the objective of preventing problems with drug therapy. Some comments argued that through therapeutic outcomes monitoring, a physician, a pharmacist, and a patient can work together to prevent problems with drug therapy by being constantly alert to signs of trouble. One comment said that indicator data can be routinely reported to a central collection point for utilization review by health care professionals, followed by educational programs to further improve the efficacy of drug therapy.

The postmarketing restrictions set forth in the proposal and in this final rule are intended to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction. Therapeutic outcomes monitoring does not contribute to that enhancement, and would not be required under this rule.

24. Some comments asked that FDA clarify how products will move from restrictive status to a regular prescription drug status. The comments asserted that all conditions associated with accelerated approval should automatically terminate following completion of confirmatory clinical trials; one comment urged FDA to explicitly state this in the final rule. One comment asserted that restrictions should automatically be removed 180 days after a supplemental application containing the data from the postmarketing study has been filed if FDA has not yet acted upon the supplemental application and the product should be deemed approved as if by "traditional" procedures and all other provisions of the act should apply, e.g., the applicant must have a formal hearing before removal of the product from the market.

FDA will notify the applicant when a particular restriction is no longer necessary for safe use of the product. In the case of drugs approved with a requirement for postapproval studies, FDA would expect that all of the postapproval requirements set forth in this rule, i.e., submission of promotional material and use of expedited withdrawal procedures, would no longer apply after postmarketing studies have verified and described the drug's clinical benefit. Concurrent with the review of the postmarketing studies, if requested, FDA will also review the need to continue any restrictions on distribution that have been imposed. In the case where restrictions on distribution or use have been imposed, such restrictions would be eliminated only if FDA determines that safe use of the product can be assured without them, through appropriate labeling. In

some cases, however, that assurance could not be expected and the nature of the specific safety issue raised by the product might require continued restrictions. FDA has added new §§ 314.560 and 601.46 to state when postapproval requirements will no longer apply and state that the applicant may petition the agency, in accordance with 21 CFR 10.30, at any time to remove specific postapproval requirements.

With respect to the suggested time period for removing restrictions on distribution or use following submission of a supplemental application containing the data from a postmarketing study, FDA does not believe it should prescribe any specific time period. These applications will receive a priority rating and FDA is firmly committed to expedited review of an application considered for accelerated approval and all data submitted from a postmarketing study to verify clinical benefit and believes most reviews will be completed and action taken within 180 days.

25. One comment argued that, as proposed, it is not clear how accelerated approval would apply to drugs which fall under the conditions described in §§ 314.520 and 601.42, which state the postmarketing restrictions on distribution or use that FDA may apply, because the language of these sections explicitly states that the sections apply to products "shown to be effective," which are already adequately covered by the act. To the comment, the language "shown to be effective" implies that full Phase 3 efficacy trials have been conducted, assessed, and deemed to demonstrate that the drug is effective for its proposed use. If the clinical data demonstrate that the product has an acceptable safety profile, the safe use of the drug should be addressed in the product labeling. Thus, the comment argued that §§ 314.520 and 601.42 should not be included in new subpart H of part 314 and subpart E of part 601, respectively, which deal with accelerated approval because these sections explicitly apply to products shown to be effective under a full drug development program.

Sections 314.520 and 601.42 apply not only to drugs and biological products approved on the basis of an effect on a surrogate endpoint but also to drugs and biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses using clinical endpoints and that have serious toxicity. In either case, if the products are so potentially harmful that their safe use cannot be assured through carefully

worded labeling, FDA will approve the products for early marketing only if postmarketing restrictions on distribution or use are imposed. The phrase "shown to be effective" was not intended to distinguish drugs approved under new subpart H from drugs approved under any other subpart of the regulations. All drugs approved will have had effectiveness demonstrated on the basis of adequate and well-controlled studies, whether the endpoint of the studies is a surrogate endpoint or a clinical endpoint.

26. One comment expressed concern that the proposed restricted distribution or use provisions would restrict or eliminate the wholesale distribution of drugs approved through the accelerated approval process.

The limitations on distribution or use required under this rule are imposed on the applicant. Therefore, the burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed. This rule does not specify how a manufacturer will distribute its product to those receiving the product under the approval terms. FDA will only determine which facilities or physicians may receive the drug, and the applicant will have agreed to this limitation on distribution or use.

27. One comment expressed concern that the proposed postmarketing restriction provision does not preclude a physician to whom restricted distribution applies from prescribing drugs approved under the accelerated approval process for unapproved (off-label) uses.

The comment is correct that this rule does not itself prevent a physician from prescribing a drug granted accelerated approval for an unapproved use. Under the act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and that FDA has approved. Physicians may choose to prescribe the drug for a condition not recommended in labeling. Such off-label use would, of course, be carried out under the restrictions imposed under this section. FDA also believes that physicians will be cognizant of the product's special risks and will use such drugs with particular care. The labeling of products approved under this rule will include all necessary warnings and full disclosure labeling would generally reflect the extent of clinical exposure to the drug.

F. Postmarketing Studies

28. Three comments argued that FDA does not have the authority to require

postmarketing studies to be performed as a condition of approval based on a "surrogate" endpoint. One comment stated that it is widely accepted that the act empowered the agency to define the type and extent of efficacy data necessary to approve a product application. If a surrogate marker can be shown to be sufficiently related to actual patient benefit, then, the comment asserted, data regarding the effect of a drug on a surrogate marker constitute acceptable proof of efficacy under the act. Two comments urged FDA to continue to ask applicants to agree voluntarily to perform postmarketing studies when medically warranted as is the current policy under the traditional approval process. One comment expressed concern that requiring postmarketing studies may become the norm rather than the exception.

The agency's response to comment 1 explained the circumstances in which FDA might conclude that a drug should be marketed on the basis of an effect on a surrogate endpoint reasonably likely to predict clinical benefit only if studies were carried out to confirm the presence of the likely benefit. As discussed in the preamble to the proposed rule (57 FR 13234 at 13236), FDA believes that it is authorized by law to require postmarketing studies for new drugs and biological products. Section 505(d) of the act provides for the approval of new drugs for marketing if they meet the safety and effectiveness criteria set forth in section 505(d) of the act and the implementing regulations (21 CFR part 314). As discussed in the proposed rule, to demonstrate effectiveness, the law requires evidence from adequate and well-controlled clinical studies on the basis of which qualified experts could fairly and responsibly conclude that the drug has the effect it is purported to have. Under section 505(e) of the act, approval of a new drug application is to be withdrawn if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if new information shows that the drug's labeling is false or misleading.

Section 505(k) of the act authorizes the agency to promulgate regulations requiring applicants to make records and reports of data or other information that are necessary to enable the agency to determine whether there is reason to withdraw approval of an NDA. The agency believes that the referenced reports can include additional studies to evaluate the clinical effect of a drug approved on the basis of an effect on a surrogate endpoint. Section 701(a) of the act generally authorizes FDA to issue

regulations for the "efficient enforcement" of the act.

With respect to biological products, section 351 of the PHS Act provides legal authority for the agency to require postmarketing studies for these products. Licenses for biological products are to be issued only upon a showing that they meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations (42 U.S.C. 262(d)). The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)).

The agency notes that it has in the past required postmarketing studies as a prerequisite for approval for some drugs (see 37 FR 201, January 7, 1972; and 37 FR 26790, December 15, 1972).

29. One comment recommended that FDA require that specific timelines for completion of the required postmarketing studies be included in the marketing application. The comment further suggested that, if the sponsor fails to meet its timelines, approval of its application be withdrawn, or in the event it is difficult to withdraw approval of drugs for serious or life-threatening diseases, FDA should establish substantial fines and penalties for sponsors that deliberately withhold information from FDA regarding the preliminary results and the progress of their postmarketing studies, or delay the completion of such studies. The comment also urged FDA to publish in the *Federal Register* identification of manufacturers who are not meeting their obligation to complete the required postmarketing studies on time. These recommendations were prompted by the comment's concern that once a manufacturer is granted approval for its product, the manufacturer will have little incentive to complete postmarketing studies in a timely manner, especially if the preliminary results of such studies indicate that the drug may not be safe and/or effective. Another comment urged FDA to include in the final rule language that requires the participation of pharmacists in postmarketing studies because pharmacists can serve as an additional source of information on therapeutic outcomes of patients taking drugs approved under this rule and monitoring for such drugs.

The agency expects that the requirement for postmarketing studies will usually be met by studies already underway at the time of approval and that there will be reasonable enthusiasm for resolving the questions posed by those studies. The plan for timely completion of the required postmarketing studies will be included

in the applicant's marketing application. In addition, in accord with the annual reporting requirements at § 314.81(b)(2)(vii) (21 CFR 314.81(b)(2)(vii)), an NDA applicant is required to provide FDA with a statement of the current status of any postmarketing studies. FDA declines to impose the sanctions suggested by the comment for failure of an applicant to meet its plans for completion of a postmarketing study. FDA believes this rule applies appropriate regulatory sanctions. Under the proposed rule and this final rule, FDA may withdraw approval of an application if the applicant fails to perform the required postmarketing study with due diligence.

FDA believes that it is not within the scope of this rule to establish the role of pharmacists in postmarketing studies. That role should more properly be defined by the clinical investigator and each institution or facility at which a postmarketing study is conducted.

30. One comment asserted that the proposal sets forth an inherent contradiction between the way FDA evaluates the benefit and risk for drugs today and the way the proposal contemplates. The comment argued that now, if postmarketing data raise questions about the risk associated with a drug product, FDA considers that data along with the other data known about the product, and determines whether, based on the overall knowledge about the drug, there is a need to seek withdrawal of approval. Under this proposal, if the postmarketing study data raised questions about the risk of the product, FDA would seek withdrawal of approval, whether or not the new data really made a fundamental difference to what is known about the benefit and risk of the product.

FDA does not agree that the contradiction described by the comment exists. Under the circumstances of accelerated approval, approval would be based on a weighing of the benefit suggested by the effect on the surrogate endpoint against known and potential risks of the drug. Should well-designed postapproval studies fail to demonstrate the expected clinical benefit, the benefit expected at the time of approval (reasonably likely to exist) would no longer be expected and the totality of the data, showing no clinical benefit, would no longer support approval. This evaluation of the data is not different from considerations that would apply in evaluating data in the case of a drug approved under other provisions of the regulations.

31. Two comments expressed the view that the proposed requirement for postmarketing studies may raise

important ethical questions because once a drug product is approved, it may be unethical, depending on the circumstances, for a physician to conduct a study using a placebo control. One comment also contended that a postmarketing study requirement could compromise the NDA holder's ability to enroll sufficient numbers of patients in the study when the new approved drug and possible alternative therapies are widely available to patients.

Usually, and preferably, because of problems suggested in the comment, the requirement for postmarketing studies will be met by studies already underway at the time of approval, e.g., by completion of studies that showed an effect on the surrogate. FDA recognizes that ethical considerations will play a central role in the type of study carried out, a choice that will depend upon the type and seriousness of the disease being treated, availability of alternative therapies, and the nature of the drug and the patient population. There often are alternatives to use of a placebo control, including active control designs and dose-response studies that can satisfy both the demands of ethics and adequacy of design.

32. One comment contended that the term "postmarketing study" is used inconsistently in the proposed rule. The comment argued that "postmarketing study" is an accepted regulatory term of art which, to this point, has referred to studies conducted to confirm safety (not efficacy), after an approval has been granted, whereas in this proposal, a "postmarketing study" refers to a study required to establish clinical efficacy (i.e., a Phase 3 study), but not necessarily safety, although safety data will be collected. To prevent confusion and to differentiate between these required postmarketing confirmatory efficacy studies and safety studies traditionally conducted after approval and to clarify that products granted accelerated approval have been approved on the basis of Phase 2 (surrogate endpoint) data, the comment suggested changing the term "postmarketing study" to "Phase 3 study" in this rule except where traditional postmarketing studies are intended. The comment also suggested that the term "Phase 3 study" be defined as a study required to confirm findings of efficacy based upon surrogate data collected in Phase 2, which will be conducted after an accelerated approval has been granted and will be required before restrictions set forth in § 314.520 are removed.

The agency does not believe that the comment has accurately described accepted meanings of various terms.

The term postmarketing study does not refer to any particular kind of study, but to studies carried out after a drug is marketed, often as part of an agreement by a sponsor to do so. These have included pharmacokinetic, drug-drug interaction, and pediatric studies, studies of dose-response or of higher doses, and studies of new uses. The term is not limited to safety studies. Moreover, Phase 2 and 3 studies are not distinguished by the endpoints chosen. Phase 3 hypertension studies, for example, still measure blood pressure, not stroke rate. The agency believes that the use of the "postmarketing study" in the final rule is appropriate and consistent.

G. Withdrawal of Approval

33. One comment supported the proposed withdrawal of approval procedure. Other comments asserted that the proposed procedure does not provide the applicant with the procedural safeguard of a formal evidentiary hearing guaranteed by section 505 of the act and the Administrative Procedure Act (APA). As an example, the comments said that based on a finding of a single study failing to show clinical benefit or misuse of any promotional material, an approved new drug would be subject to withdrawal from the market with only a minimal opportunity for the NDA holder to be heard. The comments argued that section 505(e) of the act guarantees applicants "due notice and opportunity for a hearing" on withdrawal of an NDA in compliance with APA hearing standards, thus FDA must conduct hearings on withdrawals of NDA's using the formal adjudicatory procedures of the APA. One comment asserted that, under the proposed procedure, there is the absence of a discernible legal standard, an inability to cross-examine, the prosecuting attorney and judge are one and the same person, and there is a lack of even minimal formal evidentiary procedures. The comment expressed doubt that the proposed procedure would be sufficient to create a record suitable for review by a Court of Appeals, which must be able, on the basis of such a record, to determine whether the approval is supported by "substantial evidence."

FDA believes the withdrawal procedures set forth in proposed §§ 314.530 and 601.43 and in this final rule are consistent with relevant statutes and provide applicants adequate due process. As stated in the proposed rule, in issuing its general procedural regulations, FDA decided to afford NDA holders an opportunity for a formal evidentiary hearing even though the

courts had not decided that such a hearing was necessarily legally required (see 40 FR 40682 at 40691, September 3, 1975). In promulgating its procedural regulations, FDA also determined that a formal evidentiary hearing is not required before withdrawing approval of biological products, but that it would be appropriate to apply the same procedures to biological products as to drug removal (see 40 FR 40682 at 40691).

Through the hearing process in this final rule, as in the proposed rule, applicants will be afforded the opportunity to present any data and information they believe to be relevant to the continued marketing of their product. The proposed process also would have permitted the presiding officer, the advisory committee members, a representative of the applicant, and a representative of the Center that initiates the withdrawal proceedings to question any person during or at the conclusion of the person's presentation. As discussed below in response to a comment, FDA has decided to allow up to three representatives of the applicant and of the Center to question presenters. Participants could comment on or rebut information and views presented by others. As with ordinary 21 CFR part 15 hearings, the hearing will be transcribed. Subsequent to the hearing, the Commissioner of Food and Drugs would render a final decision on the matter. The agency believes that the administrative record created through this process would be sufficient for judicial review.

The agency emphasizes that, as part of the approval process under this rule, applicants will have agreed that these withdrawal procedures apply to the drug for which they seek approval; applicants objecting to these procedures may forego approval under these regulations and seek approval under the traditional approval process. Under such circumstances, applicants would not have the benefit of accelerated approval; if the drug were subsequently approved, however, before withdrawal of the approval, the applicant would have an opportunity for a 21 CFR part 12 hearing.

34. One comment noted that the "imminent hazard" provision of section 505(e) of the act allows FDA to suspend approval of a product, immediately, if it is found to pose an imminent hazard to the public health. As an alternative to the proposed withdrawal procedure or in addition to the "imminent hazard" statutory provision, the comment suggested that, when confronted with a dangerous product on the market, FDA

could request that the applicant voluntarily withdraw its product, and most applicants would comply if a legitimate hazard exists.

As noted in the proposed rule, FDA and applicants have often reached mutual agreement on the need to remove a drug from the market rapidly when significant safety problems have been discovered. However, applicants usually have been unwilling to enter into such agreements when doubts about effectiveness have arisen, such as following the review of effectiveness of pre-1962 approvals carried out under the Drug Efficacy Study Implementation (DESI) program. For drugs approved under the accelerated procedure regulations, the risk/benefit assessment is dependent upon the likelihood that the surrogate endpoint will correlate with clinical benefit or that postmarketing restrictions will enable safe use. If the effect on the surrogate does not translate into a clinical benefit, or if restrictions do not lead to safe use, the risk/benefit assessment for these drugs changes significantly. FDA believes that if that occurs, rapid withdrawal of approval as set forth in this rule is important to the public health.

35. Under the proposed withdrawal procedures, in addition to other persons, one representative of the Center that initiates the withdrawal proceedings may question participants at a withdrawal of approval hearing. One comment objected to limiting the Center to one representative because detailed knowledge about a drug product is likely to be available from several scientists.

The proposed limitation of questioning to single representatives of the initiating Center and the applicant was intended to make the proceedings manageable. On further consideration, the agency has determined that it would be appropriate and manageable to allow up to three persons to be designated as questioners for the applicant and for FDA. Sections 314.530(e)(2) and 601.43(e)(2) have been revised accordingly.

36. Some comments questioned FDA's ability to withdraw approval under the proposed procedures efficiently or effectively because of: (1) The lack of assurance that the results of postmarketing studies will be promptly provided to FDA; (2) limited agency resources to review study results and act upon them promptly; (3) the difficulties associated with establishing that an approved drug is "ineffective;" and (4) political pressure not to rescind the approval of NDA's for drug products that may lack evidence of effectiveness,

especially if no clearly effective alternative treatments are available. One comment offered the opinion that where a drug shows only modest evidence of benefit, perhaps on a surrogate endpoint, and only shows equivocal evidence of clinical efficacy in postmarketing studies it would be difficult and socially disruptive to withdraw approval and remove the drug from the market if the drug has become well established and accepted, and there is no issue of toxicity. Another comment believed it would be difficult to withdraw approval of a drug that may be beneficial in a subpopulation but which, in fact, has not been shown to be efficacious in broader patient population studies. The comments suggested the need for a lesser sanction.

Another comment suggested that expediting removal of a product from the market could be accomplished by using a procedure like the "imminent hazard" provision of the act, i.e., immediate removal of the drug from the market if any of the conditions listed in proposed § 314.530 were met followed by a hearing.

Although the potential difficulties cited by the comments are real, they are not fundamentally different from determinations FDA regularly must make in carrying out its responsibilities. The new regulations provide for an expedited procedure to withdraw approval; they do not guarantee that results of studies will be wholly unambiguous or that FDA will always be able to prevail in its view as to the need for withdrawal, any more than current withdrawal procedures do. The studies being carried out under these provisions will be conspicuous and important and their completion will be widely known. There is no reason to believe their results would or could be long hidden. A study that fails to show clinical effectiveness does not prove a drug has no clinical effect but it is a study that, under § 314.530, will lead to a withdrawal procedure because it has failed to show that the surrogate endpoint on which approval was based can be correlated with a favorable clinical effect. This may have occurred because the study was poorly designed or conducted; while FDA will make every effort to avoid this, the commercial sponsor has the responsibility for providing the needed evidence confirming clinical benefit. As previously discussed, §§ 314.510 and 601.41 have been revised to clarify that required postmarketing studies must also be adequate and well-controlled. The possibility that an ineffective drug has become "accepted" is not a basis for continued marketing. FDA intends to

implement the provisions of § 314.530 as appropriate; data that are ambiguous will inevitably lead to difficult judgments.

A drug with clear clinical effectiveness in a subset of the population, but not in the population described in labeling, would have its labeling revised to reflect the data. Withdrawal would be inappropriate under such circumstances.

If an imminent hazard to the public health exists, the Secretary of Health and Human Services may suspend approval of an application and then afford the applicant an opportunity for an expedited hearing. In the absence of a significant hazard requiring immediate withdrawal, FDA believes the expedited procedure described in the rule satisfies the need for prompt action while, at the same time, allowing opportunity for discussion and debate before withdrawal.

37. One comment noted that the proposed rule would allow FDA to withdraw approval for failure to perform the required postmarketing studies with due diligence. The comment asserted that the act does not permit FDA to withdraw approval on this ground. Another comment, however, suggested that because proposed §§ 314.530 and 601.43 cite grounds for withdrawal of approval that are not grounds under the act, the language of these proposed sections should be revised to use language that closer aligns to that used in the act, e.g., describe a "postmarketing study" in statutory language.

FDA reaffirms the position expressed in the preamble to the proposal (57 FR 13234 at 13239) that there is adequate authority under the act to withdraw approval of an application for the reasons stated under proposed §§ 314.530 and 601.43, which include failure of an applicant to perform the required postmarketing study with due diligence. Section 505(e) of the act authorizes the agency to withdraw approval of an NDA if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if the applicant has failed to maintain required records or make required reports. In addition, approval may be withdrawn if new information, along with the information considered when the application was approved, shows the labeling to be false or misleading.

For biological products, section 351(d) of the PHS Act authorizes approval of license applications under standards designed to ensure continued safety, purity, and potency. "Potency"

for biological products includes effectiveness (21 CFR 600.3(s)). The PHS Act does not specify license revocation procedures, except to state that licenses may be suspended and revoked "as prescribed by regulations."

For drugs approved under § 314.510, FDA will have determined that reports of postmarketing studies are critical to the risk/benefit balance needed for approval; if those reports are not forthcoming, then, under authority of section 505(d) of the act, the drug cannot on an ongoing basis meet the standards of safety and efficacy required for marketing under the act. Therefore, it is important to ensure that the applicant make a good faith effort to complete any required postmarketing studies in a timely manner so that FDA can rapidly determine whether the surrogate endpoint upon which the drug was approved has been confirmed to correlate with clinical benefit. Failure to submit the study results in a timely fashion would also constitute failure to make a required report. Similarly, without submission of the information from required postmarketing studies on biological products approved under these procedures, the biological product is not assured of continued safety and effectiveness. The license application may, therefore, appropriately be revoked as described in § 601.43.

FDA does not find the statements of the grounds for withdrawal of approval under §§ 314.530 and 601.43 of this rule inconsistent with statutory language or ambiguous. The agency notes that, in the event none of the grounds for withdrawal specifically listed in § 314.530 or § 601.43 applies, but another ground for withdrawal under section 505 of the act or section 351 of the PHS Act and implementing regulations at 21 CFR 314.150 or 601.5 does apply, the agency will proceed to withdraw approval under traditional procedures.

38. Two comments expressed concern that it may be difficult for the agency to enforce the requirement that postmarketing studies be pursued with due diligence. The comments asked what would happen if a sponsor using due diligence is unable to recruit enough patients, or if the sponsor questions the validity of the data from the required postmarketing study, and would clumsy data management be seen as sufficient reason to rescind approval for a marketed drug? Another comment stated that once a product is approved and, by definition, provides a "meaningful therapeutic benefit over existing therapies," study accrual may drop off dramatically as patients may refuse to receive the "old" therapy or

placebo, or physicians may consider it unethical not to treat all patients with the approved indication with the new drug or biological product. Under these circumstances, the comment expressed the opinion that neither the sponsor nor the product should be penalized, nor should there be a threat to withdraw approval. Based on FDA's past history in postmarketing studies, which one comment characterized as resulting in poorly done studies, studies conducted much later than agreed upon, or not at all, the comment expressed the opinion that the "due diligence" with which applicants are expected to carry out postmarketing studies may be an overly great expectation. One comment asked FDA to give examples of when it may withdraw approval if "other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use" (proposed §§ 314.530(a)(6) and 601.43(a)(6)).

FDA does not agree that it will be difficult to enforce the "due diligence" provision of this rule. The "due diligence" provision was designed to ensure that the applicant makes a good faith effort to conduct a required postmarketing study in a timely manner to confirm the predictive value of the surrogate marker or other indicator. Any requirement for postmarketing studies will have been agreed to by the applicant at the time of approval, and if the study is not conducted in a timely manner as agreed to by the applicant, approval of the applicant's application will be withdrawn. FDA will expect any required postmarketing study to be conducted in consultation with the agency. Therefore, should the applicant encounter problems with subject enrollment in a study or ethical difficulties about the type of study to conduct, FDA expects the applicant to discuss these problems with the agency and reach agreement on their resolution.

Examples of other evidence demonstrating the drug product is not shown to be safe and effective could include further studies of the effect of the drug and the surrogate endpoint that fail to show the effect seen in previous studies, new evidence casting doubt on the validity of the surrogate endpoint as a predictor of clinical benefit, or new evidence of significant toxicity.

39. Some comments objected to withdrawal of approval of a drug product approved under the accelerated approval process because of perceived misconduct by the applicant, such as failure to perform a required postmarketing study with due diligence or use of promotional materials that are false or misleading. The comments argued that the primary purpose of the

accelerated approval process is to provide improved treatments to desperately ill patients at the earliest possible time, and withdrawal of approval of the new treatments for reasons not directly related to safety or efficacy undermines the purpose of the proposed rule. Two comments suggested that correction of the promotional material without interruption of access to the drug would be a better approach. Another comment suggested that there may be circumstances where continued access to the drug, if accompanied by informed consent, would be appropriate even if substantial questions arise about a product's safety and effectiveness. One comment urged that anticipated withdrawal of approval be preceded by measures to ensure that patients and their physicians will have an uninterrupted supply until alternative treatment arrangements can be made.

The need for "due diligence" in conducting the agreed to postmarketing studies is discussed in paragraph 37. The reasons for concern about misleading promotional materials are discussed under paragraph 16. With respect to promotional materials, FDA expects that, in most cases, any disagreements between the applicant and FDA will be resolved through discussion and modification of the materials, so that the drug or biological product can continue to be marketed. If, however, FDA concludes that the promotional materials adversely affect the risk/benefit conclusion supporting the drug's marketing, the agency intends to minimize the risk to the public health by removing the product from the market through the withdrawal procedures in this rule.

40. One comment expressed concern that the proposed withdrawal procedure may give the appearance of bias or preconceived notions on the part of the agency because the final decision to withdraw approval of a drug would be made by the Commissioner of Food and Drugs and the intention to withdraw approval of the drug will already have been determined by the agency.

Under the withdrawal provisions of this rule, FDA's CDER or CBER, rather than the Commissioner, will initiate the withdrawal proceedings. The withdrawal process will begin with a letter from CDER or CBER notifying the applicant that the Center proposes to withdraw marketing approval and stating the reasons for the proposed action. Although separation of functions will not apply under the provisions of §§ 314.530 or 601.43, the Commissioner's decision regarding withdrawal would not occur until after

the applicant had an opportunity for hearing as described in those sections. The Commissioner would then expect to review the issues with objectivity and fairness having had the benefit of the presentations and discussions at the hearing and of the advisory committee's recommendations.

H. Safeguards for Patient Safety

41. One comment asked if drugs approved under the accelerated approval process will be held to the same standards concerning postmarketing safety as drugs approved by the traditional process.

As discussed in the preamble to the proposed rule, applicants gaining approval for new drugs through the accelerated approval procedures will also be expected to adhere to the agency's longstanding requirements for postmarketing recordkeeping and safety reporting (see 21 CFR 314.80 and 314.81). Information that comes to FDA from the applicant or elsewhere that raises potential safety concerns will be evaluated in the same manner that such information is evaluated for drugs approved under the agency's traditional procedures. If the postmarketing information shows that the risk/benefit assessment is no longer favorable, the agency will act accordingly to remove the drug from the market.

42. One comment urged FDA, if the proposed rule were adopted, to require written informed consent so that patients would know that the drugs with which they were being treated had risks and that the benefits had not been adequately established.

The agency does not agree that patients using drug products approved under the accelerated approval regulations should be asked to provide written informed consent. Drugs approved under these provisions are not considered experimental drugs for their approved uses. Like all approved drugs, drugs approved under these provisions will have both risks and benefits. As previously discussed in this preamble, for drugs approved based on studies showing an effect on a surrogate endpoint, the approved labeling will describe that effect. In addition, the labeling will contain information on known and potential safety hazards and precautionary information. As with all prescription drugs, the physician has the responsibility for appropriately advising the patient regarding the drug being prescribed.

43. One comment asked that FDA require manufacturers to maintain an updated list of names, addresses, and phone numbers of physicians prescribing their products approved

under this rule, and in the case of recall or withdrawal of approval, require manufacturers to contact these physicians and encourage them to notify their patients.

FDA does not believe such a procedure is necessary. Furthermore, maintaining such a registry for drugs prescribed through pharmacies would be very difficult. Agency experience with recalls and product withdrawals indicates that the methods of notification that have been developed for such circumstances are adequate.

44. One comment recommended that FDA require patient package inserts (PPI's) for all drugs granted accelerated approval that would state the specific restrictions placed on a drug product and/or the reason for requiring postmarketing studies. In addition, the comment recommended that FDA require the manufacturer to include an adverse drug reaction "hotline" phone number in the PPI along with an FDA phone number. The PPI should inform the patient to report immediately any adverse drug reaction experienced to his or her doctor, the manufacturer, and FDA, and the manufacturer should be required to contact FDA immediately after receiving a report of a serious adverse reaction.

FDA concludes that patient package inserts are not routinely needed for drugs granted accelerated approval, although if circumstances made one appropriate, one would be developed for a particular drug. As with any prescription drug, the approved labeling for a product granted accelerated approval will contain information about the safe and effective use of the product, including all necessary warnings and the extent of clinical exposure. In addition, the conditions of use will be carefully worded to reflect the nature of the data supporting the product's approval. Physicians have the responsibility to inform patients about the safe and effective use of an approved product. Labeling includes suggestions to the physician concerning information to be provided to patients.

The agency notes that in this final rule limited editorial changes have been made to the wording of the proposed rule. The agency has determined that these changes do not affect the intent of the proposed rule.

V. Economic Impact

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this final rule and has determined that it is not a major rule as defined by the Order. Indeed, because firms will not be forced to use the accelerated approval mechanism,

applicants will most probably choose to take advantage of the program only where its use is expected to reduce net costs. Similarly, the final rule does not impose a significant economic impact on a substantial number of small entities so as to require a regulatory flexibility analysis under the requirements of the Regulatory Flexibility Act of 1980.

VI. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Paperwork Reduction Act of 1980

This rule does not contain new collection of information requirements. Section 314.540 does refer to regulations that contain collection of information requirements that were previously submitted for review to the Director of the Office of Management and Budget (OMB) under section 3504 of the Paperwork Reduction Act of 1980 (Adverse Drug Experience Reporting, OMB No. 0190-0230).

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 314 and 601 are amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 376).

2. Subpart H consisting of §§ 314.500 through 314.560 is added to read as follows:

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

Sec.
314.500 Scope.

Sec.

- 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
- 314.520 Approval with restrictions to assure safe use.
- 314.530 Withdrawal procedures.
- 314.540 Postmarketing safety reporting.
- 314.550 Promotional materials.
- 314.560 Termination of requirements

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

§ 314.500 Scope.

This subpart applies to certain new drug and antibiotic products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug 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. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

§ 314.530 Withdrawal procedures.

(a) For new drugs and antibiotics approved under §§ 314.510 and 314.520, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

- (1) A postmarketing clinical study fails to verify clinical benefit;
- (2) The applicant fails to perform the required postmarketing study with due diligence;
- (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;
- (4) The applicant fails to adhere to the postmarketing restrictions agreed upon;
- (5) The promotional materials are false or misleading; or
- (6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 314.510 or § 314.520. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the **Federal Register** in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter

will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 314.540 Postmarketing safety reporting.

Drug products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

§ 314.550 Promotional materials.

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants 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. 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.

§ 314.560 Termination of requirements.

If FDA determines after approval that the requirements established in § 314.520, § 314.530, or § 314.550 are no longer necessary for the safe and effective use of a drug product, it will so notify the applicant. Ordinarily, for drug products approved under § 314.510, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the drug product's clinical benefit and the drug product

would be appropriate for approval under traditional procedures. For drug products approved under § 314.520, the restrictions would no longer apply when FDA determines that safe use of the drug product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

PART 601—LICENSING

3. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 706, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 376, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

4. Subpart E consisting of §§ 601.40 through 601.46 is added to read as follows:

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

Sec.

- 601.40 Scope.
- 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
- 601.42 Approval with restrictions to assure safe use.
- 601.43 Withdrawal procedures.
- 601.44 Postmarketing safety reporting.
- 601.45 Promotional materials.
- 601.46 Termination of requirements.

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

§ 601.40 Scope.

This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the 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. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 601.42 Approval with restrictions to assure safe use.

(a) If FDA concludes that a biological product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the biological product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the biological product.

§ 601.43 Withdrawal procedures.

(a) For biological products approved under §§ 601.40 and 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for

Biologics Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 601.40 or § 601.41. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the *Federal Register* in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a

petition for a stay of action under § 10.35 of this chapter.

§ 601.44 Postmarketing safety reporting.

Biological products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

§ 601.45 Promotional materials.

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants 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. 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.

§ 601.46 Termination of requirements.

If FDA determines after approval that the requirements established in § 601.42, § 601.43, or § 601.45 are no longer necessary for the safe and effective use of a biological product, it will so notify the applicant. Ordinarily, for biological products approved under § 601.41, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the biological product's clinical benefit and the biological product would be appropriate for approval under traditional procedures. For biological products approved under § 601.42, the restrictions would no longer apply when FDA determines that safe use of the biological product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

Dated: December 7, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

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