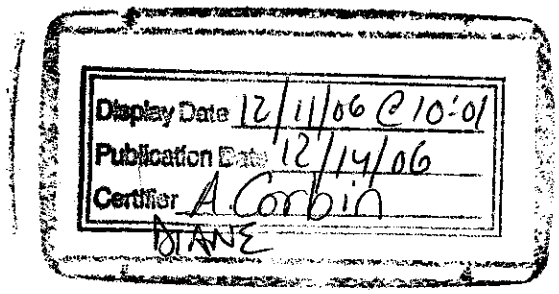
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration



[Docket No. 2006N–0062]

RIN 0910–AF14

21 CFR Part 312

Expanded Access to Investigational Drugs for Treatment Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

(OMB change P39)

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations on access to investigational new drugs for the treatment of patients. The proposed rule would clarify existing regulations and add new types of expanded access for treatment use. Under the proposal, expanded access to investigational drugs for treatment use would be available to individual patients, including in emergencies; intermediate-size patient populations; and larger populations under a treatment protocol or treatment investigational new drug application (IND). The proposed rule is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions, who lack other therapeutic options and who may benefit from such therapies.

DATES: Submit written or electronic comments by [*insert date 90 days after date of publication in the* **Federal Register**]. Submit written comments on the information collection requirements by [*insert date 30 days after date of publication in the* **Federal Register**].

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ADDRESSES: You may submit comments, identified by Docket No. 2006N–0062 and RIN 0910–AF14, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov.* Follow the instructions for submitting comments.

- Agency Web site: *http://www.fda.gov/dockets/ecomments.* Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.

- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

Instructions: All submissions received must include the agency name and docket number and Regulatory Information Number (RIN) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

The Office of Management and Budget (OMB) is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Desk Officer for FDA, FAX: 202–395–6974.

FOR FURTHER INFORMATION CONTACT: Colleen L. Locicero, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 4200, Silver Spring, MD 20993–0002, 301–796–2270; or Steve Ripley, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–6210.

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I. Background

A. Informal Access to Drugs for Treatment Use

FDA has a long history of permitting access to investigational drugs to treat serious or immediately life-threatening diseases or conditions without adequate available therapy under INDs, generally for drugs being evaluated in clinical studies intended to support marketing. The distinction between these and the usual studies covered under an IND is that the treatment uses are not primarily to answer safety or effectiveness questions about the drug, but are intended to treat the patient. Before 1987, there was no formal recognition of such treatment use in the IND regulations, but investigational drugs were made available for treatment use informally. "Compassionate use INDs," "single-patient protocol exceptions," and "large open protocols" are some of the terms that have been used to refer to such informal access. The vast majority of these INDs were used to make an investigational drug available to an individual patient, but some of the expanded access programs made particularly promising investigational drugs available to large populations. For example, more than 10,000 patients obtained access through treatment access programs to the first cardioselective beta-blockers and the first calcium channel blockers for vasospastic angina.

B. Current Regulations Concerning Expanded Access for Treatment Use

In 1987, FDA revised the IND regulations in part 312 (21 CFR part 312) to explicitly provide for one specific kind of treatment use of investigational drugs (52 FR 19466, May 22, 1987). Section 312.34 authorizes broad access to investigational drugs under a treatment protocol or treatment IND when the following criteria are met:

- The drug is intended to treat a serious or immediately life-threatening disease;
- There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;
- The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and
- The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

Section 312.34 states that for a serious disease, data from phase 3 trials or, in appropriate circumstances, data from phase 2 trials would ordinarily be needed to permit treatment use in a substantial population. For an immediately life-threatening disease, less evidence of safety and effectiveness is needed for treatment use. The standard for treatment use for immediately life-threatening conditions is that the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the drug may be effective and would not expose patients to an unreasonable and significant additional risk of illness or injury. FDA estimates that more than 100,000 patients have received investigational drugs through treatment INDs.

The 1987 IND regulations recognized only one kind of treatment use, the treatment protocol or treatment IND, generally providing availability to a broad population. However, it also implicitly acknowledged the existence of other kinds of treatment use, notably use in individual patients, by adding a provision describing an expedited procedure to obtain an investigational drug for treatment use in an emergency situation (§ 312.36). However, § 312.36 does not describe criteria or requirements that must be met to authorize individual patient treatment use.

C. Concerns About Treatment Use Programs

FDA has been criticized for its failure to explain in regulation or guidance the basis for agency decisionmaking on individual patient treatment use and other treatment use programs not currently described in FDA's regulations. One concern is that the lack of specific criteria and submission requirements results in disparate access to treatment use for different types of patients and diseases. Some have asserted that knowledge of FDA's policies on these other kinds of treatment use tends to be concentrated among physicians in academic medical centers who are familiar with investigational drugs and FDA procedures. Consequently, according to this line of criticism, patients treated outside of academic medical centers are less likely to have access to investigational drugs for treatment use. There has also been concern that access to investigational drugs for treatment use has focused primarily on cancer- and human immunodeficiency virus (HIV)-related conditions, and that patients with other types of serious diseases or conditions have not had comparable access to appropriate treatment use of unapproved drugs.

D. The Food and Drug Administration Modernization Act of 1997

In response to these concerns about inconsistent policies, inequitable access, and preferential access for certain categories of disease, in the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105–115), Congress amended the Federal Food, Drug, and Cosmetic Act (the act) to include specific provisions concerning expanded access to investigational drugs for treatment use (Expanded Access to Unapproved Therapies and Diagnostics, section 561 (21 U.S.C. 360bbb) of the act). By incorporating specific expanded access provisions in the statute, Congress intended to emphasize that "opportunities to participate in expanded access

programs are available to every individual with a life-threatening or seriously debilitating illness for which there is not an effective, approved therapy" (Joint Explanatory Statement of the Committee of Conference in House Report 105–399, November 9, 1997, p. 100).

Section 561(a) of the act provides specific statutory authority to make investigational drugs available for the diagnosis, monitoring, or treatment of a serious disease or condition in an emergency situation. The Secretary of Health and Human Services (the Secretary) is to determine appropriate conditions under which an investigational drug may be made available in an emergency situation.

Section 561(b) of the act permits any person, acting through a licensed physician, to request access to an investigational drug to diagnose, monitor, or treat a serious disease or condition provided that the following conditions are met:

- The licensed physician determines that the person has no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition, and that the probable risk from the investigational drug is not greater than the probable risk from the disease or condition;
- The Secretary determines that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug;
- The Secretary determines that provision of the investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval; and
- The sponsor or clinical investigator submits a protocol consistent with the requirements of section 505(i) of the act (21 U.S.C 355(i)) and its

implementing regulations in part 312, which describe use of the drug in a single patient or a small group of patients.

Section 561(c) of the act closely tracks existing § 312.34 of the IND regulations. Section 561(c) authorizes the Secretary to permit an investigational drug to be made available for widespread access if the following determinations have been made:

1. The investigational drug is intended for use in the diagnosis, monitoring, or treatment of a serious or immediately life-threatening disease or condition;

2. There is no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat that stage of disease or condition in a particular patient population;

3. The investigational drug is under investigation in a controlled clinical trial under an IND, or all clinical trials necessary for approval of the use have been completed;

4. The sponsor of the controlled clinical trial is actively pursuing marketing approval with due diligence;

5. The provision of the investigational drug will not interfere with the enrollment of patients in ongoing clinical investigations;

6. In the case of serious diseases, there is sufficient evidence of safety and effectiveness to support the use;

7. In the case of immediately life-threatening diseases, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for its intended use and would not expose patients to an unreasonable and significant risk of illness or injury.

Section 561(c) also provides that a protocol for an expanded access treatment IND shall be subject to the requirements of section 505(i) of the act and FDA's implementing regulations in part 312.

To specifically address concerns that physicians and their patients are often unaware of the availability of investigational drugs under access programs, section 561(c) of the act also allows the Secretary to inform national, State, and local medical associations and societies, voluntary health associations, and other appropriate persons about the availability of expanded access treatment INDs or treatment protocols.

II. Why FDA Is Proposing This Rule

This proposed rule is intended to further address the concerns that motivated Congress to include in the act specific provisions on expanded access to investigational drugs for treatment use. As discussed in section I of this document, these concerns included inconsistent application of access policies and programs and inequities in access based on the relative sophistication of the setting in which a patient is treated or on the patient's disease or condition. By describing in detail in the proposed rule the criteria, submission requirements, and safeguards for the different types of expanded access for treatment uses of investigational drugs, the agency seeks to increase awareness and knowledge of expanded access programs and the procedures for obtaining investigational drugs. Increased knowledge and awareness about expanded access options should make investigational drugs more widely available in appropriate situations. Clearly articulated procedures for obtaining investigational drugs for treatment use should ease the administrative burdens on individual physicians seeking investigational drugs for their patients, as well as the burdens on sponsors who make investigational drugs available for

treatment use. In addition, we expect that clearly articulating procedures and standards for expanded access will result in more patients with serious or immediately life-threatening diseases or conditions getting the earliest possible access to these therapies.

III. Goals and Limitations of the Proposed Rule

Recognizing that FDA's authority derives from the act, the proposed rule attempts to reconcile individual patients' desires to make their own decisions about their health care with society's need for drugs to be developed for marketing. It recognizes the need for the risks and benefits of drugs to be well characterized and the need for appropriate protection of human subjects in an investigation. These interests are not always easily reconciled. Allowing individual patients relatively unfettered access to an investigational drug at a preliminary stage in its development, for example, may expose them to significant and unacceptable risks.

In addition, patients may find participation in a clinical trial less desirable than receiving the drug for treatment use for a variety of reasons. For example, clinical trial participants may receive a treatment other than the study drug, and clinical trials may have more onerous monitoring requirements (such as laboratory and other tests). Thus, a system of blindly permitting uncontrolled access to investigational drugs could make it difficult or impossible to enroll adequate numbers of patients in clinical trials to establish the safety and effectiveness of the drug for marketing approval.

FDA has a statutory responsibility to ensure that marketed drugs are safe and effective, and its rules should not compromise the integrity of the drug development process. In this proposed rule, as envisioned by the act, the agency has tried to strike the appropriate balance between authorizing access

to promising drugs for treatment use under our expanded access authority and ensuring the integrity of the drug approval process.

While this proposed rule aims to clarify, and thereby expand, the situations in which expanded access to unapproved drugs could be available, under its existing authority, FDA cannot compel a drug manufacturer to provide access to investigational drugs for treatment use.

IV. Description of the Proposed Rule

FDA is proposing to amend its regulations on INDs by removing the current sections on treatment use, revising the section on clinical holds, and adding subpart I on expanded access. The term "expanded access" is used here to refer to all types of treatment uses. The term "treatment protocol or treatment IND" continues to refer to one specific kind of treatment use, the large access protocol.

A. Sections Removed

The proposed rule would remove the following three sections of FDA's regulations:

- Current § 312.34 concerning the treatment use of an investigational new drug;
- Current § 312.35 concerning submissions for treatment use; and
- Current § 312.36 concerning emergency use of an investigational new drug.

B. Clinical Holds

The proposed rule would amend § 312.42 *Clinical holds and requests for modification* by providing for clinical holds, when necessary, of any of the types of expanded access uses described in this proposed rule. A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical

investigation or suspend an ongoing investigation (§ 312.42(a)). Proposed § 312.42(b)(3)(i) provides that FDA may place an expanded access IND or protocol[1] on clinical hold if it is determined that the pertinent criteria in proposed subpart I for permitting the expanded access use to begin are not satisfied or the IND or protocol does not comply with the requirements for expanded access submissions in proposed subpart I.

Proposed § 312.42(b)(3)(ii) provides that FDA may place an ongoing expanded access IND or protocol on clinical hold if it is determined that the pertinent criteria in proposed subpart I for permitting the expanded access are no longer satisfied (e.g., a satisfactory alternative therapy becomes available).

C. Expanded Access Overview

The agency is proposing to add new subpart I to part 312. Proposed subpart I describes the following ways that expanded access to treatment use of investigational drugs would be available:

- Expanded access for individual patients, including emergency procedures;
- Expanded access for intermediate-size patient populations (smaller than those typical of a treatment IND or treatment protocol); and
- Expanded access treatment IND or treatment protocol (described in current §§ 312.34 and 312.35).

The following items are set forth in the proposed rule: (1) Criteria that must be met to authorize the expanded access use, (2) requirements for expanded access submissions, and (3) safeguards to protect patients and preserve the ability to develop meaningful data about treatment use.

[1]A submission seeking to allow an expanded access use of an investigational drug may come to FDA either in the form of a new, separate IND or as a new protocol submitted to an already existing IND.

D. General Provisions

Proposed § 312.300(a) states that the aim of subpart I is to facilitate the availability of investigational new drugs to seriously ill patients when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. Proposed § 312.300(b) provides a definition of the term "immediately life-threatening disease" as a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

E. Requirements for All Expanded Access Uses (Proposed § 312.305)

Proposed § 312.305 contains the general requirements for the use of investigational drugs when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition, rather than to generate safety and effectiveness data to support a marketing application. Proposed § 312.305 contains criteria, submission requirements, and safeguards that apply to all expanded access uses described in proposed subpart I. Additional criteria, submission requirements, and safeguards that apply to specific types of expanded access use are described in the sections of the proposed rule describing those expanded access types.

1. Criteria for All Expanded Access Uses

Proposed § 312.305(a) sets forth three criteria that apply to all types of expanded access use:

a. *First criterion.* Under proposed § 312.305(a)(1), FDA must determine that the patient (or patients) to be treated has a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.

Because, by definition, the risks and benefits of investigational drugs are not as well characterized as those of approved drugs, the agency believes, and the act contemplates, that expanded access to investigational drugs is warranted only under these conditions. Section 561(c)(1) and (c)(2) of the act expressly requires FDA to make these determinations in order to authorize a treatment IND or treatment protocol, and section 561(b)(1) and (b)(2) of the act likewise requires FDA to determine that there is sufficient evidence of safety and effectiveness to support the use of the unapproved drug in treating an individual patient or a small group of patients. Determining that the patient has a serious or immediately life-threatening disease or condition and that there is no comparable or satisfactory alternative therapy are integral parts of determining whether there is sufficient evidence of safety and effectiveness to support the proposed use in the situation described by the physician or sponsor seeking the authorization.

In various documents, the agency has described or illustrated what is meant by a serious condition (see, e.g., FDA's guidance for industry entitled "Fast Track Drug Development Programs—Designation, Development, and Application Review" (63 FR 64093, November 18, 1998), revised 2004, pp. 3–4; preamble to the 1992 proposed rule on accelerated approval of new drugs for serious or life-threatening illnesses (57 FR 13234 at 13235, April 15, 1992)). As discussed in these documents, the "serious disease or condition" requirement refers to conditions that have an important effect on functioning (e.g., stroke, schizophrenia, rheumatoid arthritis, osteoarthritis) or on other aspects of quality of life (e.g., chronic depression, seizures). Alzheimer's dementia, Amyotrophic Lateral Sclerosis (ALS), and narcolepsy are specific examples of serious conditions for which FDA has granted expanded access

to investigational drugs in the past. Short-lived and self-limiting morbidity will usually not be sufficient to qualify a condition as serious, but the morbidity need not be irreversible, provided it is persistent or recurrent. Similarly, the proposed requirement here that treatment be for a "serious disease or condition" is not intended to be unnecessarily restrictive. It is primarily intended to exclude expanded access to investigational drugs for conditions that are clearly not serious (e.g., symptomatic relief of minor pain or allergic symptoms and other self-limiting conditions not associated with major morbidity). Because of the difficulty of specifically describing the criteria that characterize a "serious disease or condition," the proposed rule itself does not provide a definition of "serious," though it does provide a definition of "immediately life-threatening." See proposed § 312.300(b). We solicit comments on this approach. If a disease or condition were to be both serious and immediately life-threatening, for the purpose of this proposed rule, it would be considered "immediately life-threatening."

Ordinarily, a lack of comparable or satisfactory therapeutic alternatives would mean that there exists no other available therapy to treat the patient's condition or that the patient has tried available therapies and failed to respond adequately or is intolerant to them. Available therapy, as defined in FDA's guidance for industry entitled "Available Therapy" (69 FR 44039, July 23, 2004), generally refers to FDA-approved products that are labeled to be used for the relevant disease or condition. In some cases, however, available therapy might mean a treatment that is not regulated by FDA (e.g., surgery) or one that is not labeled for use for the relevant disease or condition, but is supported by compelling literature evidence.

b. *Second criterion.* Under proposed § 312.305(a)(2), FDA must determine that the potential patient benefit justifies the potential risks of the treatment use and that those potential risks are not unreasonable in the context of the disease or condition to be treated. FDA is required to make this determination under sections 561(b)(2), (c)(6), and (c)(7) of the act.

c. *Third criterion.* Under proposed § 312.305(a)(3), FDA must determine that providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use. Section 561(b)(3) and (c)(5) of the act requires FDA to make this determination. The most efficient and effective way to make a drug available to all those who can benefit from the drug, is to market it. Therefore, it is important to ensure that expanded access use does not compromise enrollment in the trials needed to demonstrate the safety and effectiveness of the drug.

Proposed § 312.305(a) does not elaborate on the safety and/or effectiveness showing that must be made to merit authorization of the expanded access use. Rather, the showing is described in the criteria that pertain to each type of expanded access because the evidence needed to demonstrate the safety and potential benefit of a proposed use varies with the size of the population to be treated and the relative seriousness of the disease or condition to be treated. Treatment of a large patient population through a treatment IND or treatment protocol[2] generally would require more evidence of safety and effectiveness

[2]This proposed rule continues to describe the specific type of expanded access for treatment use that makes investigational drugs available to large populations as the "treatment IND" or "treatment protocol." We recognize that it may be confusing to carry over this terminology from our current regulations (§§ 312.34 and 312.35). However, this terminology has been used since 1987, and we believe it would be more confusing to change terminology when the nature of this type of treatment use remains essentially unchanged.

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than treatment of just a few patients. The evidence required to support expanded access for an intermediate-size patient population would be somewhere between that needed for expanded access for an individual patient and that needed for a treatment IND or treatment protocol.

In addition, as the seriousness of the disease increases, it may be appropriate to authorize expanded access use based on less data, still taking the size of the population into account. For example, to support expanded access for an individual patient when the patient has an immediately life-threatening condition that is not responsive to available therapy, ordinarily, completed phase 1 safety testing in humans at doses similar to those to be used in the treatment use, together with preliminary evidence suggesting possible effectiveness, would be sufficient to support such a use. In some cases, however, there may be no relevant clinical experience, and the case for the potential benefit may be based on preclinical data or on the mechanism of action.

In contrast, much more safety and effectiveness data would be needed to support a treatment IND or treatment protocol that anticipated enrollment of several thousand patients with a serious, but not imminently life-threatening, condition. Ordinarily, evidence of safety and effectiveness from phase 3 clinical trials would be needed to support such an expanded access use in these significantly larger populations. If the disease being treated under a treatment IND or treatment protocol were immediately life-threatening, however, compelling data from phase 2 trials might be sufficient to permit expanded access use.

The broader term "expanded access" refers to all kinds of treatment use. We solicit comment on this approach.

2. Submission Requirements for All Expanded Access Uses

Proposed § 312.305(b)(1) states that an expanded access submission is required for each type of expanded access use. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

Proposed § 312.305(b)(2) describes the expanded access submission requirements. The following items must be included:

- A cover sheet (Form FDA 1571) meeting the requirements of § 312.23(a);
- The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;
- The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;
- The method of administration of the drug, dose, and duration of therapy;
- A description of the facility where the drug will be manufactured;
- Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;
- Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for treatment use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and

- A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

If this proposed rule becomes final, FDA will make educational programs and materials available to help physicians and sponsors understand the expanded access use submission requirements in general, as well as the additional information necessary to justify the different types of expanded access.

Proposed § 312.300(b)(3) requires the expanded access submission and its mailing cover to be plainly marked "EXPANDED ACCESS SUBMISSION." If the expanded access submission is for a treatment IND or treatment protocol, the applicable box on Form FDA 1571 must be checked.

3. Safeguards for All Expanded Access Uses

Proposed § 312.305(c) explains how the responsibilities of sponsors and investigators set forth in subpart D of part 312 apply to expanded access.

Proposed § 312.305(c)(1) states that a licensed physician under whose immediate direction an investigational drug is administered or dispensed for expanded access use under subpart I is considered an *investigator* for purposes of part 312 and must comply with the responsibilities for investigators set forth in subpart D of part 312 to the extent they are applicable to the expanded access use. A nonexclusive list of duties of investigators—those duties that apply in all types of expanded access—is set forth in proposed § 312.305(c)(4), and is explained further in the following paragraphs.

Proposed § 312.305(c)(2) provides that an individual or entity that submits an IND or protocol for expanded access under subpart I is considered a *sponsor* for purposes of part 312 and must comply with the responsibilities for sponsors

set forth in subpart D of part 312 to the extent they are applicable to the expanded access use.

Proposed § 312.305(c)(3) provides that a licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND for expanded access under subpart I, is considered a sponsor-investigator for purposes of part 312 and must comply with the responsibilities for sponsors and investigators set forth in subpart D of part 312 to the extent they are applicable to the expanded access use. Proposed § 312.305(c)(4) provides that, in all types of expanded access, investigators have the following responsibilities:

- Reporting adverse drug experiences to the sponsor,
- Ensuring that the informed consent requirements of 21 CFR part 50 are met,
- Ensuring that Institutional Review Board (IRB) review of the expanded access use is obtained in a manner consistent with the requirements of part 56 (21 CFR part 56), and
- Maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of § 312.62.

However, this list of duties under subpart D of part 312 is not exclusive, and other requirements may apply, depending on the particular type of expanded access.

Proposed § 312.305(c)(5) provides that, in all cases, sponsors have the following responsibilities:

- Submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required by §§ 312.32 and 312.33,

- Ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use,
- Providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (e.g., providing the investigator's brochure, if there is one),
- Maintaining an effective IND for the expanded access use, and
- Maintaining adequate drug disposition records and retaining records in a manner consistent with the requirements of § 312.57.

As with the list of investigator's duties under proposed § 312.305(c)(4), this list of sponsor's duties under subpart D of part 312 is not exclusive, and other requirements may apply, depending on the particular type of expanded access.

4. When Expanded Access Use May Begin

Proposed § 312.305(d) explains when expanded access use may begin, assuming FDA has not placed a clinical hold on the expanded access use. Under IND rules, a study described in a protocol in a newly submitted IND can begin 30 days after FDA receipt of the IND (or on earlier notification by FDA that the study may proceed), unless FDA puts the study on hold. Once there is an IND in place, new protocols submitted to that IND may begin on the date of submission.

Proposed § 312.300(d)(1) states that an expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA that the expanded access use may begin, consistent with FDA's normal practice.

Proposed § 312.300(d)(2) explains when expanded access use may begin, if the expanded access submission is in the form of a new protocol submitted under an existing IND. The proposed rule states that expanded access use

under a protocol submitted under an existing IND may begin as described in § 312.30(a). Section 312.30(a) provides that the study under the protocol may begin provided two conditions are met: (1) The sponsor has submitted the protocol to FDA for its review and (2) the protocol has been approved by the IRB with responsibility for review and approval of the study in accordance with the requirements of part 56. Section 312.30(a) states that the sponsor may comply with these two conditions in either order.

The proposed rule provides two exceptions to the general rules concerning when expanded access use under a new protocol may begin. First, proposed § 312.305(d)(2)(i) provides that treatment under a protocol for individual patient expanded access in an emergency situation may begin when it is authorized by the FDA reviewing official. Second, proposed § 312.305(d)(2)(ii) states that expanded access use under proposed § 312.320 (the treatment IND or treatment protocol described in §§ 312.34 and 312.35 of the current IND regulations) may begin 30 days after FDA receives the protocol (or on earlier notification by FDA that the treatment use may begin); that is, there would be a 30-day wait even for a protocol submitted under an existing IND. Expanded access use under a treatment IND or treatment protocol often involves thousands of patients. The agency believes it is important to build in time for agency review of a proposed expanded access use with the potential to affect so many people.

Proposed § 312.300(d)(3) states that FDA may place any expanded access IND or protocol on clinical hold as described in § 312.42.

F. Expanded Access for Individual Patients (Proposed § 312.310)

Proposed § 312.310 would permit an investigational drug to be used for the treatment of an individual patient by a licensed physician.

1. Expanded Access for Individual Patients—Criteria

In addition to the proposed criteria for all expanded access uses, proposed § 312.310(a) sets forth two criteria for permitting an investigational drug to be used for the treatment of an individual patient by a licensed physician.

- First, the physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition (proposed § 312.310(a)(1)).

- Second, FDA must determine that the patient cannot obtain the drug under another type of IND (proposed § 312.310(a)(2)). (Section 561(b)(3) of the act requires that FDA determine that provision of the investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval.) Thus, expanded access for an individual patient would not be available, for example, if the patient can participate in a clinical trial of the investigational drug. However, participation in a clinical trial may not be possible for many reasons. A patient may have a stage of the disease different from the stage being studied. The patient may have failed on, or be intolerant of, the active control in a randomized active-control trial. It may be geographically impossible for the patient to participate in a clinical trial.

One of the proposed general criteria for any expanded access use is that FDA must determine that the potential benefit to the patient justifies the potential risks of the expanded access use and those potential risks are not unreasonable in the context of the disease or condition to be treated. The evidence needed to make this determination for expanded access for an individual patient will vary. For a patient with an immediately life-threatening condition, the evidentiary burden could be very low—little if any clinical

evidence to suggest a potential benefit or possibly only animal data to support safety of the use. For a patient with a serious, but not immediately life-threatening, condition who could expect to enjoy a reasonable quality of life for an extended time without any treatment, the evidentiary burden would be higher.

2. Expanded Access for Individual Patients—Submission Requirements

In addition to the proposed submission requirements for all expanded access uses, proposed § 312.310(b) provides that the expanded access submission must include information adequate to demonstrate that the general criteria for expanded access use and those specific to expanded access for individual patients have been met.

Proposed § 312.310(b) provides that if the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician. A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access. Sponsors are strongly encouraged to include individual patient expanded access protocols under their own INDs.

Proposed § 312.310(b) provides that a licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the individual patient expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient). Obtaining a right of reference is consistent with current practice. Sponsors who agree to make an investigational drug available to an individual patient, but prefer that it be provided under an IND obtained by the licensed physician rather than under

the sponsor's IND, routinely provide a right of reference to necessary information in the existing IND, and such a right of reference is necessary for FDA to be able to make the necessary determinations about whether the expanded access use may proceed.

3. Expanded Access for Individual Patients—Safeguards

Proposed § 312.310(c) sets forth safeguards that apply specifically to expanded access for individual patients. These proposed safeguards are listed as follows:

- Treatment of an individual patient with an investigational drug is generally limited to a single course of therapy for a specified duration, unless FDA expressly authorizes multiple courses or chronic therapy.
- FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration.
- At the conclusion of treatment, the licensed physician or sponsor (whoever made the expanded access submission) must provide a written summary of the results of the treatment use, including unexpected adverse drug experiences.
- When FDA receives a significant number of similar requests for individual patient expanded access, the agency may ask the sponsor to submit an IND or protocol for the use under § 312.315 or § 312.320.

What constitutes a significant number of similar requests will vary depending on the indication, the number of patients with no available therapeutic options, and the extent to which the drug has the potential to benefit those patients. In general, when the agency receives 10 or more requests for the same individual patient expanded access use within a relatively short time period (e.g., less than 6 months), FDA will consider whether to request

that a potential sponsor submit an intermediate-size patient population IND or protocol for the expanded access use and, possibly, conduct a clinical trial of the expanded access use.

4. Expanded Access for Individual Patients—Emergency Procedures

Proposed § 312.310(d) sets out emergency procedures for expanded access for individual patients. If there is an emergency that requires a patient to be treated before a written submission can be made, FDA may authorize the expanded access use to begin without a written submission. Under the proposed rule, the FDA reviewing official may authorize the emergency use by telephone. Emergency expanded access use may be requested by telephone, facsimile, or other means of electronic communications. The proposed rule also provides phone numbers for requests for investigational drugs and investigational biological drug products, and an after-hours contact number.

Proposed § 312.310(d)(2) requires the licensed physician or sponsor to explain how the expanded access use will meet the requirements of proposed §§ 312.305 and 312.310 and requires agreement to submit an expanded access submission that complies with proposed §§ 312.305 and 312.310 within 5 working days of FDA's authorization of the expanded access use.

For individual patient expanded access use situations in which there is time to make a written submission, the expedited procedures would not be available. Lack of a prior written submission decreases FDA's ability to review the proposed use. Furthermore, FDA's experience with emergency treatment use is that the written submission and followup information on the outcome of the treatment use frequently have not been provided. By limiting use of the emergency procedures to true emergencies, the agency hopes to better monitor individual patient expanded access use.

G. Expanded Access for Intermediate-Size Patient Populations (Proposed § 312.315)

Proposed § 312.315 provides for expanded access use by patient populations smaller than those typical in treatment INDs or treatment protocols. FDA may ask a sponsor to consolidate expanded access use under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use.

Proposed § 312.315(a) states that expanded access use under the section may be needed in the following situations:

- Drug not being developed. The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial. Nonetheless, the drug may represent the only promising therapy for the people with the disease or condition (proposed § 312.315(a)(1)).

- Drug being developed. The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. Patients may not be able to participate in the trial, for example, because they have a different disease or stage of disease from the one being studied or otherwise do not meet the enrollment criteria; because enrollment in the trial is closed; or because the trial site is not geographically accessible (proposed § 312.315(a)(2)).

- Approved or related drug. The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application (proposed § 312.315(a)(3)(i)), or the drug contains the same active moiety as an approved

drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage (proposed § 312.315(a)(3)(ii)).

When a drug is no longer marketed due to safety reasons, there may be a subset of patients for whom the benefits of treatment are believed to outweigh the risks and who lack satisfactory alternative therapies. Under proposed § 312.315(a)(3)(i), those patients could continue to receive the drug under an intermediate-size patient population IND for expanded access use.

This provision is also intended to allow uninterrupted therapy when an approved drug is not being manufactured in a manner consistent with the specifications on which the approval is based (good manufacturing practice (GMP) violations) and therefore cannot be marketed under the new drug application (NDA). Under proposed § 312.315(a)(3)(i), the drug could be made available to patients for whom the drug is a medical necessity until the GMP violations are addressed (assuming that, despite those violations, the product does not pose a risk that is unreasonable in the context of the disease or condition to be treated, per proposed § 312.305(a)(2)). If the product does pose a risk because of GMP concerns, proposed § 312.315(a)(3)(ii) could be used to make available an unapproved drug product containing the same active moiety (e.g., a drug product approved in another country).

Proposed § 312.315(a)(3)(ii) could also be used in a drug shortage situation to make available an unapproved drug containing the same active moiety as the approved drug that is in short supply (e.g., a drug product approved in another country).

1. Expanded Access for Intermediate-Size Patient Populations—Criteria

In addition to the proposed criteria for all expanded access uses, proposed § 312.315(b) sets forth the criteria that apply specifically to expanded access use for intermediate-size patient populations.

- The first criterion requires that there be enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug for expanded access use (proposed § 312.315(b)(1)).

In ordinary drug development, it is usual practice to gradually increase the number of subjects exposed to a drug (from first human exposure in a very small number of subjects through large phase 3 trials). This practice limits the risk from drugs that turn out to have significant adverse effects, as more and better information (e.g., about dosing) is obtained about the drug before larger numbers of subjects are treated. The same rationale would apply in the expanded access use setting. There should be more clinical experience for an intermediate-size patient population than for an individual patient, and the amount of clinical experience to justify expanded access use in a certain population should be roughly the same as would justify a clinical trial in that size population. FDA anticipates that the typical intermediate-size patient population treatment use IND or protocol will provide access to between 10 and 100 patients.

- The second criterion requires that there be at least preliminary clinical evidence of effectiveness of the drug or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population (proposed § 312.315(b)(2)).

2. Expanded Access for Intermediate-Size Patient Populations—Submission Requirements

In addition to the proposed submission requirements for all expanded access uses, proposed § 312.315(c) sets forth the submission requirements that apply specifically to expanded access use by intermediate-size patient populations. The expanded access use submission must do the following:

- State whether the drug is being developed or is not being developed and describe the patient population to be treated (proposed § 312.315(c)(1));
- Include an explanation by the sponsor, if the drug is not being actively developed, of why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed (proposed § 312.315(c)(2)); and
- Include an explanation by the sponsor, if the drug is being studied in a clinical trial, of why the patients to be treated cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients (proposed § 312.315(c)(3)).

3. Expanded Access for Intermediate-Size Patient Populations—Safeguards

Proposed § 312.315(d) sets forth the safeguards that apply specifically to expanded access use by intermediate-size populations. Upon review of the IND annual report, FDA will determine whether it is appropriate for the use to continue under this section. If the drug is not being actively developed or if the expanded access use is not being developed (but another use is being developed), FDA will consider whether it is possible to conduct a clinical study to develop the expanded access use for marketing (proposed § 312.315(d)(1)(i)). If the drug is being actively developed, FDA will consider whether providing the investigational drug for expanded access use is

interfering with the clinical development of the drug (proposed § 312.315(d)(1)(ii)). As the number of patients enrolled increases, FDA will also consider whether to request that a sponsor submit a treatment IND or treatment protocol as described in § 312.320 for the expanded access use (proposed § 312.315(d)(1)(iii)). The sponsor is responsible for monitoring the expanded access protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators (proposed § 312.315(d)(2)).

H. Expanded Access Treatment IND or Treatment Protocol (Proposed § 312.320)

Proposed § 312.320 describes the treatment IND or treatment protocol mechanism that is currently provided in §§ 312.34 and 312.35. Proposed § 312.320 retains the basic terminology "treatment IND" and "treatment protocol" from current §§ 312.34 and 312.35.

1. Expanded Access Treatment IND or Treatment Protocol—Criteria

In addition to the proposed criteria for all expanded access uses, proposed § 312.320(a) provides the criteria that apply specifically to a treatment IND or treatment protocol.

Proposed § 312.320(a)(1) requires that either the drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use (proposed § 312.320(a)(1)(i)), or all clinical trials of the drug have been completed (proposed § 312.320(a)(1)(ii)).

In addition, the sponsor must be actively pursuing marketing approval of the drug for the expanded access use with due diligence (proposed § 312.320(a)(2)).

Proposed § 312.320(a)(3)(i) provides that, when the expanded access use is for a serious disease or condition, there must be sufficient clinical evidence

of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials.

Proposed § 312.320(a)(2)(ii) provides that, when the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

2. Expanded Access Treatment IND or Treatment Protocol—Submission Requirements

In addition to the proposed submission requirements for all expanded access uses, proposed § 312.320(b) states that the expanded access submission must include information adequate to satisfy FDA that the general criteria for expanded access use and those specific to the treatment IND or treatment protocol have been met.

3. Expanded Access Treatment IND or Treatment Protocol—Safeguards

Proposed § 312.320(c) provides a safeguard that applies specifically to treatment protocols. The sponsor is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

I. Open-Label Safety Studies

The primary purpose of the treatment IND or treatment protocol is to make investigational drugs available to patients with serious or immediately life-

threatening diseases or conditions when there is a reasonable evidentiary basis to support the use in a substantial population, but the evidence needed for marketing approval either has not been entirely collected or has been collected but not yet analyzed and reviewed by the agency.

FDA is concerned that sponsors have used programs other than treatment INDs or treatment protocols to make investigational drugs available to large populations for treatment use, particularly by identifying such programs as "open-label safety studies." The goal of an open-label safety study is to better characterize the safety of a drug late in its development. However, in practice, many studies that are described as open-label safety studies have characteristics that appear to be more consistent with treatment INDs or treatment protocols. For example:

- The investigators are not selected by the sponsor but can be any physician (sometimes with specified qualifications),
- The population receiving the drug is quite large,
- Collection of data is minimal, and
- The studies may not generate the kind of reliable information that would be developed in a study designed to meaningfully assess safety endpoints.

Consequently, in the future, the agency intends to evaluate whether proposals for open-label safety studies should be treatment INDs or treatment protocols that would have to meet the criteria in proposed § 312.320. A study described as an open-label safety study that provides broad access to an investigational drug in the later stages of development, but lacks planned, systematic data collection and a design appropriate to evaluation of a safety issue is likely to be considered a treatment IND or treatment protocol. The agency believes treatment INDs or treatment protocols are more appropriate

programs to provide treatment because the authorization for such expanded access uses will require a more formal review process that would explicitly consider the impact of expanded access on enrollment in clinical trials and the progress of drug development generally.

J. Continuation Phase of a Clinical Trial

The continuation phase of a clinical trial may have characteristics in common with open-label safety studies or expanded access, or both. In the continuation phase of a clinical trial, patients have the option of receiving the study drug after completing the controlled portion of the trial (continue on the study drug or cross over from a control treatment to the study drug), often as an inducement to enroll in the clinical study. All patients receive the study drug. The primary intent may be to develop additional safety data or to treat the patient's condition. Notwithstanding the intent, however, because enrollment is limited to only clinical study participants, the use is considered a part of the clinical study rather than an expanded access use for purposes of proposed subpart I.

V. Legal Authority

The agency believes it has the authority to impose requirements regarding expanded access to investigational drugs under various sections of the act, including sections 505(i); 561; and 701(a) (21 U.S.C. 371(a)).

Section 505(i) of the act directs the agency[3] to issue regulations exempting from the operation of the new drug approval requirements drugs intended solely for investigational use by experts qualified by scientific training and expertise to investigate the safety and effectiveness of drugs. The proposed rule

[3]In light of section 903(d) of the act (21 U.S.C. 393(d)) and the Secretary's delegations to the Commissioner of Food and Drugs, statutory references to "the Secretary" in the discussion of legal authority have been changed to "FDA" or "the agency."

explains procedures for obtaining FDA authorization for expanded access uses of investigational drugs and factors relevant to making necessary determinations.

Section 561 of the act, added by FDAMA, provides significant additional authority for this proposed rule. Section 561(a) of the act states that FDA may, under appropriate conditions determined by the agency, authorize the shipment of investigational drugs for the diagnosis, monitoring, or treatment of a serious disease or condition in emergency situations. This proposed rule sets forth factors that the agency will consider in determining whether to authorize shipment of investigational drugs in emergency situations.

Section 561(b) of the act allows any person, acting through a physician licensed in accordance with State law, to request from a manufacturer or distributor an investigational drug for the diagnosis, monitoring, or treatment of a serious disease or condition if four conditions are met: (1) The physician must determine that the person has no comparable or satisfactory alternative therapy available and the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; (2) FDA must determine that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug in the particular case; (3) FDA must determine that provision of the investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval; and (4) the sponsor or clinical investigator of the investigational drug submits a clinical protocol consistent with the provisions of section 505 of the act describing the use of the investigational drug in a single patient or a small group of patients. The proposed rule sets forth factors that FDA will consider in making the necessary

determinations and explains the procedures and criteria for physicians, sponsors, and/or investigators to make the necessary representations and submissions to FDA.

Section 561(c) of the act specifically authorizes expanded access under a treatment IND if FDA makes the following determinations: (1) Under the treatment IND, the investigational drug is intended for use in diagnosing, monitoring, or treating a serious or immediately life-threatening disease or condition; (2) there is no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat that stage of disease or condition in the population of patients to which the investigational drug is intended to be administered; (3) the investigational drug is already under investigation in a controlled clinical trial for the same use under an IND under section 505(i) of the act, or all clinical trials necessary for approval of that use of the investigational drug have been completed; (4) the sponsor of the controlled clinical trials is actively pursuing marketing approval of the investigational drug, with due diligence, for the same intended use; (5) provision of the investigational drug will not interfere with the enrollment of patients in ongoing clinical investigations under section 505(i) of the act; (6) in the case of serious diseases, there is sufficient evidence of safety and effectiveness to support the intended use; and (7) in the case of immediately life-threatening diseases, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for its intended use and would not expose patients to an unreasonable and significant risk of illness and injury. The proposed rule sets forth factors that FDA will consider in making the necessary determinations.

Section 561 of the act further requires that protocols submitted under section 561 be subject to section 505(i) of the act including regulations issued under section 505(i). Section 561(d) of the act permits the agency to terminate expanded access for failure to comply with the requirements of section 561 of the act. The proposed rule sets forth the conditions under which FDA will place an expanded access use on clinical hold.

In this proposed rule, the agency proposes three categories of expanded access. While authority for individual patient access is based on section 561(b) of the act, and authority for treatment INDs and treatment protocols is based on section 561(c) of the act, there is also authority in the statute for FDA to issue regulations for intermediate-size patient populations. Section 561(b)(4) of the act requires submission of a protocol for the expanded access use that is consistent with the requirements of the IND regulations describing the use of the investigational drug in a single patient or a small group of patients. The provisions of the proposed rule concerning expanded access for intermediate-size patient populations address the use of the investigational drug in the small groups of patients mentioned in the statute.

Section 701(a) of the act provides general authority to issue regulations for the efficient enforcement of the act. By clarifying the criteria and procedures relating to expanded access to investigational products, this proposed rule is expected to aid in the efficient enforcement of the act.

VI. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not an economically significant regulatory action as defined by the Executive Order.

OMB added "economically"

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Currently, the agency does not believe that the proposed rule will have a significant economic impact on a substantial number of small entities. Nevertheless, we recognize our uncertainty regarding the number and size distribution of affected entities, as well as the economic impact of the proposed rule on those entities. Therefore, this economic analysis, together with other relevant sections of this document, constitutes the agency's initial regulatory flexibility analysis. The agency specifically requests detailed public comment regarding the number of affected small entities as well as the potential economic impact of the proposed rule on those entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more

(adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is approximately $122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

A. Objectives of the Proposed Action

FDA is proposing this action to describe in greater detail all of the ways patients may obtain expanded access to investigational drugs for treatment use. Specifically, the proposed rule establishes eligibility criteria, submission requirements, and safeguards for the expanded access use of investigational drugs by individual patients, including in emergencies; intermediate size patient populations; and larger populations under a treatment protocol or treatment IND. The proposal is also intended to increase public knowledge and awareness of expanded access and, thus, to make investigational drugs more widely available. In addition, by establishing clear eligibility criteria and submission requirements, the proposed rule would ease administrative burdens on physicians seeking investigational drugs for their patients and on sponsors who are willing to make promising unapproved therapies available for treatment use. The agency believes that the proposed rule would achieve these objectives in a way that fairly addresses the interests of patients, drug sponsors, and society as a whole.

B. Nature of the Problem Being Addressed

The fundamental problem addressed by the proposed rule is one of incomplete information. In some circumstances, a lack of clearly defined eligibility criteria and submission requirements has created inefficiencies that limit patient access to potentially beneficial investigational drugs. The

proposed rule is also intended to address concerns that, historically, cancer and AIDS patients have had better access to investigational drugs than patients with other serious diseases or conditions, and that patients under the care of physicians based in academic medical centers are more likely to obtain such access than patients whose physicians practice outside such centers. In addition, the lack of clearly defined eligibility criteria and submission requirements has led some physicians and drug sponsors to devote more resources than necessary to the preparation of expanded access submissions. Through this proposed rule, the agency seeks to correct these shortcomings.

The proposed rule establishes general eligibility criteria, submission requirements, and safeguards for the expanded access use of investigational drugs. The requirements that apply to all types of expanded access use are described in detail in section IV.E of this document. The proposed rule also describes more specific eligibility criteria, submission requirements, and safeguards for three specific categories of expanded access: (1) Expanded access for individual patients, (2) expanded access for intermediate-size patient populations, and (3) expanded access under a treatment protocol or treatment IND. These types of expanded access uses are described in detail in sections IV.F, IV.G, and IV.H of this document, respectively.

C. Baseline for the Analysis

During the period 1997 through 2005, FDA received an average of 2,046.6 INDs per year. Of this number, on average, approximately 659, or 32.2 percent (0.322 = 659 / 2,046.6) were individual patient or emergency INDs. In addition, FDA received approximately 4.6 treatment IND or treatment protocol submissions per year during this time period. Thus, treatment IND or treatment protocol submissions represent about 0.2 percent (0.022 = 4.6 / 2,046.6) of all

INDs received by the agency each year. Because expanded access for intermediate size patient populations is not currently established in regulation, FDA does not have a record of the number of submissions in this category. However, based on an internal survey of drug review divisions, FDA estimates that approximately 55 other expanded access submissions were received each year between 2000 and 2002. While it is not possible to determine the precise number that would be considered intermediate size patient population expanded access submissions, FDA experts believe that most of the 55 other submissions each year would fall under this category. Thus, approximately 2.7 percent (0.0268 = 55 / 2,046.6) of all INDs received by FDA each year may be associated with intermediate size patient population expanded access requests. The information presented above is summarized in table 1 of this document.

TABLE 1.—BASELINE DATA FOR THE NUMBER OF INDS AND EXPANDED ACCESS REQUESTS BY CATEGORY

Category	Total INDs	Individual Patient or Emergency IND	Treatment IND or Protocol	Other
Number	2,046.6	659.0	4.6	55.0
Percent of all INDs	100%	32.2%	0.2%	2.7%

D. Nature of the Impact

The proposed rule would affect patients who lack effective therapeutic alternatives and may benefit from access to investigational drugs, physicians attempting to obtain investigational drugs for their patients, drug sponsors who make investigational drugs available to patients, and FDA in its oversight role in the process for making investigational drugs available for expanded access use. As discussed further in section I.D of this document, a major purpose of this proposed rule is to expand access to investigational drugs for patients with serious and immediately life-threatening conditions who lack satisfactory therapeutic alternatives. Therefore, FDA anticipates that the proposed rule

would increase the number of patients who obtain access to investigational drugs for treatment use. This increase in volume would lead to more expanded access submissions from sponsors and physicians seeking investigational drugs for their patients and, as a consequence, would require FDA to review more submissions. Given the relatively small percentage of all INDs received by the agency that are associated with expanded access use submissions, FDA expects that the overall impact of the proposed rule will not be significant.

The proposed rule also attempts to minimize the potential administrative burdens for physicians, sponsors, and FDA that would result from an increased volume of patients obtaining investigational drugs for expanded access use. The proposed rule encourages the consolidation of multiple individual patient INDs or protocols for a given use under an intermediate-size patient population IND or protocol (see sections VII.D.2 and VII.F of this document for additional discussion). By reducing the total volume of submissions that would have been prepared if all patients were to obtain a drug under individual patient INDs or protocols, consolidation will limit the additional administrative burdens from increased patient access. In addition, by explicitly clarifying the eligibility criteria and submission requirements for expanded access, the proposed rule should make the process of obtaining access to investigational drugs more efficient for all affected parties.

It is expected that any increase in the volume of submissions would result primarily from greater numbers of patients obtaining investigational drugs under expanded access INDs or protocols for individual patients and intermediate-size patient populations. Because this proposed rule does not significantly change the existing regulation concerning treatment INDs or

treatment protocols, the number of patients receiving investigational drugs under these mechanisms should be largely unaffected.

1. Individual Patient Expanded Access Submissions

By increasing awareness of the ways individual patients can obtain expanded access to investigational drugs for treatment use, and decreasing the perceived difficulty of obtaining such access, the proposed rule should increase the number of individual patients seeking access to investigational drugs. FDA anticipates that this increase in individual patient expanded access submissions would be greatest in the years immediately following implementation of a final rule and would at some point level off, or possibly even decline. This leveling off or decline would occur when a significant volume of individual patient expanded access has accumulated for a variety of drugs, and the individual patient expanded access INDs or protocols for those drugs are then replaced with intermediate-size patient population INDs or protocols that enroll multiple subjects. Making the transition from multiple individual patient INDs or protocols to a single intermediate-size patient population IND or protocol should reduce the overall administrative burden associated with making a particular investigational drug available for treatment use.

From 1997 to 2005, FDA received, on average, approximately 659 individual patient and emergency IND submissions per year. Although FDA is confident this proposed rule would increase this volume, it is difficult to predict with precision the extent of the increase. There is uncertainty concerning the extent to which patients who desire expanded access to investigational drugs are unable to obtain them; the extent to which better information about the mechanisms and processes for obtaining access to

investigational drugs will stimulate more patients, or their physicians, to seek investigational drugs for expanded access use; and the extent to which drug manufacturers will be willing to make investigational drugs more broadly available for expanded access use. Although FDA is confident there will be an increase in the volume of individual patient expanded access use if this rulemaking is finalized, because of these uncertainties the agency can provide only an estimate of the range of potential increase. FDA believes, after publication of a final rule, that it is reasonable to anticipate a 40 to 60 percent increase in the volume of individual patient expanded access submissions by year 3. As discussed previously in this document, we anticipate that growth would be most rapid in the years immediately following publication of a final rule and would eventually plateau, or possibly even decline. The implications of these assumptions for the total number of individual patient expanded access submissions are summarized in table 2 of this document.

TABLE 2.—EXPECTED PERCENT INCREASE AND ESTIMATED NUMBER OF INDIVIDUAL PATIENT EXPANDED ACCESS SUBMISSIONS

Year After Implementation of Final Rule	Expected Percent Increase in Individual Patient Submissions	Expected Number of Individual Patient Submissions[1]
1	20% to 40%	791 to 923
2	30% to 50%	857 to 988
3	40% to 60%	923 to 1,054
4	0%	923 to 1,054
5	0%	923 to 1,054

[1]Based on the current average of 659 individual patient treatment use submissions per year and the estimated percent increases in column 2.

2. Intermediate Size Patient Population Expanded Access Submissions

Although intermediate-size patient population expanded access has not previously been described in regulation, this general type of mechanism has been used informally to make investigational drugs available for treatment use. Based on an internal survey of review divisions, FDA estimates that for the period 2000 through 2002 it received approximately 55 submissions per year

that would be considered intermediate size patient population expanded access submissions under the proposed criteria. The agency anticipates that this proposed rule would increase the number of such submissions. Because this previously informal mechanism will be described in regulation for the first time, there will be greater awareness, which is likely to stimulate submissions. In addition, the anticipated increase in volume of individual patient expanded access submissions discussed previously in this document is expected to increase the number of intermediate size patient population expanded access submissions because the proposed rule encourages the consolidation of multiple individual patient INDs or protocols for a given expanded access use.

The extent to which submissions for expanded access for intermediate-size patient populations will increase is uncertain. Section 312.315 of the proposed rule concerns expanded access for intermediate-size patient populations. This section provides that FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use. FDA does not have historical information that would permit us to accurately predict what portion of individual patient expanded access submissions are likely to be appropriate for consolidation. Based on our experience, we believe that many of the individual patient expanded access submissions we receive will be appropriate for consolidation. However, some individual patient expanded access submissions will be for expanded access uses that are sufficiently rare that it is unlikely that there will be enough similar uses to consolidate them under an intermediate-size patient population IND or protocol. There is also uncertainty about the extent to which sponsors will be willing to make investigational drugs available for expanded access use

under intermediate-size patient population INDs or protocols. Although FDA is confident that there will be growth in the volume of intermediate-size patient population expanded access INDs or protocols, because of the uncertainties identified, we can provide only an estimate of the range of potential increase. FDA believes it is reasonable to anticipate a 25 to 50 percent growth in the volume of submissions for intermediate-size population expanded access INDs or protocols over a 5-year period.

Compared to the growth in individual patient expanded access submissions, this increase is likely to be more gradual in the years immediately following implementation of a final rule, and will increase more sharply after 2 to 3 years as some of the increase in volume of individual patient expanded access submissions is shifted to intermediate size population INDs or protocols. As in the case of expanded access for individual patients, growth in the number of submissions is expected to plateau or even decline after a few years. The implications of these assumptions for the number of individual patient expanded access submissions are summarized in table 3 of this document.

TABLE 3.—EXPECTED PERCENT INCREASE AND ESTIMATED NUMBER OF INTERMEDIATE SIZE PATIENT POPULATION EXPANDED ACCESS SUBMISSIONS

Year After Implementation of Final Rule	Expected Percent Increase in Intermediate Size Patient Population Submissions	Expected Number of Intermediate Size Patient Population Submissions[1]
1	5% to 10%	58 to 61
2	10% to 20%	61 to 66
3	20% to 40%	66 to 77
4	25% to 50%	69 to 82
5	0%	69 to 82

[1]Based on the current average of 55 intermediate size patient population submissions per year and the estimated percent increases in column 2.

3. Expanded Access Under Treatment INDs and Treatment Protocols

The number of treatment INDs and treatment protocols should be largely unaffected by the proposed rule. The concept of large access programs is well

established and most drugs that meet an unmet medical need for a serious or immediately life-threatening condition have had some kind of large access program late in their development. Therefore, the number of large access programs is primarily a function of the number of new drugs to treat serious and immediately life-threatening conditions that reach the latter stages of drug development (e.g., become NDA submissions). This rule is unlikely to influence that number.

As discussed previously in this document, sponsors have instituted large expanded access programs under treatment INDs or treatment protocols or under less formal open-label or open-access protocols (see section IV.I of this document). The agency intends to be more vigilant in ensuring that a use of an investigational drug that has the characteristics of a treatment IND or treatment protocol is submitted and authorized as such, rather than as an open-label protocol. While this increased vigilance may increase the number of treatment INDs or treatment protocols, any increase will be primarily attributable to reclassifying open-label safety studies as treatment INDs or treatment protocols rather than a net increase in the overall number of large access programs. This reclassification should also improve safety monitoring of large access programs without significantly increasing administrative costs, because the costs for a treatment IND or treatment protocol and an open-label protocol are similar.

Reclassification of an open-label protocol as a treatment IND or treatment protocol may also increase publicity for, and awareness of, the access program. Sponsors of treatment INDs or treatment protocols are required to list those programs at *http://www.clinicaltrials.gov*, a Web site maintained by the National Institutes of Health as a resource for patients seeking to enroll in

clinical trials or obtain access to investigational drugs for treatment use. The additional exposure generated by this site may attract more patients than would have had access under an open-label protocol. As a result, any given treatment IND or treatment protocol may be somewhat more costly than a less publicized open-label protocol due to the volume of patients enrolled. FDA is not able to predict the impact on patient volume as a result of reclassifying open-label or open-access protocols as treatment INDs or treatment protocols. However, FDA anticipates that there would be some economies of scale, so that the incremental costs would be relatively small on a per-patient basis. FDA believes any added costs would be justified by the potentially greater number of patients who would benefit from access to investigational drugs.

E. Benefits of the Proposed Rule

Because FDA currently has no data that would allow us to predict the extent to which the proposed amendments to existing IND regulations would generate direct benefits for consumers, it is not possible to accurately quantify the magnitude of any expected incremental benefits at this time. The number of patients obtaining expanded access to investigational drugs is expected to increase. However, because eligible patients will have serious or immediately life-threatening conditions that have failed to respond to available therapies, and because the investigational drugs are unproven, FDA cannot predict the extent to which individual patients would benefit from access to these drugs. Thus, the following discussion describes, in general terms, the nature of the potential benefits associated with the proposed rule.

The benefits of the proposed rule are expected to result from improved patient access to investigational drugs generally and from expanded access being made available for a broader variety of disease conditions and treatment

settings. In particular, the clarification of eligibility criteria and submission requirements would enhance patient access by easing the administrative burdens on individual physicians seeking investigational drugs for their patients and on sponsors who make investigational drugs available for expanded access use. Expanded access to investigational drugs may generate both private and social benefits. Private benefits would accrue to individual patients receiving drugs for expanded access use, whereas social benefits would accrue if these private benefits are also valued by society at large, or if any information obtained contributes to the development of new therapies generally.

The proposed rule is also designed to address concerns that many physicians and their patients, particularly those outside of academic medical centers, are unaware of the availability of investigational drugs for expanded access use. In FDAMA, Congress included language in section 561(c) of the act to authorize the Secretary to inform medical associations, medical societies, and other appropriate persons of the availability of investigational drugs under treatment INDs or treatment protocols. FDA believes that this action, along with detailed eligibility criteria and submission requirements established in the proposed rule, would improve access to investigational drugs and result in making expanded access use more widely available to patients regardless of treatment setting.

In formulating the proposed rule, FDA considered its statutory mandate, the interests of individuals and special patient populations, drug sponsors, and the general public. The agency found that in many situations, individuals or special patient populations have benefited from increased access to a drug that has not yet been approved for marketing (e.g., in the case of cancer or HIV

therapies, etc.). These individuals or patient groups generally have serious or immediately life-threatening conditions and have not responded to available therapies or cannot participate in ongoing clinical trials for some reason.

On the other hand unrestricted access to investigational drugs for treatment use could negatively affect enrollment in the clinical trials required to demonstrate safety and efficacy in support of new drug marketing applications. If expanded access to investigational drugs were to adversely affect the marketing approval process, the general population would experience diminished social benefits due to the reduced or delayed availability of new therapies approved for marketing by FDA.

The proposed rule addresses these competing interests by allowing investigational drugs to be made available for expanded access use only if providing the drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval, or otherwise compromise the potential development of the expanded access use. In this way, the proposed rule effectively balances the interests of those patient populations who would benefit from having greater access to investigational drugs, with the broader interests of society in having safe and effective new therapies approved for marketing and widely available.

The agency is also aware that allowing expanded access to investigational drugs before they are fully evaluated for safety may have adverse consequences for the seriously ill patients who receive them. The safeguards in the proposed rule are also designed with this concern in mind. Authorization of a particular expanded access use is generally contingent upon a number of factors, including some evidence of the drug's safety and effectiveness, obtaining the informed consent of the patient, approval of an IRB, and a careful assessment

of the potential risks and benefits to the patient. In addition, the proposed rule would place limits on the scope and duration of certain types of expanded access use, require that sponsors of such INDs or protocols monitor the expanded access use and comply with safety and annual reporting requirements for INDs, and subject ongoing INDs or protocols to periodic reassessment. The agency believes these safeguards would adequately protect the safety and welfare of patients who would seek, and may benefit from, expanded access to investigational drugs.

F. Costs of the Proposed Rule

To the extent that the proposed rule results in an increase in the number of expanded access submissions, drug sponsors and physicians requesting investigational drugs on behalf of their patients will incur some additional costs. Because the proposed rule does not include any mandatory reporting requirements, the agency believes that the one-time costs associated with this rule will be negligible. Thus, the incremental burden imposed by this proposed rule will be in the form of additional annual or recurring costs associated with the increased number of expanded access submissions estimated previously in this document.

The agency estimates that preparation and submission of an individual patient expanded access submission would require a total of approximately 8 hours. This time burden would be divided among physicians (approximately 15 percent or 1.2 hours) and nurses, nurse practitioners, or medical administrators (approximately 85 percent or 6.8 hours). According to the U.S. Department of Labor, Bureau of Labor Statistics,[4] total employer costs per hour

[4]See *http://www.bls.gov/news.release/ecec.toc.htm.* (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

worked for employee compensation for registered nurses in the health care and social assistance sector was $36.21 as of June 24, 2004. Thus, the cost of the estimated 6.8 hours of nurse time required to prepare and submit an individual patient expanded access submission would be approximately $245 ($36.21 per hour x 6.8 hours).

Historically, most of the treatment use requests submitted to the agency have been prepared by physicians in the hematology/oncology specialty category. Data available on the Internet indicate that the median expected total compensation for a hematologist/oncologist in the United States was $287,016 as of October 2004.[5] This median total compensation figure corresponds to approximately $138 per hour ($137.99 = $287,016 / 2,080 hours). Thus the cost for the 1.2 hours of physician time required to prepare and submit an individual patient expanded access submission is about $165 ($138 per hour x 1.2 hours). Therefore, the agency estimates that the total cost to prepare and submit an individual patient expanded access submission would be about $410 ($410 = $245 + $165). Applying this cost figure to the number of additional individual patient expanded access submissions estimated previously in this document suggests the pattern of incremental annual costs summarized in table 4 of this document.

TABLE 4.—NUMBER OF ADDITIONAL INDIVIDUAL PATIENT EXPANDED ACCESS SUBMISSIONS AND ESTIMATED ANNUAL COSTS

Year After Implementation of Final Rule	Expected Increase in the Number of Individual Patient Submissions[1]	Expected Cost of Additional Individual Patient Submissions[2]
1	132 to 264	$54,120 to $108,240
2	198 to 329	$81,180 to $134,890
3	264 to 395	$108,240 to $161,950
4	264 to 395	$108,240 to $161,950

[5]See *http://swz.salary.com/salarywizard/layouthtmls/swzl_compresult_national_HC07000054.html.* (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

TABLE 4.—NUMBER OF ADDITIONAL INDIVIDUAL PATIENT EXPANDED ACCESS SUBMISSIONS AND ESTIMATED ANNUAL COSTS—Continued

Year After Implementation of Final Rule	Expected Increase in the Number of Individual Patient Submissions[1]	Expected Cost of Additional Individual Patient Submissions[2]
5	264 to 395	$108,240 to $161,950

[1]Based on increases in the number of individual patient expanded access submissions implied by the estimates presented in table 2 of this document.
[2]Based on an estimated cost of $410 per individual patient expanded access submission.

Preparation and submission of an intermediate size patient population expanded access IND or protocol is expected to require a total of about 120 hours of staff time. This time burden would be divided between a Director of Clinical Research, typically a medical doctor (approximately 50 percent or 60 hours), a Director of Regulatory Affairs (approximately 20 percent or 24 hours), and a Clinical Research Associate (approximately 30 percent or 36 hours).

Information available on the Internet and from industry sources suggests that the average salary for a Director of Clinical Research is about $200,000 per year.[6] Assuming that benefits represent approximately 30 percent of salary implies a total annual compensation estimate of $260,000. This translates into an estimated hourly total compensation figure of about $125 ($260,000 / 2,080 hours). Thus, the cost associated with the 60 hours of Clinical Research Director time required to prepare and submit an intermediate size patient population expanded access submission is approximately $7,500 (60 hours x $125).

Information available on the Internet and from industry sources also indicates that the average salary for a Director of Regulatory Affairs is approximately $160,000 per year.6 Assuming that benefits represent about 30 percent of this salary implies a total annual compensation estimate of

[6]See *http://www.executivesonly.com/preview/exresults.cfm* under the Pharmaceutical specialty category. Viewed January 3, 2005. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

$208,000. This translates into an estimated hourly total compensation figure of about $100 ($209,000 / 2,080 hours). Thus, the cost associated with the 24 hours of Director of Regulatory Affairs time required to prepare and submit an intermediate size patient population expanded access submission is approximately $2,400 (24 hours x $100).

Finally, information available on the Internet indicates that the median total compensation for a Clinical Research Associate is approximately $70,000 per year.[6] This translates into an estimated hourly total compensation figure of about $33.65 ($70,000 / 2,080 hours). Thus, the cost associated with the 36 hours of Clinical Research Associate time required to prepare and submit an intermediate size patient population expanded access submission is approximately $1,200 (36 hours x $33.65).

Based on the information presented, the agency estimates that the total cost to prepare and submit an intermediate size patient population expanded access submission would be approximately $11,100 ($11,100 = $7,500 + $2,400 + $1,200). Applying this figure to the increases in the number of intermediate size patient population expanded access submissions estimated previously in this document suggests the pattern of annual cost increases summarized in table 5 of this document.

TABLE 5.—NUMBER OF ADDITIONAL INTERMEDIATE SIZE PATIENT POPULATION EXPANDED ACCESS SUBMISSIONS AND ESTIMATED ANNUAL COSTS

Year After Implementation of Final Rule	Expected Increase in the Number of Intermediate Size Patient Population Submissions[1]	Expected Cost of Additional Intermediate Size Patient Population Submissions[2]
1	3 to 6	$33,300 to $66,600
2	5 to 11	$55,500 to $122,100
3	11 to 22	$122,100 to $244,200
4	14 to 27	$155,400 to $299,700
5	14 to 27	$155,400 to $299,700

[1]Based on increases in the number of intermediate size patient population expanded access submissions implied by the estimates presented in table 3 of this document.

[2]Based on an estimated cost of $11,000 per intermediate size patient population expanded access submission.

For reasons discussed previously in this document, the agency does not expect that the proposed rule will have an impact on the overall number of treatment INDs or treatment protocols. Therefore, FDA does not expect the provisions of this proposed rule regarding treatment INDs or treatment protocols to impose any incremental cost burden.

The total estimated annual and annualized cost burdens associated with this proposed rule are summarized in table 6 of this document.

TABLE 6.—COST SUMMARY

Year After Implementation of Final Rule	One-Time Cost	Annual Cost	Annualized Cost[1]
1	$0	$87,240 to $174,840	$87,240 to $174,840
2	$0	$136,680 to $256,990	$136,680 to $256,990
3	$0	$230,340 to $406,150	$230,340 to $406,150
4	$0	$263,340 to $461,650	$263,340 to $461,650
5	$0	$263,340 to $461,650	$263,340 to $461,650

[1]Since estimated one-time costs are negligible, annual costs and annualized costs will be the same regardless of the interest rate.

For reasons discussed previously in this document, the agency expects that the total one-time costs of the proposed rule will be negligible. FDA expects that the annual and annualized costs of this proposed rule will range from a low of about $87,000 to $175,000 in the first year following publication of any final rule based on this proposal, to a high of about $263,000 to $406,000 in the fourth and fifth years. These estimates suggest total annual and annualized costs for the proposed rule of between $1.0 and $1.8 million for the 5-year period following implementation of any final rule based on this proposal.

The agency expects that the estimated incremental cost burdens associated with this proposed rule are likely to be widely dispersed among affected entities for several reasons. First, given the historical volume of various types of treatment use submissions, the agency believes that a particular drug sponsor—or a physician acting on behalf of a patient—would submit a request

for expanded access to investigational drugs fairly infrequently. Second, as noted previously, the proposed rule encourages the consolidation of multiple expanded access INDs or protocols for individual patients for a particular expanded access use under an intermediate size patient population expanded access IND or protocol. Such consolidation should, to some extent, offset incremental administrative burdens caused by increased patient access. Making the transition from multiple individual patient expanded access INDs or protocols to a single IND or protocol for an intermediate size patient population should reduce for sponsors the administrative burdens associated with making a drug available for expanded access use. In addition, provisions of the proposed rule are designed to minimize the amount of information and paperwork required to support a particular expanded access request. Physicians and drug sponsors would need to review the rule to become familiar with its provisions and to gather the evidence and information necessary to support an expanded access submission. However, in instances where a current IND already exists, a sponsor need only submit an amendment describing the information relevant to the expanded access protocol. Also, another sponsor or individual physician acting on behalf of a patient may, with the written permission of the original sponsor, reference information in the current IND already on file. The agency believes that a majority of expanded access submissions would have such a right of reference, either because the sponsor is also the drug developer or the developer would generally be willing to grant the request. To the extent that these provisions minimize the informational burden on potential sponsors or physicians, the proposed rule would enhance both efficiency and cost effectiveness.

G. Minimizing the Impact on Small Entities

The agency does not believe the proposed rule will have a significant economic impact on a substantial number of small entities. Nevertheless, we recognize our uncertainty regarding the number and size distribution of affected entities, as well as the economic impact of the proposed rule on those entities. Therefore, the agency specifically requests detailed public comment on these issues.

Agency records indicate that the majority of submissions for treatment use of investigational drugs (about 78 percent) are submitted by commercial drug sponsors. Other entities making treatment use submissions include government agencies (approximately 14 percent), individual physicians (7 percent), and academic institutions (1 percent). Thus, the agency believes that the vast majority (92 percent) of sponsors of expanded access INDs or protocols (consisting of commercial drug sponsors or government agencies) would not be considered small entities. The remaining 8 percent of treatment use submissions are made by individual physicians and academic institutions that the agency believes would meet Small Business Administration small business criteria.

Of the average of 659 individual patient treatment use submissions submitted annually, very few are associated with commercial sponsors. The vast majority are submitted by individual physicians and various other unidentified sponsors for research purposes. Because nearly all individual patient treatment use submissions are made by various types of entities for research purposes, the agency believes that most of these entities would be classified as small entities.

Because there is currently no formal mechanism in place for tracking the other types of expanded access (e.g., intermediate size patient population submissions), no data exist that would allow the agency to identify the number of sponsors in this category that would qualify as small entities.

Thus, while highly uncertain, the agency believes that at least some of the entities submitting expanded access requests would qualify as small entities. Because of this uncertainty, the agency specifically requests detailed public comment regarding the number and size distribution of entities affected by the proposed rule. As discussed in section VII.E of this document, the agency expects that any incremental burden associated with the proposed rule will be small and widely dispersed among affected entities.

FDA considered several alternatives to the proposed rule. They are discussed in the following paragraphs.

1. Do Not Propose Implementing Regulations for the Expanded Access Provisions of FDAMA

FDAMA revised the act to specifically authorize the use of investigational new drugs by licensed physicians to diagnose, monitor, or treat individual patients who have a serious disease or condition if, among other things, the physician determines that the person has no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition, and that the probable risk from the investigational drug is not greater than the probable risk from the disease or condition; and FDA determines that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug. FDAMA also largely incorporated into the act FDA's current regulation concerning treatment INDs or treatment protocols under which large populations currently receive investigational drugs for treatment

use. Because FDAMA did not require that FDA adopt implementing regulations, the agency could have chosen not to do so.

However, the agency believes that implementing regulations would further improve expanded access to investigational drugs for treatment use. One of the major criticisms about access to investigational drugs is that the criteria for authorizing access are unclear and that there is not broad knowledge among affected, or potentially affected, parties about the mechanisms or procedures to obtain access. FDA believes the proposed regulations are needed to address these concerns. The regulations provide to sponsors, patients, and licensed physicians who will be seeking investigational drugs for their patients clear direction about the criteria for authorizing expanded access and what information must be submitted to the agency to enable it to evaluate a proposed expanded access submission. Clearer direction and greater knowledge of the mechanisms and procedures for obtaining investigational drugs for expanded access use should reduce barriers to access.

2. Propose a Regulation Describing Only Individual Patient Expanded Access and the Treatment IND or Treatment Protocol

As discussed in the previous paragraphs, FDAMA specifically authorized the use of investigational new drugs by licensed physicians to diagnose, monitor, or treat individual patients in certain circumstances. FDAMA also essentially repeated FDA's current regulation concerning treatment INDs or treatment protocols under which large populations currently receive investigational drugs for treatment use.

FDA could have chosen to adopt regulations that described only these two categories of expanded access. However, FDA has had a long history of using an informal mechanism to make investigational drugs available to intermediate

size patient populations. This mechanism would not be appropriate for either expanded access for individual patients or for treatment INDs or treatment protocols. The agency concluded that, consistent with the terminology of section 561(b)(4) of the act, it would be preferable to establish an intermediate category for expanded access, with additional criteria and monitoring requirements, that would be used for more than an individual patient, but fewer than the large numbers of patients in treatment INDs or treatment protocols.

In FDA's experience, there is often a need for a middle ground between an individual patient IND or protocol and a treatment IND or treatment protocol. For some drugs in development, there is considerable demand for expanded access before the use meets the criteria for a treatment IND or treatment protocol. There are also situations in which investigational drugs that are not being actively developed are the best available therapy for a significant number of patients and should be made available to patients under an expanded access process. In these situations, making the drug available under a series of individual patient expanded access INDs or protocols is burdensome on physicians, sponsors, and FDA, and makes it difficult to monitor the expanded access use to identify significant safety concerns such as serious adverse events.

Describing this intermediate category in regulation is also consistent with FDA's goal of maximizing awareness of expanded access programs by being more transparent about the processes for making drugs available for expanded access. As stated previously, FDA has used this intermediate category informally in the past and believes it will have reason to use this category in the future. Therefore, FDA believes it is appropriate to formalize and fully

describe in regulation the intermediate expanded access category, as well as the two other categories of expanded access.

3. Propose a Regulation Describing More Than Three Expanded Access Categories

FDA also considered proposing a rule that would include more than three expanded access categories, but rejected this alternative. In internal discussions, FDA found that the distinctions between the proposed categories and the additional categories it considered were unclear. FDA was concerned that the additional categories would create confusion, rather than provide the clarity that is the goal of the proposed regulations. FDA concluded that the additional categories could be merged into the three proposed categories and that these categories will be able to provide access to investigational drugs in all situations FDA is likely to encounter.

VIII. Paperwork Reduction Act of 1995

This proposed rule contains collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). "Collection of information" includes any request or requirement that persons obtain, maintain, retain, or report information to the agency, or disclose information to a third party or to the public (44 U.S.C. 3502(3) and 5 CFR 1320.3(c)). The title, description, and respondent description of the information collection are shown in the following paragraphs with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques and other forms of information technology, when appropriate.

Title: Expanded Access to Investigational Drugs for Treatment Use

Description: The proposed rule would clarify existing regulations and expand on them by adding new types of expanded access for treatment use. Under the proposal, expanded access to investigational drugs would be available to individual patients, including in emergencies; to intermediate size patient populations; and to larger populations under a treatment protocol or IND. The proposed rule is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from such therapies.

A. The Proposed Rule

1. Submission Requirements for All Expanded Access Uses

Proposed § 312.305(b) describes the submission requirements applicable to all types of expanded access. Proposed § 312.305(b)(1) states that an expanded access submission is required for each type of expanded access. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to

pertinent information contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

Proposed § 312.305(b)(2) describes the expanded access submission requirements. The following items must be included:

- A cover sheet (Form FDA 1571) meeting the requirements of § 312.23(a);
- The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;
- The criteria for patient selection; or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments used for the disease or condition;
- The method of administration of the drug, dose, and duration of therapy;
- A description of the facility where the drug will be manufactured;
- Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;
- Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and
- A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

2. Individual Patient Expanded Access

Proposed § 312.310(b) contains additional submission requirements that apply to use of an investigational drug for the treatment of an individual

patient by a licensed physician. The expanded access submission must include information adequate to satisfy FDA that the criteria for all expanded access uses and those specific to individual patient expanded access have been met. The individual patient expanded access criteria are: (1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition and (2) FDA must determine that the patient cannot obtain the drug under another type of IND.

Proposed § 312.310(b)(1) states that if the drug is the subject of an existing IND, the expanded access submission may be made by a commercial sponsor or by a licensed physician. Proposed § 312.310(b)(2) states that a sponsor may satisfy the submission requirements by amending its existing IND to include an individual patient expanded access protocol. Proposed § 312.310(b)(3) states that a licensed physician may satisfy the submission requirements by obtaining a right of reference to pertinent information in the IND and providing any other required information not contained in the IND (usually only the information specific to the individual patient).

3. Intermediate Size Patient Populations

Proposed § 312.315(c) states that an expanded access submission for an intermediate size patient population must include information adequate to satisfy FDA that the criteria for all expanded access uses and those specific to intermediate size patient populations have been met. The intermediate size patient population criteria are: (1) There is enough evidence that the drug is safe at the dose and duration proposed for treatment use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug for treatment use and (2) there is at least preliminary clinical evidence

of effectiveness of the drug or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

Proposed § 312.315(c) contains additional submission requirements that apply to use of an investigational drug for intermediate size patient populations. The expanded access submission must state whether the drug is being developed or is not being developed and describe the patient population to be treated. If the drug is not being actively developed, the sponsor must explain why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed. If the drug is being studied in a clinical trial, the sponsor must explain why the patients to be treated cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients.

4. Treatment IND or Protocol

Proposed § 312.320 describes the treatment IND or treatment protocol currently codified in §§ 312.34 and 312.35. Proposed § 312.320(b) states that the expanded access submission must include information adequate to satisfy FDA that the criteria for all expanded access uses and those specific to the treatment IND or protocol have been met. The criteria specific to a treatment IND or treatment protocol are: (1) The drug is being investigated in a controlled clinical trial designed to support a marketing application for the expanded access use or all clinical trials of the drug have been completed, (2) the sponsor is pursuing marketing approval of the drug for the expanded access use with due diligence, and (3) there is sufficient clinical evidence of safety and effectiveness to support the treatment use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from

completed phase 2 trials. When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, could provide a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

B. Estimates of Reporting Burden

FDA's estimate of the amount of time required to complete an expanded access submission is based on the assumption that either the submission will be made by the drug developer or the submitter will have obtained a right of reference from the drug developer. FDA expects that, if finalized, the proposed rule would result in an increase in the number of submissions for expanded access for individual patients and for intermediate size patient populations.

1. Individual Patient Expanded Access

From 1997 to 2005, FDA received on average approximately 659 submissions for the treatment use of investigational drugs by individual patients per year. This estimate is based on FDA records on the number of individual patient IND submissions (primarily from physicians) and a survey of review divisions on the prevalence of individual patient protocol exception submissions received from commercial drug sponsors. The agency expects an increase in the number of individual patient expanded access submissions as a result of the proposed rule because the proposed rule would increase awareness of the option for individual patients to gain access to investigational drugs and decrease the perceived difficulty of obtaining such access. FDA

anticipates that the increase in individual patient expanded access INDs or protocols would be greatest in the years immediately following implementation of a final rule and would at some point level off, or possibly even decline. This leveling off or decline would occur when a significant volume of individual patient expanded access INDs or protocols have accumulated for a variety of drugs, and the individual patient expanded access INDs or protocols for those drugs are then replaced with intermediate size patient population expanded access INDs or protocols that enroll multiple subjects.

The agency estimates that preparation and submission of an individual patient expanded access IND or protocol submission would require a total of approximately 8 hours.

2. Intermediate Size Patient Population Expanded Access

Although intermediate size patient population expanded access INDs or protocols have not previously been described in regulation, investigational drugs have been made available informally for treatment use to such populations. Based on an internal survey of review divisions, FDA estimates that, for the period 2000 through 2002, it received approximately 55 submissions per year that would be considered expanded access for an intermediate size patient population under the proposed criteria. The agency anticipates that this proposed rule would increase the number of such submissions because there will be greater awareness of this option. In addition, the anticipated increase in volume of submissions for expanded access for individual patients discussed previously is expected to increase the number of submissions for expanded access for intermediate size patient populations because the proposed rule encourages the consolidation of multiple individual patient INDs or protocols for a given expanded access use.

Information provided by FDA review division staff indicates that preparation and submission of an intermediate size patient population IND would require a total of about 120 hours of staff time.

3. Treatment IND or Treatment Protocol

The agency does not expect that the proposed rule will have an impact on the overall number of treatment INDs or treatment protocols because this type of expanded access is already established in FDA's regulations. Therefore, FDA does not expect the provisions of this proposed rule regarding treatment INDs or treatment protocols to impose any increased paperwork burden.

4. Capital Costs

There are capital costs associated with this proposed rulemaking. These costs are discussed in section VII of this document, "Analysis of Economic Impacts."

Description of Respondents: Licensed physicians and manufacturers, including small business manufacturers. Table 7 of this document presents the annualized reporting burden for the total number of expanded access submissions, broken down by type of expanded access use. The figures in the table are based on the analysis of economic impacts (section VII of this document) and are derived by averaging the projected number of submissions for the first 3 years after implementation of a final rule based on this proposed rule.

TABLE 7.—ESTIMATED REPORTING BURDEN

21 CFR section	No. of Respondents	No. of Responses per Respondent	Total Responses	Hours per Response	Total Hours
312.310(b) Individual patient expanded access and 310.305(b) submission requirements generally	1,054	1	1,054	8	8,432
312.315(c) Intermediate size patient population expanded access and 310.305(b) submission requirements generally	77	1	77	120	9,240
312.320 Treatment IND or protocol and 310.305(b) submission requirements generally	5	1	5	300	1,500

TABLE 7.—ESTIMATED REPORTING BURDEN—Continued

21 CFR section	No. of Respondents	No. of Responses per Respondent	Total Responses	Hours per Response	Total Hours
Total					19,172

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection (see **ADDRESSES**).

IX. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

X. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has tentatively determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has tentatively concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

List of Subjects in 21 CFR Part 312

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 312 be amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR part 312 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.

§ 312.34 [Removed]

2. Section 312.34 *Treatment use of an investigational new drug* is removed.

§ 312.35 [Removed]

3. Section 312.35 *Submissions for treatment use* is removed.

§ 312.36 [Removed]

4. Section 312.36 *Emergency use of an investigational new drug (IND)* is removed.

5. Section 312.42 is amended by revising paragraph (b)(3) to read as follows:

§ 312.42 Clinical holds and requests for modification.

* * * * *

(b) * * *

(3) *Clinical hold of an expanded access IND or expanded access protocol.* FDA may place an expanded access IND or expanded access protocol on clinical hold under the following conditions:

(i) *Proposed use.* FDA may place a proposed expanded access IND or treatment use protocol on clinical hold if it is determined that:

(A) The pertinent criteria in subpart I of this part for permitting the expanded access use to begin are not satisfied; or

(B) The expanded access IND or expanded access protocol does not comply with the requirements for expanded access submissions in subpart I of this part.

(ii) *Ongoing use.* FDA may place an ongoing expanded access IND or expanded access protocol on clinical hold if it is determined that the pertinent criteria in subpart I of this part for permitting the expanded access are no longer satisfied.

* * * * *

6. Part 312 is amended by adding and reserving subpart H, and by adding subpart I, consisting of §§ 312.300 through 312.320, to read as follows:

Subpart H—[Reserved]

Subpart I—Expanded Access to Investigational Drugs for Treatment Use

Sec.

312.300 General.

312.305 Requirements for all expanded access uses.

312.310 Individual patients, including for emergency use.

312.315 Intermediate size patient populations.

312.320 Treatment IND or treatment protocol.

§ 312.300 General.

(a) *Scope.* This subpart contains the requirements for the use of investigational new drugs when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of this subpart is to facilitate the availability of investigational new drugs to seriously ill patients when there

is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

(b) *Definition.* In this subpart, the term immediately life-threatening disease means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

§ 312.305 Requirements for all expanded access uses.

The criteria, submission requirements, safeguards, and beginning treatment information set out in this section apply to all expanded access uses described in this subpart. Additional criteria, submission requirements, and safeguards that apply to specific types of expanded access are described in §§ 312.310 through 312.320.

(a) *Criteria.* FDA must determine that:

(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

(b) *Submission.* (1) An expanded access submission is required for each type of expanded access described in this subpart. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information

contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

(2) The expanded access submission must include:

(i) A cover sheet (Form FDA 1571) meeting the requirements of § 312.23(a);

(ii) The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;

(iii) The criteria for patient selection; or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;

(iv) The method of administration of the drug, dose, and duration of therapy;

(v) A description of the facility where the drug will be manufactured;

(vi) Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;

(vii) Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and

(viii) A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

(3) The expanded access submission and its mailing cover must be plainly marked "EXPANDED ACCESS SUBMISSION." If the expanded access submission is for a treatment IND or treatment protocol, the applicable box on Form FDA 1571 must be checked.

(c) *Safeguards.* The responsibilities of sponsors and investigators set forth in subpart D of this part are applicable to expanded access use under this subpart as described in this paragraph.

(1) A licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use under this subpart is considered an *investigator,* for purposes of this part, and must comply with the responsibilities for investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(2) An individual or entity that submits an expanded access IND or protocol under this subpart is considered a *sponsor,* for purposes of this part, and must comply with the responsibilities for sponsors set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(3) A licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND for expanded access use under this subpart is considered a *sponsor-investigator,* for purposes of this part, and must comply with the responsibilities for sponsors and investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(4) *Investigators.* In all cases of expanded access, investigators are responsible for reporting adverse drug experiences to the sponsor, ensuring that the informed consent requirements of part 50 of this chapter are met, ensuring that IRB review of the expanded access use is obtained in a manner consistent with the requirements of part 56 of this chapter, and maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of § 312.62. Depending on the type

of expanded access, other investigator's responsibilities under subpart D may also apply.

(5) *Sponsors.* In all cases of expanded access, sponsors are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required by §§ 312.32 and 312.33, ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use, providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (e.g., providing the investigator's brochure, if there is one), maintaining an effective IND for the expanded access use, and maintaining adequate drug disposition records and retaining records in a manner consistent with the requirements of § 312.57. Depending on the type of expanded access, other sponsor's responsibilities under subpart D may also apply.

(d) *Beginning treatment.* (1) *INDs.* An expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA that the expanded access use may begin.

(2) *Protocols.* With the following exceptions, expanded access use under a protocol submitted under an existing IND may begin as described in § 312.30(a).

(i) Expanded access use under the emergency procedures described in § 312.310(d) may begin when the use is authorized by the FDA reviewing official.

(ii) Expanded access use under § 312.320 may begin 30 days after FDA receives the protocol or upon earlier notification by FDA that use may begin.

(3) *Clinical holds.* FDA may place any expanded access IND or protocol on clinical hold as described in § 312.42.

§ 312.310 Individual patients, including for emergency use.

Under this section, FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician.

(a) *Criteria.* The criteria in § 312.305(a) must be met; and the following determinations must be made:

(1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and

(2) FDA must determine that the patient cannot obtain the drug under another type of IND or protocol.

(b) *Submission.* The expanded access submission must include information adequate to demonstrate that the criteria in § 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of § 312.305(b).

(1) If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician.

(2) A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access.

(3) A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).

(c) *Safeguards.* (1) Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy.

(2) At the conclusion of treatment, the licensed physician or sponsor must provide a written summary of the results of the expanded access use, including unexpected adverse effects.

(3) FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration.

(4) When a significant number of similar individual patient expanded access requests have been submitted, FDA may ask the sponsor to submit an IND or protocol for the use under § 312.315 or § 312.320.

(d) *Emergency procedures.* If there is an emergency that requires the patient to be treated before a written submission can be made, FDA may authorize the expanded access use to begin without a written submission. The FDA reviewing official may authorize the emergency use by telephone.

(1) Emergency expanded access use may be requested by telephone, facsimile, or other means of electronic communications. For investigational biological drug products regulated by the Center for Biologics Evaluation and Research, the request should be directed to the Office of Communication, Training, and Manufacturers Assistance, Center for Biologics Evaluation and Research, 301–827–2000, e-mail: *octma@cber.fda.gov*. For all other investigational drugs, the request for authorization should be directed to the Division of Drug Information, Center for Drug Evaluation and Research, 301–827–4570, e-mail: *druginfo@cder.fda.gov*. After normal working hours, the request should be directed to the FDA Office of Emergency Operations, 301–443–1240, e-mail: *emergency.operations@fda.hhs.gov*.

(2) The licensed physician or sponsor must explain how the expanded access use will meet the requirements of §§ 312.305 and 312.310 and must agree to submit an expanded access submission within 5 working days of FDA's authorization of the use.

§ 312.315 Intermediate-size patient populations.

Under this section, FDA may permit an investigational drug to be used for the treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use.

(a) *Need for expanded access.* Expanded access under this section may be needed in the following situations:

(1) *Drug not being developed.* The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.

(2) *Drug being developed.* The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.

(3) *Approved or related drug.* (i) The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application, or

(ii) The drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage.

(b) *Criteria.* The criteria in § 312.305(a) must be met; and FDA must determine that:

(1) There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and

(2) There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

(c) *Submission.* The expanded access submission must include information adequate to satisfy FDA that the criteria in § 312.305(a) and paragraph (b) of this section have been met. The expanded access submission must meet the requirements of § 312.305(b). In addition:

(1) The expanded access submission must state whether the drug is being developed or is not being developed and describe the patient population to be treated.

(2) If the drug is not being actively developed, the sponsor must explain why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed.

(3) If the drug is being studied in a clinical trial, the sponsor must explain why the patients to be treated cannot be enrolled in the clinical trial and under

what circumstances the sponsor would conduct a clinical trial in these patients.

(d) *Safeguards.* (1) Upon review of the IND annual report, FDA will determine whether it is appropriate for the expanded access to continue under this section.

(i) If the drug is not being actively developed or if the expanded access use is not being developed (but another use is being developed), FDA will consider whether it is possible to conduct a clinical study of the expanded access use.

(ii) If the drug is being actively developed, FDA will consider whether providing the investigational drug for expanded access use is interfering with the clinical development of the drug.

(iii) As the number of patients enrolled increases, FDA may ask the sponsor to submit an IND or protocol for the use under § 312.320.

(2) The sponsor is responsible for monitoring the expanded access protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

§ 312.320 Treatment IND or treatment protocol.

Under this section, FDA may permit an investigational drug to be used for widespread treatment use.

(a) *Criteria.* The criteria in § 312.305(a) must be met, and FDA must determine that:

(1) *Trial status.* (i) The drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or

(ii) All clinical trials of the drug have been completed; and

(2) *Marketing status.* The sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence; and

(3) *Evidence.* (i) When the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials; or

(ii) When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

(b) *Submission.* The expanded access submission must include information adequate to satisfy FDA that the criteria in § 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of § 312.305(b).

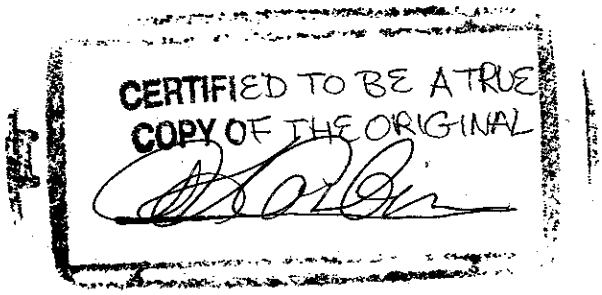
(c) *Safeguard.* The sponsor is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

Dated: 12/6/06

December 6, 2006.

Jeffrey Shuren

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 06–????? Filed ??–??–06; 8:45 am]

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