addition to the direct costs described in paragraph (d)(1)(i) of this section, a sponsor may recover the costs of monitoring the expanded access IND or protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access IND.

(3) To support its calculation for cost recovery, a sponsor must provide supporting documentation to show that the calculation is consistent with the requirements of paragraphs (d)(1) and, if applicable, (d)(2) of this section. The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculations.

Dated: July 20, 2009.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 312 and 316

[Docket No. FDA–2006–N–0238] (formerly Docket No. 2006N–0062)

RIN 0910–AF14

Expanded Access to Investigational Drugs for Treatment Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations on access to investigational new drugs for the treatment of patients. The final rule clarifies existing regulations and adds new types of expanded access for treatment use. Under the final rule, expanded access to investigational drugs for treatment use is 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 final 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. Elsewhere in this issue of the **Federal Register**, FDA is publishing the final rule on Charging for Investigational Drugs Under an Investigational New Drug Application which clarifies the circumstances in which charging for an investigational drug in a clinical trial is appropriate, sets forth criteria for charging for an investigational drug for the different types of expanded access for treatment use described in this final rule, and clarifies what costs can be recovered for an investigational drug.

DATES: This rule is effective October 13, 2009.

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SUPPLEMENTARY INFORMATION:

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I. Background

In the **Federal Register** of December 14, 2006 (71 FR 75147), FDA proposed to amend its regulations permitting access to investigational drugs to treat patients with serious or immediately life-threatening diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

As discussed in greater detail in the preamble to the proposed rule (71 FR 75147 at 75148 to 75149), there have been several statutory and regulatory efforts to expand access to investigational drugs for treatment use. Before 1987, there was no formal recognition of treatment use in FDA's regulations concerning INDs, but investigational drugs were made available for treatment use informally. 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 authorized access to investigational drugs for a broad population under a treatment protocol or treatment IND when certain criteria were met. Section 312.35 described the submission requirements for such treatment use. The 1987 IND regulations also implicitly acknowledged the existence of other kinds of treatment use, notably use in individual patients, by adding a provision for obtaining an investigational drug for treatment use in an emergency situation (§ 312.36). However, § 312.36 did not describe criteria or requirements that must be met to authorize individual patient treatment use.

In response to criticisms that this lack of criteria and submission requirements resulted in inconsistent policies, inequitable access, and preferential access for certain categories of patients, Congress included in the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105–115), which amended the Federal Food, Drug, and Cosmetic Act (the act), specific provisions concerning expanded access to investigational drugs for treatment use (Expanded Access to Unapproved Therapies and Diagnostics, section 561 of the act (21 U.S.C. 360bbb)).

FDA proposed this rule in December 2006 to further address the concerns that motivated the FDAMA changes, including problems of 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 final rule the criteria, submission requirements, and safeguards for the different types of expanded access for treatment use of investigational drugs, FDA hopes to increase awareness and knowledge of expanded access programs and the procedures for obtaining investigational drugs for treatment use. The agency believes that the final rule appropriately authorizes access to promising drugs for treatment use, while protecting patient safety and avoiding interference with the development of investigational

drugs for marketing under approved applications.

In 2007, after the proposed rule on expanded access was published, Congress passed the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110–85). One provision, codified in 505–1(f)(6) of the act (21 U.S.C. 355–1(f)(6)), requires the Secretary of Health of Human Services (the Secretary) to promulgate regulations concerning how a physician may provide a drug under the mechanisms of section 561 when the drug is subject to elements to assure safe use under a risk evaluation and mitigation strategy (REMS). The expanded access mechanisms described in this final rule can be used by a patient seeking access to a drug with a REMS in the event that the drug is not available to the patient under the criteria of the REMS, provided the drug and the patient meet the criteria for an expanded access program. Therefore, this rule fulfills the FDAAA requirement.

This final rule applies both to drug products that are subject to section 505 of the act (21 U.S.C. 355) and biological products subject to the licensing provisions of the Public Health Service Act (42 U.S.C. 201 *et seq.*) and 21 CFR part 601. This is consistent with the previous regulations on treatment use, which applied to both drug and biological products.

II. Overview of the Final Rule Including Changes to the Proposed Rule

A. Overview

The final rule amends FDA regulations by removing the current sections on treatment use of investigational drugs (§§ 312.34, 312.35, and 312.36), revising § 312.42 on clinical holds, and adding subpart I of part 312 on expanded access. Subpart I describes the following ways that expanded access to treatment use of investigational drugs are available:

- Expanded access for individual patients, including in emergencies;
- 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 previous §§ 312.34 and 312.35).

The final rule provides the following: (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.

B. Changes to the Proposed Rule

The final rule has been revised in response to comments received on the proposed rule. The responses are discussed in section III of this document. The final rule:

- Revises proposed § 312.300(a) to clarify that subpart I is intended to apply not only to the use of investigational new drugs but also to approved drugs whose availability is limited because the drugs are subject to a risk evaluation and mitigation strategy (REMS) in accordance with section 505–1(f)(6) of the act.
- Also revises proposed § 312.300(a) to clarify that subpart I is intended to apply to all those with a serious disease or condition, regardless of whether the patient would currently be considered seriously ill with that disease or condition.
- Revises proposed § 312.300(b) to include a definition of ''serious disease or condition.''
- Revises proposed § 312.305(c)(5) to clarify that a sponsor should make an investigator's brochure available to licensed physicians in an expanded access program whenever such a brochure exists.
- Revises proposed § 312.310(a)(2) to omit the words ''type of.''
- Revises proposed § 312.310(c)(2) to clarify that the summary of the expanded access use should include all adverse effects, not merely unexpected ones, and that the summary should be submitted to FDA.
- Revises proposed § 312.310(d)(2) to extend the time in which to make written submissions to 15 working days after FDA's authorization of emergency use.

The agency did not propose to amend the text of § 316.40. However, because § 316.40 references the requirements of § 312.34, which is being withdrawn, FDA has revised § 316.40 to remove the reference to § 312.34.

III. Comments on the Proposed Rule

The agency received 119 comments on the proposed rule. Comments were received from individuals (persons with serious or immediately life-threatening diseases or conditions, persons with family members with such diseases or conditions, and other interested persons), healthcare and consumer advocacy organizations, healthcare professionals (physicians and pharmacists), pharmaceutical and biotechnology companies, trade organizations representing pharmaceutical and biotechnology companies, health insurance companies, a trade organization representing health insurance companies, hospitals, a trade organization representing hospitals, and a professional society representing oncologists.

A. General Comments on the Proposed Rule

Most of the comments strongly supported the goal of expanding access to investigational drugs for treatment use. The vast majority of these comments expressed strong support for the proposed rule as a way to expand access. As a category, the largest volume of comments came from individuals, and the vast majority of those supported the proposed rule. Healthcare and consumer advocacy organizations provided the next largest volume of comments. Comments from these organizations spanned the spectrum from strongly supportive to strongly negative. Many healthcare and consumer advocacy organizations commented that they believe the rule strikes the appropriate balance between increased access and patient safety without impeding enrollment in clinical trials or otherwise jeopardizing the development of new drugs for marketing approval.

Healthcare and consumer advocacy organizations who opposed the proposed rule had widely divergent views. Some of these commenters expressed the view that the rule did not go far enough in removing the obstacles to patient access to investigational drugs for treatment use and argued that, after phase 1 safety testing, there should be largely unfettered access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions and no alternative therapies. One of these organizations urged that the rule be withdrawn and a substantially more permissive access policy (one that affords individual patients greater autonomy) be developed and implemented.

Some healthcare and consumer advocacy organizations expressed the view that the proposed rule went much too far in making investigational drugs available to patients for treatment use. One comment argued that expanded access as described in the proposed rule would eliminate the incentive for patients to enroll in clinical trials that provide the evidence necessary to make effective use of new therapies, would be harmful to patients exposed to therapies for which there is limited safety and effectiveness information, and raises issues of fairness because of the potential that the supply of the drug may not be adequate to make it available to all those seeking access. Some

comments argued that there should be access only in the very late stages of clinical development, ideally not until phase 3 testing had been completed.

Comments from pharmaceutical and biotechnology companies and their trade organizations were the next largest category of comments. These comments were generally supportive of the goal of expanding access, but expressed concern about the potential for expanded access, as described in the proposed rule, to impede drug development and add new administrative burdens or expense for companies.

FDA's response to these general comments is that we believe the final rule appropriately addresses the competing concerns surrounding expanded access. As discussed in detail in the preamble to the proposed rule (71 FR 75147 at 75160), the key question in making investigational drugs available for treatment use is how to address the various interests—individual patients' desires to make their own decisions about their healthcare, including decisions about using experimental therapies in advance of such treatments being approved for marketing, society's interest in the efficient development of new therapies to treat serious and immediately life-threatening diseases or conditions, and the need to protect vulnerable patients from unnecessary and unacceptable risks. FDA recognizes that these issues are complex and can have life-or-death implications, both for individuals seeking access to investigational drugs and for large populations of patients with a given disease or condition who desire that innovative therapies for their disease or condition be developed and marketed as quickly as possible. Therefore, it is not surprising that there are a range of perspectives about how best to reconcile these competing interests and highly impassioned defenses of the various perspectives.

FDA's perspective in attempting to address and, where possible, reconcile these different views, is intended to be consistent with its statutory mandate to ensure that drug therapies developed and marketed for serious and immediately life-threatening diseases or conditions are safe and effective (which requires substantial evidence from clinical trials) and that individuals exposed to investigational therapies under an IND, whether in a clinical trial or for an expanded access use, are not subject to unnecessary and unacceptable risks. FDA acknowledges the varied positions expressed on access to investigational drugs for treatment use. The agency recognizes that this rule may not be satisfactory to all; sometimes it is not possible to reconcile the more disparate views. FDA has made its best effort to set forth a regulatory policy that is consistent with its statutory mandate, taking into account the views of those who commented. FDA believes it has addressed these competing issues in a way that affords patients a meaningful and reasonable measure of autonomy over their own healthcare decisions while preserving the integrity of the drug approval process and protecting patient safety.

Specific issues raised by the comments and the agency's responses follow.

B. Comments Related to the Proposed Rule as a Whole

1. Public Awareness and Physician and Patient Education Programs

(Comment 1) In the preamble to the proposed rule (71 FR 75147 at 75149), FDA stated that the major goals of this rulemaking are to broaden the scope of expanded access and to address concerns about inequities in access to investigational drugs under expanded access programs. FDA explained that by describing in detail in regulation the criteria, submission requirements, and safeguards for the different types of expanded access programs, FDA hoped to increase knowledge and awareness of expanded access programs and the procedures for obtaining investigational drugs under such programs and, as a result, facilitate wider availability of investigational drugs in appropriate circumstances. FDA also explained that it wished to address concerns that in the past, access to investigational drugs has been primarily available to patients with certain serious or immediately life-threatening diseases or condition—particularly cancers, Human Immunodeficiency Virus (HIV) disease, and HIV-related conditions—and hoped that the greater awareness and clarity fostered by this rulemaking would facilitate access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions who may have been underserved in the past.

Several comments expressed the view that this rulemaking alone would not be sufficient to accomplish these goals. One comment argued that promulgating expanded access regulations is an ineffective vehicle to increase knowledge and awareness of expanded access programs because FDA regulations are not widely read by healthcare providers and consumers. Another comment stated that **Federal Register** notices are not the best way of disseminating information to the lay public or their healthcare providers and complained that the proposed rule did not mention any additional efforts to disseminate the new policies.

Several comments recommended that FDA do more to publicize its expanded access regulations, educate and train physicians, and/or improve communications with patients and patient advocacy organizations. One comment stated that patients are sometimes confused about the reasons they are not able to enroll in an expanded access program or obtain individual access and urged FDA to consider ways to improve communication to patients about the standards for expanded access to minimize this confusion. One comment recommended that training materials and information be made available to the general public in an easily accessible format and medium, such as on FDA's Web site, so that patients and patient advocates can obtain the instructions for submitting an expanded access request. Another comment from a patient advocacy group recommended that FDA provide guidance on each of the specific types of expanded access. The comment stated that not all physicians will have the time or inclination to inform themselves about the expanded access mechanisms and processes and, therefore, it is important that patients and patient advocates be informed about expanded access and FDA's requirements for expanded access so that they can inform their physicians.

(Response) FDA believes that clearly specifying in regulations the mechanisms and processes for obtaining investigational drugs for treatment use is the essential and fundamental platform on which to build awareness of, and accessibility to, expanded access programs. FDA agrees, however, that new expanded access regulations alone will not be sufficient to increase knowledge and awareness about expanded access to an extent that will meet FDA's goals for broader and more equitable access. Therefore, in conjunction with publication of this final rule, FDA intends to develop and engage in a broad range of publicity and educational efforts in a variety of forums and media to increase awareness of the mechanisms for obtaining investigational drugs for treatment use.

(Comment 2) Some comments stated that additional steps would be needed to address complaints that access to investigational drugs was biased toward cancer and HIV disease patients. One comment recommended that FDA work more closely on early access programs with disease-specific institutes at the

National Institutes of Health (NIH) in addition to the National Cancer Institute and the Office of AIDS Research in the National Institute for Allergy and Infectious Disease. One comment recommended outreach to better inform minorities about access to investigational drugs for treatment use. The comment suggested a program specifically directed at African-American women because of their low rates of cancer survival relative to white women.

FDA's Office of Special Health Issues (OSHI) works closely with individual patients and patient organizations, including minority and special disease groups, and with the healthcare provider community and organizations. The office responds to questions about expanded access and directs inquiries for specific treatment uses of investigational products to the appropriate staff within FDA. The office maintains a Web site with general information about expanded access and other ways of getting promising therapies to seriously ill patients (see *http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/default.htm*).

(Comment 3) Some comments urged that all expanded access INDs and protocols be listed on ClinicalTrials.gov (*http://www.clinicaltrials.gov*), the Web site maintained by NIH that is intended to include a listing of controlled clinical trials for drugs in development. One comment asked that FDA clarify whether the public notification provision (the provision that describes what should be listed on ClinicalTrials.gov) applies to access programs for intermediate-size patient populations.

(Response) ClinicalTrials.gov is governed by section 402(j) of the Public Health Service Act (PHS Act) (42 U.S.C. 282(j)). The law, as amended by FDAAA, requires the registration of certain controlled clinical trials on ClinicalTrials.gov and specifically requires information to be included about whether expanded access to an investigational drug under section 561 of the act is available for those who do not qualify for enrollment in the clinical trial and how to obtain information about such access (section 402(j)(2)(A)(ii)(II)(gg) of the PHS Act). The ClinicalTrials.gov provisions only apply to certain controlled clinical trials (see definition of ''applicable drug clinical trial'' in section 402(j)(1)(iii) of the PHS Act). Thus, information about expanded access is required to appear in ClinicalTrials.gov when the drug at issue is the subject of certain controlled clinical trials (i.e., other than phase 1 trials in which one group of participants is given an investigational drug subject to FDA's jurisdiction, while the control group receives either a standard treatment for the disease or a placebo). If expanded access is for an investigational drug that is not the subject of certain controlled clinical trials, the statute does not require information about the expanded access in ClinicalTrials.gov. Thus, for example, information about an expanded access program for an intermediate-size patient population for a drug that is being developed (see § 312.315(a)(2)) would be included in ClinicalTrials.gov as long as the other requirements for inclusion are met. However, information about an expanded access program for an intermediate-size patient population for a drug that is not being developed under a clinical trial (see § 312.315(a)(1)) and therefore is not subject to the mandatory registration provisions in section 402(j) of the PHS Act would not be required to be included in ClinicalTrials.gov.

2. Administrative Burdens Associated With Obtaining Expanded Access

(Comment 4) A number of comments, particularly from patient advocacy groups, stated that the administrative burdens associated with expanded access could undermine FDA's efforts to broaden access. The general concern was that the requirements, particularly for physicians seeking individual patient INDs, are too onerous and, therefore, physicians will be reluctant or unwilling to seek investigational drugs for treatment use for their patients. Two comments argued that the burden would be greatest in nonacademic settings because physicians in those settings are typically not as familiar with IND regulations and Institutional Review Board (IRB) requirements. The comments recommended that the requirements for expanded access for individual patients be simplified and disconnected from compliance with other sections of part 312 (e.g., investigator and sponsor responsibilities in subpart D (Responsibilities of Sponsors and Investigators)). Another comment stated that administrative burdens are a particular problem in the academic research setting, where intensive IRB approval and oversight, combined with the data collection requirements of the protocols, have forced some centers to forego participation in expanded access programs until they can find a source of funding.

(Response) FDA shares the concern that the requirements for obtaining access to investigational drugs, if perceived as burdensome, may be a deterrent to obtaining access to investigational drugs for treatment use. However, FDA believes the evidentiary, submission, and data collection requirements are generally non-labor intensive, straightforward, and appropriate to the kind of assurances needed to permit treatment use of investigational drugs. We acknowledge that compliance with the expanded access requirements might pose particular challenges for physicians (whether in academic or nonacademic settings) who are not very familiar with IND and IRB regulations, as well as for medical centers in which existing administrative burdens already test the limits of available resources. However, we believe that the burdens associated with IND compliance and IRB review under expanded access programs have been minimized to the extent possible while still ensuring patient safety.

The majority of the data necessary to satisfy the IND submission requirements for a licensed physician obtaining an IND for an individual patient will, in most cases, be provided by reference to the content of an IND held by a sponsor who is developing the investigational drug for marketing. (In the case of treatment access to an approved drug that is subject to a REMS, reference to a sponsor's IND may not be necessary.) Therefore, in making an IND submission, the physician will ordinarily only be required to provide a narrative explaining the rationale for the intended use and dose, why there are no comparable or satisfactory therapeutic alternatives, a description of the patient's disease or condition (including recent medical history and previous treatments), and the monitoring, testing, or other procedures needed to minimize the risks of the drug to the patient. For the post-treatment submission, the physician must provide a written summary of the results of the expanded access use, including adverse effects. The information needed for each of these submissions is the same kind of information that is captured during routine patient care and, consequently, is already known to the physician or can be readily accessed. Therefore, FDA does not consider these submission requirements to be a burden that is out of proportion with the risks inherent in using an investigational product for treatment use (see response to comment 60 for discussion of IRB review issues). FDA intends to engage in educational efforts to help physicians understand the individual patient requirements and how to navigate those requirements in a way that minimizes the administrative

burdens. These efforts will be directed at physicians in both academic and nonacademic settings.

For multi-patient expanded access INDs, FDA agrees that there are steps that could be taken to minimize administrative burdens at participating sites. As with any use of investigational agents, FDA encourages the use of centralized IRBs and standardized data collection documentation across expanded access IND sites when there are multiple sites. As part of its ongoing outreach efforts on expanded access, FDA intends to work with constituents in patient advocacy, clinical settings, and the pharmaceutical industry to minimize the burdens associated with multi-patient expanded access programs generally, as well as the burdens associated with specific multi-patient access programs as they arise.

FDA does not believe that licensed physicians and sponsors should be exempt from compliance with the sponsor and investigator requirements in subpart D of part 312. It is crucial to keep in mind that expanded access involves use of an investigational therapy in a vulnerable population, so the rationale for oversight, monitoring, recordkeeping and human subject protections applicable to clinical trials is equally applicable in the treatment use context. Accordingly, § 312.305(c) of the final rule provides that investigators, sponsors, and sponsor-investigators 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. Section 312.305(c)(1) provides that a licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use is considered an investigator. Section 312.305(c)(2) provides that an individual or entity that submits an expanded access IND or protocol is considered a sponsor. Section 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 use, is considered a sponsor-investigator.

3. Equitable Access

The preamble to the proposed rule (71 FR 75147 at 75149) explains that, by describing in detail the categories of expanded access use and the criteria and submission requirements for such use, and otherwise increasing awareness of the mechanisms and processes for obtaining investigational drugs for treatment use, FDA hopes to make investigational drugs for treatment use more accessible for diseases and conditions and in clinical settings that have purportedly been underserved by expanded access programs.

(Comment 5) Several comments agreed that certain diseases, conditions, and regions have been underserved by expanded access programs. Some comments maintained that minority populations, in particular African-Americans and women, have been underserved by expanded access programs and that these populations should be the focus of efforts to make access to investigational drugs for treatment use more equitable.

(Response) FDA agrees that regions, diseases, or populations that have been underserved by expanded access programs should be the focus of efforts to ensure more equitable access. FDA's OSHI is committed to working with any underserved constituencies to help address inequities in the access to investigational drugs for treatment use.

(Comment 6) One comment expressed concern that the implications of one of FDA's stated goals—to improve access to investigational therapies outside academic medical centers—are unknown and may be harmful. The comment suggested that a possible reason that access to investigational drugs for treatment use is more likely in academic medical centers is that these centers tend to treat more patients with serious and immediately life-threatening diseases or conditions who have exhausted all available conventional treatment options. The comment noted that there is a lack of information in the proposed rule concerning differences in patient outcomes between patients treated with investigational drugs in academic medical centers and those treated elsewhere and suggested that, absent such data, it is not necessarily desirable for the use of investigational drugs for treatment use to become significantly more prevalent outside academic medical centers.

(Response) FDA acknowledges that patients who have the diseases or conditions for which treatment use of investigational drugs is generally sought may be found in greater numbers in academic medical centers specializing in the treatment of serious and immediately life-threatening conditions. FDA does not agree, however, that the intent to facilitate access in all settings requires data on comparative quality of care across different settings, any more than it would require such a comparison among academic centers in geographic regions. FDA believes it is important to foster use of investigational drugs for treatment use in all settings in which eligible patients receive care, provided there are appropriate controls and oversight, as set forth in this final rule.

4. Supplies of Investigational Drugs

(Comment 7) Several comments were concerned that there seemed to be an implicit assumption in the proposed rule that there will be an adequate supply of an investigational drug to meet the demand for the drug generated by potentially broader access over an indefinite period of time. Some comments pointed out that increasing demand for an investigational drug could create supply constraints, which could make it impossible to provide a drug for treatment use to all those who seek it and could also threaten the completion of clinical studies of the drug. One comment argued that expanded access programs should focus on investigational drugs with an adequate supply to meet the potential demand. Two comments stated that access should be fair and equitable in situations in which the supply cannot meet the demand. One comment recommended that the treatment IND provisions in the final rule include a way to ensure fair and equitable access in situations in which there is not enough supply of a drug to meet the demand.

(Response) FDA agrees that, in cases when there is not sufficient supply of an investigational drug to make it available to all patients who seek it, access to the drug for treatment use should be as equitable as reasonably possible. FDA does not agree that expanded access programs should be limited to only those situations in which there is an adequate drug supply for all potential subjects. Mechanisms to fairly allocate limited drug supply (e.g., lotteries) have been used in the past to provide drugs to at least some of the patients who could benefit. FDA supports the use of these mechanisms where they are needed.

However, FDA does not believe that it is necessary to include in the final rule a requirement that fair and equitable distribution mechanisms be used to allocate an investigational drug in the event of insufficient supply. Current IRB regulations require an IRB to determine that selection of subjects, in this case patients to be treated, is equitable (21 CFR 56.111(a)(3)). FDA believes that provision is adequate to ensure equitable access in cases in which the drug supply is not adequate to meet the demand.

FDA anticipates that the most appropriate distribution mechanism for a drug with limited supply will be very case specific, for example, requiring

identification of threshold clinical parameters for possible access and a mechanism to randomly select from those who meet the parameters. Therefore, FDA believes it is advisable for the sponsor to work with the relevant patient or disease advocacy organizations, professional societies, and other affected constituencies to devise the most appropriate mechanism for allocating a limited drug supply in a specific situation. However, it should be noted that FDA has no authority to compel sponsors to participate in that collaboration or to make their investigational products available for treatment use.

5. Industry Support or Incentives to Broaden Expanded Access

(Comment 8) Some comments argued that the proposed rule would not increase expanded access because a substantial increase in access would require industry support. Some comments suggested that FDA offer financial incentives to industry, such as extending periods of exclusivity or expediting drug review, to encourage drug companies to make drugs available for treatment use.

(Response) FDA is aware that, for a variety of reasons, there may be reluctance among pharmaceutical and biotechnology companies to make investigational drugs available under expanded access programs. FDA's charging rule, published elsewhere in this issue of the **Federal Register**, is intended to address concerns about financial barriers to providing access by allowing companies to charge an amount for an investigational drug that enables them to recover the costs associated with making the drug available. Other financial incentives are beyond the scope of this regulation and FDA's statutory authority. For example, FDA's existing authority to extend marketing exclusivity to induce certain behavior derives from congressional mandates.

FDA also does not believe that a promise to expedite review of new drug applications (NDAs) is a reasonable option to encourage broader access to investigational drugs for treatment use. The types of drug products that meet the requirements for treatment use—investigational therapies to treat serious and immediately life-threatening diseases or conditions—are likely to already be eligible for the shortest review times currently available (6 months). Given the complexity of NDAs, FDA does not believe it can routinely review applications in less time while maintaining the integrity of the review process.

6. Data Obtained from Expanded Access Use

(Comment 9) One comment asked whether data generated in expanded access programs must be submitted to the NDA for the drug product and, if so, how FDA evaluates this information when determining the safety and efficacy of the drug for the proposed indication and patient population. Another comment stated that FDA's historical reluctance to consider efficacy information from expanded access uses as evidence of efficacy in an NDA or supplemental NDA has been a disincentive for some companies to make a product available for expanded access. The comment maintained that it would be appropriate to consider safety and efficacy information from an expanded access IND or protocol in assessing the safety and effectiveness of a drug when the use and patient population in the expanded access IND or protocol are similar to the use and population for which approval is sought. The comment asked that FDA revise the proposed rule to explicitly inform sponsors, investigators, patients, and patient representatives that any safety and efficacy data collected in expanded access are expected to be reported in the initial NDA seeking approval for the drug or biological product. One comment argued that a company that makes a drug available for treatment use under an expanded access IND or protocol runs the risk of being adversely affected by unfavorable safety observations from use in the expanded access population, notwithstanding that the patients receiving the drug under an expanded access IND or protocol are often sicker, nonresponders to prior treatments, and otherwise not representative of the population evaluated in controlled clinical trials, but there is no commensurate benefit to the company from favorable efficacy observations in the expanded access population.

(Response) As with any IND, sponsors of expanded access INDs must provide FDA with information on patient outcomes and adverse events observed during an expanded access use. This information must be included in IND annual reports (§ 312.33) and/or IND safety reports (§ 312.32) and, typically, an NDA must also contain at least a summary of the expanded access experience with a drug. The information obtained from an expanded access use can be useful to a drug's safety assessment. For example, a relatively rare adverse event might be detected during expanded access use, or such use might contribute safety information for a population not exposed to the drug in clinical trials. However, a control group is more important to the utility of effectiveness data than safety data. Because expanded access programs are typically uncontrolled exposure (with limited data collection), it is very unlikely that an expanded access IND would yield effectiveness information that would be useful to FDA in considering a drug's effectiveness. However, if a sponsor believes that effectiveness information from expanded access use can contribute to a determination that there is substantial evidence of effectiveness, it should submit the information and an explanation of its relevance to FDA.

There are examples in which FDA has made use of adverse events information from expanded access use in the safety assessment of a drug. There are a small number of cases in which an important adverse event was first identified during expanded access use and those adverse events were included in product labeling. This is not a negative from a public health perspective—the sooner important adverse events are identified the better. Even from the sponsor's viewpoint, early discovery of a rare adverse event is, on the whole, a benefit. Although adverse events first identified during expanded access use of certain drugs have been included in the drugs' approved product labeling, we are unaware of any cases in which adverse event information obtained from expanded access use has resulted in denial of approval for a product.

(Comment 10) One comment observed that data from expanded access might provide helpful information about use of a drug in patients who are sicker than those patients enrolled in clinical trials.

(Response) FDA agrees that expanded access use in a population with a particular disease or condition that is sicker than the population in the clinical trials might yield some helpful insights into the tolerability profile, but typically would not provide insight into the response to the drug (effectiveness) because of the uncontrolled nature of the access program and limited data collection.

(Comment 11) Some comments recommended that investigational drugs be made available for expanded access only under protocols that are designed to capture some scientific knowledge. One comment recommended that the final rule require all categories of expanded access to be conducted under a clearly defined research protocol. The comment recommended that the final rule require that: (1) An appropriate sponsor be responsible for collecting patient outcomes data, (2) reports be

submitted in a timely fashion to FDA, and (3) patients be required by FDA to participate in official data-gathering processes within a formal cohort study or patient registry.

(Response) FDA does not agree that investigational drugs should be made available only under expanded access protocols designed to obtain meaningful scientific data, or contingent on enrolling patients in a formal cohort study or registry. As explained in § 312.300(a) of this final rule, the primary purpose of expanded access is to diagnose, monitor, or treat a patient's disease or condition, not to generate scientific data intended to characterize the drug. However, FDA agrees that there should be efforts to optimize the information obtained from expanded access exposures with an eye toward detecting any unexpected outcomes or events.

(Comment 12) FDA received several comments advocating more systematic collection of data on outcomes of expanded access programs, including adverse events. One comment maintained that current data collection practices for expanded access programs rarely yield useful information and that better collection of safety data might identify previously unknown safety concerns. One comment stated that data collection should focus on elements such as drug start and stop dates, dose, patient treatment outcomes, and significant adverse events, and that collection of adverse events could use standardized reporting forms (e.g., MedWatch), which might promote more consistent collection of reliable information. One comment also stated that FDA should consider compiling a database of evidence derived from expanded access uses for use by patients, clinicians, manufacturers, and researchers to help identify areas that researchers might pursue for new treatments and therapies.

(Response) FDA agrees that more standardized data collection methods and forms could ease some of the documentation burdens associated with expanded access. However, FDA does not believe it is in a position, at this time, to be able to describe in regulation or guidance the form and content of data collection programs specific to expanded access uses. FDA is willing to participate in collaborative efforts with interested constituents to develop better data collection methods. FDA does not believe that data collected from expanded access use would, in most cases, be in a form that would be useful for hypothesis generation. It is important to note, however, that information about some expanded access uses (those involving applicable drug clinical trials) will be included in the ClinicalTrials.gov results database (see response to comment 3 and *http://www.clinicaltrials.gov*).

7. Assessing the Impact of Expanded Access

(Comment 13) One comment encouraged FDA to develop a tracking system to evaluate how well the expanded access program is working and to identify factors, such as economic obstacles, that might be impeding access to investigational drugs for treatment use. The comment recommended that the system include information on patients and investigators, whether or not requests for expanded access are granted, and if not, the reason for not granting such requests, the outcomes of the treatments, and costs, if any, to patients who pay for their treatments.

(Response) FDA believes this final rule, in conjunction with implementation of electronic format INDs and the expanded ClinicalTrials.gov information, will make it easier for the agency to compile information about the types of diseases or conditions that are or are not being treated under expanded access INDs. That information could, for example, identify disease categories that appear to be underserved by expanded access INDs. FDA does not foresee that such information would be able to specifically identify economic or other obstacles to obtaining access for certain diseases or conditions, but it could be used to initiate discussions among patient and disease advocacy organizations, the relevant medical specialty professional society, pharmaceutical companies with products that could possibly be made available for expanded access, FDA, and other interested parties to help identify barriers to access. As to the comment's specific recommendation that a tracking system include information on patients and investigators, whether or not requests for expanded access are granted, and if not, the reason for not granting such requests, the outcomes of the treatments, and costs, if any, to patients who pay for their treatments, FDA does not believe that such a system is necessary at this time, nor do resources permit establishment of such a system.

8. Open-Label Safety Studies

In the preamble to the proposed rule (71 FR 75147 at 75155), FDA expressed concern 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. FDA stated that, in the future, it intends to evaluate submissions identified as open-label safety studies to determine whether those studies are more characteristic of treatment INDs or treatment protocols. The proposed rule stated that 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.

(Comment 14) Several comments expressed support for FDA's position that programs that make investigational drugs available to large populations for treatment use should be treatment INDs or treatment protocols, not open-label safety studies. One comment stated that mischaracterizing a treatment IND as an open-label safety study afforded the study more credibility than it deserved. Several comments opposed FDA's position, stating that open-label safety studies are important in elucidating the safety profile of investigational drugs prior to approval, the time required for formal review could affect expediting drug development, and FDA's plan would result in fewer expanded access programs.

(Response) In enunciating this policy, FDA did not intend to limit the conduct of open-label safety studies intended to evaluate particular safety concerns, such as long-term followup of subjects initially enrolled in a randomized trial, safety studies in pediatric development programs, and other safety studies. These types of studies are legitimate open-label protocols and are an integral part of a drug development program. FDA will continue to encourage such studies as appropriate.

However, FDA continues to believe that the treatment IND process is a more appropriate vehicle for providing access to investigational drugs for treatment use to large populations outside controlled clinical trials late in a drug's development. The treatment IND provides appropriate patient safeguards and permits FDA the necessary oversight over the development program. And as FDA explained in the

preamble to the proposed rule (71 FR 75147 at 75155), authorization of expanded access use is subject to a more formal review process that explicitly considers the impact of expanded access on enrollment in any ongoing clinical trials and the progress of drug development generally. The time for review of a treatment use program should not affect the timing of drug development because the need for such an expanded access program and the protocol for the program can be considered in advance and put in place when needed. Therefore, FDA does not believe this policy will result in fewer expanded access programs.

(Comment 15) One comment asked whether only patients with a serious disease or condition could be enrolled in open-label studies that FDA would consider to be treatment INDs.

(Response) One of the threshold criteria for a treatment IND is that the population to be enrolled has a serious or immediately life-threatening disease or condition. Therefore, only protocols intended to treat patients with serious or life-threatening diseases or conditions are subject to this requirement.

It should be noted that FDA has not taken the position that the agency will consider all open-label safety studies to be treatment INDs. FDA will not consider an open-label safety study to be a treatment IND when the purpose of the study is actually to study the safety profile of the drug.

9. Insurance Coverage for Investigational Drugs and Related Patient Care Drug Coverage

(Comment 16) Several comments were concerned about the potential implications of the proposed rule on coverage decisions by health insurers and other third-party payers. Some comments were concerned that, because the drug made available is investigational, third-party payers would deny coverage for the drug and may also deny coverage for patient care necessitated by use of the drug. One comment noted an example of a patient seeking expanded access to an investigational drug who would be required to have frequent, expensive monitoring, including electrocardiograms (EKGs) and monthly Computed Tomography (CT) scans, and who might not be able to obtain access if health insurance did not reimburse for the required monitoring. One comment argued that the goals of expanded access are illusory if third-party payers do not reimburse for drug costs (if any) and routine patient care necessitated by administration of the investigational drug.

One comment from a health insurance company stated that the design of insurance benefits already recognizes that some patients should receive benefit coverage for treatments that are not yet supported by clinical evidence, both in clinical trials and as treatment for promising but unproven treatments for life-threatening illnesses outside of clinical trials. The comment asked FDA to clarify in the rule that therapies provided under expanded access programs are experimental and not FDA-approved and that making these therapies available for treatment use does not provide evidence that such treatments are ''reasonable,'' ''necessary'' or ''medically necessary,'' as defined in benefit documents. The comment stated that third-party payers would welcome a more standardized approach to the treatment of diseases without established therapies, particularly because these rules raise questions about responsibility for routine costs associated with otherwise excluded care.

(Response) FDA's intent in promulgating the expanded access regulation is to foster the availability of investigational drugs for treatment use to as many patients with serious and life-threatening diseases as possible who lack known effective therapies for their disease or condition. FDA recognizes that determinations that investigational drugs made available under expanded access programs, and patient care related to administration of those drugs, are not reimbursable would be likely to limit access to such therapies for some patients (e.g., those who lack the financial resources to pay out-of-pocket). It is FDA's hope, therefore, that health insurers and other third-party payers will make well-reasoned reimbursement decisions that will not impinge on the availability of investigational drugs for treatment use. To the extent that it is an insurer's policy that care necessitated by administration of an investigational drug in a clinical trial is reimbursable, FDA believes that care associated with administration of an investigational drug in an expanded access program should be treated similarly for reimbursement purposes. However, FDA recognizes it has no inherent authority to dictate reimbursement policy.

FDA also recognizes that this final rule may have implications for health insurance coverage decisions because of existing language in health insurance contracts and how that language is interpreted with respect to costs associated with investigational drugs and ancillary care provided under expanded access programs. FDA agrees that drugs made available under expanded access programs are typically investigational and not approved for marketing. However, FDA takes no position on how the terms ''reasonable,'' ''necessary,'' or ''medically necessary'' in health insurance contracts should be interpreted.

10. Waiver of Liability for Harm Related to Expanded Access

(Comment 17) One comment from a pharmaceutical company stated that the proposed rule does not address the significant liability issues for sponsors and investigators arising from making investigational drugs available for expanded access. Many comments from individuals stated that receiving investigational drugs under expanded access programs should be premised on a patient's waiver of liability for harm resulting from treatment with the investigational drug. These comments maintained that liability should be waived for doctors, hospitals, drug manufacturers, and FDA.

(Response) FDA does not believe it is appropriate to insulate investigators or sponsors, whether they are treating physicians, hospitals or other clinical settings, or drug manufacturers, from potential liability arising from the administration or provision of investigational drugs for treatment use. In fact, FDA's informed consent regulation, 21 CFR 50.20, states, ''No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.'' The scope of FDA's liability, if any, for any harm resulting from decisions concerning expanded access to investigational drugs for treatment use is determined by statute and cannot be modified by a waiver provision in a regulation.

11. Inconsistency Between Subpart I and Subpart E

The expanded access regulations use the terms ''immediately life threatening disease or condition'' and ''serious disease or condition.''

(Comment 18) One comment suggested that there was a discrepancy between terminology used in the proposed rule (subpart I of part 312) and terminology used in subpart E of part 312. The proposed rule uses the term ''immediately life-threatening,'' while

subpart E uses the term ''life-threatening.'' The proposed rule uses the term ''serious,'' while subpart E uses the term ''severely debilitating.'' The comment recommended that this final rule clear up the confusion arising from the use of similar but different terms in FDA regulations.

(Response) The subpart I regulations are being issued in response to a provision of FDAMA, now codified in section 561 of the act (21 U.S.C. 360bbb). The terms used in this final rule are consistent with and drawn from the terminology in section 561. Accordingly, any change to make the terms consistent would require revision to subpart E. This final rule deals only with subpart I, and thus the comment asks for a remedy that is outside the scope of this rule.

Moreover, we note that subpart E and subpart I have different purposes. Subpart E provides procedures to expedite the development, evaluation, and marketing of new therapies. Subpart I provides procedures for making investigational drugs available when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. Nonetheless, if subpart E were to be amended, FDA would then consider the propriety of the terminology used in subpart E.

C. Comments on Specific Provisions of the Proposed Rule

1. Scope (§ 312.300 and 312.300(a))

Proposed § 312.300(a) describes the intended scope of subpart I of part 312. It makes clear that the purpose of subpart I is to describe processes for making investigational drugs available in situations in which the primary purpose is to diagnose, monitor, or treat a serious or immediately life-threatening disease or condition in a patient who has no comparable or satisfactory alternative therapeutic options.

(Comment 19) Three comments asked that FDA clarify whether it intended that an expanded access IND be used to make an approved drug available for an unapproved indication in a situation in which a sponsor is conducting a clinical trial of the approved drug under an IND for a new indication to treat a serious disease or condition. Two of these comments urged that FDA modify the proposed rule to make clear that it applies to unapproved uses of approved drugs. The comments believed that such modification would make it more likely that health insurance companies would reimburse for unapproved use of approved drugs.

(Response) In general, for an already approved drug that is not subject to a REMS, FDA did not intend that an expanded access IND under subpart I be used to provide the approved drug to patients with a serious disease or condition when the approved drug is being used for an unapproved indication. Regardless of whether an approved drug is being tested in a clinical trial to treat a serious disease or condition that is not part of the current approved indication, use of an approved drug off-label for an unapproved indication within the practice of medicine (i.e., to treat a patient in a clinical setting) is not subject to part 312 (the IND regulations), including subpart I. By definition, in such a case, the drug is already being legally marketed.

However, in at least two situations, expanded access under subpart I may be appropriate for drugs that are already approved: First, it is conceivable that a sponsor developing an approved drug for a new indication for treatment of a serious or immediately life-threatening disease or condition may want to make the approved drug available for the new indication under a treatment IND. For example, if the new indication involves a different route of administration or dosage form, the sponsor may prefer to provide the new dosage form under a treatment IND if it believes that failure to make the drug available under a treatment IND could lead to compounding of the drug (e.g., preparation of a new dosage form of a drug by a compounding pharmacist using the active ingredient of an approved drug product) and that such compounding could expose patients to unnecessary risks. FDA would be amenable to receiving treatment INDs for unapproved uses of approved drugs in situations in which the sponsor would prefer the use of a treatment IND to make the drug available for treatment use outside the ongoing or completed controlled trials of the unapproved use.

Second, for drugs that are subject to a REMS, expanded access under subpart I may be available to allow treatment of patients who do not otherwise meet the criteria under the REMS to receive the drug.

For these reasons, we have revised § 312.300(a) to state that subpart I contains the requirements for the use of investigational new drugs and approved drugs where availability is limited by a REMS when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. This fulfills the mandate, codified in 505–1(f)(6) of the act, for the Secretary of Health of Human Services to promulgate regulations concerning how a physician may provide a drug under the mechanisms of section 561 of the act when the drug is subject to elements to assure safe use under a REMS. We will assess the impact of this rule on expanded access to drugs subject to a REMS and, if appropriate, will consider issuing a guidance on this matter.

In response to the comment on insurance reimbursement, we note that FDA does not have jurisdiction over coverage decisions by health insurance companies and, in any case, is not aware that allowing expanded access to an already approved drug under subpart I would influence coverage decisions by health insurance companies.

(Comment 20) One comment notes that § 312.300(a) states that the intent is to make investigational drugs available to ''seriously ill patients,'' while the general criteria in § 312.305(a) require that patients to be treated with an investigational drug have ''a serious or immediately life-threatening disease or condition.'' The comment pointed out that a patient can have a serious disease or condition and not be seriously ill, for example, in the early stages of a progressive disease.

(Response) FDA acknowledges that the use of the term ''seriously ill'' in the provision describing the intended scope of the access provision could be interpreted as narrower in scope than was intended, and thus inconsistent with the term ''serious or immediately life-threatening disease or condition.'' Therefore, FDA has changed § 312.300(a) to make clear that subpart I is intended to apply to all those with a serious disease or condition, whether or not the patient would currently be considered seriously ill with that disease or condition.

2. Definitions (§ 312.300(b))

a. *Immediately life-threatening disease or condition.*

Proposed section 312.300(b) defines the term ''immediately life-threatening disease'' as a stage of disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

(Comment 21) One comment expressed support for the proposed rule's definition of the term ''immediately life-threatening disease'' and encouraged FDA to include this definition in the final rule. One comment maintained that the proposed definition of immediately life-threatening was unnecessary because immediately life-threatening conditions are a subset of serious conditions and thus need not be defined.

(Response) The proposed rule defined the term ''immediately life-threatening disease'' because the evidentiary criteria

for authorizing a treatment IND under proposed § 312.320 vary depending on whether the disease or condition is merely serious or is also immediately life-threatening. There is a lower evidentiary threshold for a treatment IND for an immediately life-threatening condition. The evidentiary distinction and definition are carried over from the previous treatment IND regulation and reflect the distinction between section 561(c)(6) and (c)(7) of the act. Because the final rule retains the lower evidentiary standard for authorizing a treatment IND for an immediately life-threatening condition, FDA believes it is necessary to retain the definition.

(Comment 22) One comment from an organization representing epilepsy centers asked the agency to define immediately life-threatening in such a way that it would include status epilepticus and pointed out that the mortality rate from status epilepticus is up to 6 percent.

(Response) A disease or condition with an acute mortality rate of six percent would be considered an immediately life-threatening condition for purposes of subpart I.

b. *Serious disease or condition.*

In the preamble to the proposed rule (71 FR 75147 at 75151), the agency explained that, because of the difficulty in specifically describing regulatory criteria that characterize a ''serious disease or condition,'' the proposed rule does not provide a definition for the term. Because it is difficult to define ''serious disease or condition'' without appearing to exclude diseases or conditions that should be considered serious or include those that should not, FDA in the proposed rule elected to describe and illustrate by example what is meant by serious disease or condition in other regulatory settings where the seriousness of a disease or condition is an issue (e.g., Fast Track, Accelerated Approval) (see FDA's guidance for industry entitled ''Fast Track Drug Development Programs—Designation, Development, and Application Review'' (Fast Track guidance) (63 FR 64093, November 18, 1998)). The preamble solicited comment on this approach for purposes of expanded access—implicitly asking whether the term should be defined or the agency's previous practice of describing the concept and illustrating by example was acceptable.

(Comment 23) Several comments stated that FDA should define ''serious disease or condition.'' No comments recommended not defining the term. Three comments stated that not defining the term and relying on existing descriptions and illustrations of what is meant by the term would make access to investigational drugs for treatment use overly broad. One of those comments argued that a definition would promote more consistent application of the rule. One comment recommended that the definition err on the side of inclusiveness. One comment asked for clarification of what is meant by serious disease or condition because it is unclear what serious conditions would have an important effect on functioning or other aspects of quality of life as well as persistent or recurrent morbidity.

Some comments provided recommendations or specific language on how to define serious disease or condition. Two comments recommended relying on existing language in the Fast Track guidance (pp. 3 to 4). One comment recommended defining serious disease or condition based on the following criteria in a 1999 Institute of Medicine (IOM) Report entitled ''Definition of Serious and Complex Medical Conditions.'' The IOM report gave the following examples of descriptive criteria for serious and complex medical conditions:

- Conditions that cause serious disability, such as stroke or closed head or spinal cord injuries.
- Conditions that cause significant pain or discomfort that can cause serious interruptions to life activities, such as arthritis and sickle cell disease.
- Conditions that may require frequent monitoring, such as schizophrenia and other psychotic illnesses.
- Conditions whose treatment carries the risk of serious complications, such as most cancers or conditions requiring complex surgery.

Another comment recommended that the definition of serious disease or condition be made consistent with the definition of serious adverse drug experience in § 312.32(a) (the definition used for the IND safety reporting requirements), which defines a serious adverse drug experience as including inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

(Response) Because of the support for defining the term ''serious disease or condition'' in the comments, FDA is providing a definition in the final rule. As recommended by some comments, FDA is basing the definition on the description of a serious disease or condition in the Fast Track guidance. That description and illustration of serious disease or condition was the result of prolonged and careful deliberations concerning what should be considered a serious disease or condition and has served the agency well in its implementation of the Fast Track legislation. The Fast Track guidance (p. 4) states that whether a disease or condition is serious ''is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. * * * For a condition to be serious, the condition should be associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient but the morbidity need not be irreversible, provided it is persistent or recurrent.'' FDA believes this definition is also conceptually consistent with the criteria identified in the IOM report, the definition of serious adverse drug experience in the IND safety reporting regulation, and the description of serious disease or condition in the preamble to 21 CFR part 314, subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses). Therefore, we have adopted this definition of serious disease or condition in § 312.300(b).

FDA recognizes, based on its own experience in trying to define and describe what is meant by serious disease or condition, that this definition will be subject to various interpretations. FDA intends to be flexible in its interpretation of the term to ensure that the definition does not thwart access to an investigational drug in a situation where access would be desirable. It is foreseeable that there might even be situations in which a serious health risk in the absence of active serious disease should be considered a serious condition. For example, it may be desirable to make an experimental vaccine available as a prophylactic measure to laboratory workers who have been inadvertently exposed to a deadly pathogen but have not yet contracted the disease. Notwithstanding the potential pitfalls in defining serious disease or condition, based on the views expressed in the comments received, FDA believes that stating a definition is preferable to providing only an explanation and illustration of the concept of serious disease or condition and will facilitate more consistent and equitable application of the expanded access regulations.

(Comment 24) One comment stated that intractable epilepsy should be considered a serious disease or

condition. Another comment was concerned that in situ breast cancer would not be considered a serious disease or condition for purposes of the expanded access regulations.

(Response) FDA agrees that intractable epilepsy and in situ breast cancer would be considered serious conditions for purposes of the expanded access regulations as each would unquestionably cause morbidity and potentially premature mortality if left untreated.

3. Requirements for All Expanded Access (§ 312.305)

Proposed § 312.305 contains the general criteria for determining whether access to investigational drugs for treatment use is appropriate under the expanded access uses described in subpart I (§ 312.305(a)), the general submission requirements for the expanded access INDs described in subpart I (§ 312.305(b)), and safeguards applicable to those expanded access uses (§ 312.305(c)).

Proposed § 312.305(a)(1) states that FDA must determine that the patient or population 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.

a. *Comparable or satisfactory alternative therapy*.

(Comment 25) One comment from a cancer patient appeared to assert that there should be more flexibility in assessing whether there are comparable satisfactory or alternative therapies. The comment stated that certain comparable alternative therapies may be more toxic and patients exposed to those therapies may become too sick to survive any subsequent treatment, thus barring them from access to a promising experimental treatment.

(Response) FDA shares the comment's concern that existing alternative therapies may have greater toxicity than an experimental treatment option, especially in the oncology setting. FDA believes that the relative toxicity of potential alternative therapies is clearly an element to be considered in whether there are comparable or satisfactory alternative therapies for a given patient. The potential lower toxicity of an experimental therapy would be considered in light of the more established effectiveness profile of the approved therapy, the patient's ability to tolerate the approved therapy, and other clinical factors in assessing whether the approved therapy is a satisfactory alternative therapy.

b. *Risk/benefit assessment—evidentiary standards*.

Proposed § 312.305(a)(2) provides that FDA must determine that the potential patient benefit justifies the potential risks of the treatment use and that those risks are reasonable in the context of the disease or condition to be treated. For individual patients, proposed § 312.310(a)(1) further provides that the physician seeking access for a patient must also determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition. For intermediate-size patient populations, proposed § 312.315(b)(1) further provides that FDA must determine that 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 proposed § 312.315(b)(2) provides that FDA must determine that there is at least preliminary clinical evidence of effectiveness, or of a plausible pharmacologic effect of the drug, to make expanded access use a reasonable therapeutic option in the anticipated patient population. For treatment INDs or treatment protocols, § 312.320(a)(3)(i) further provides that for a serious disease or condition, there must be sufficient evidence of safety and effectiveness to support the use, which would ordinarily consist of data from phase 3 trials but could consist of compelling data from completed phase 2 trials. Section 312.320(a)(3)(ii) requires that, for an immediately life-threatening disease or condition, the available scientific evidence taken as whole must 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. Such evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

(Comment 26) One comment from a physician with investigational drug experience asked that FDA remove the requirement that the agency must determine that 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. The comment maintained that the seriously ill patient and his/her physician should be the ones to decide whether or not to accept the risks of the treatment and that the decision should not be made by FDA reviewers. The comment also stated that this provision ''represents a sea change'' in FDA's policy because it would regulate the practice of medicine.

Another comment stated that the risk-benefit decision to be made for individual patient expanded access should be made only by the patient's physician, not also by FDA. The comment objected to the proposed criterion that FDA 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 (§ 312.305(a)(2)). The comment argued that, in interposing itself into the risk-benefit decision, FDA had impermissibly changed the statutory standard for deciding whether to grant individual patient expanded access. The comment recognized that section 561(b)(2) of the act requires the Secretary to determine that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug in an individual patient. However, the comment stated that this provision does not empower FDA to make a risk determination.

(Response) FDA disagrees with the recommendation to remove the requirement that the agency determine whether the potential patient benefit justifies the potential risks and whether those risks are reasonable in the context of the disease or condition to be treated. FDA also rejects the characterization of this policy as a ''sea change.'' This policy reflects the essence of FDA's long-standing approach to using investigational drugs for treatment use, whether under individual patient INDs or multi-patient INDs, and reflects the act's requirement of FDA involvement in a determination of the propriety of the expanded access use (see section 561(b)(2), (b)(3), (c)(6), and (c)(7) of the act). The practice-of-medicine exemption in the IND regulations applies to use of an approved drug for an unapproved use in a clinical setting, not to the use of an unapproved drug. With regard to treatment access to an approved drug subject to a REMS, because the risk profile of such a drug means that it is not available for unrestricted use, FDA maintains a role, consistent with sections 505–1(f)(6) and 561 of the act, in assessing the appropriateness of the drug for treatment use analogous to its role regarding treatment access to investigational drugs.

As to the comment that FDA has impermissibly aggregated to itself the risk benefit decision to be made for

individual patient expanded access, the comment itself acknowledges that section 561(b)(2) of the act states that the criteria for individual patient expanded access include that the Secretary determines that there is ''sufficient evidence of safety and effectiveness to support the use of the investigational drug.'' If FDA were to accede to the comment's interpretation that the risk determination belongs solely to the physician, it would effectively read out of existence section 561(b)(2) of the act. In that section, Congress expressly directed FDA to make a determination regarding the sufficiency of the evidence of both safety and effectiveness to justify treatment use of an investigational product. While section 561(b)(1) of the act requires a physician to make a determination that the probable risk to the patient is not greater than the probable risk from the disease or condition, this finding is a necessary, but not in itself sufficient, prerequisite to providing a drug for individual treatment use. Section 561(b)(2) of the act clearly contemplates a determination by FDA regarding safety and effectiveness, and the agency cannot choose to ignore that responsibility.

(Comment 27) Some comments were concerned that the proposed rule did not provide an adequate balance between risks and benefits and, in particular, did not provide a sufficiently high evidentiary standard for providing access, and as a result would expose patients to unnecessary risks. One comment stated that because many of the drugs that would be made available under access programs are highly likely to prove ineffective in further clinical testing, exposure to such drugs may not improve patients' conditions and, in some cases, may increase patient suffering and hasten death. One comment provided an apparent illustration of the potential harm. The comment pointed out that autologous bone marrow transplants were performed on approximately 30,000 women with advanced breast cancer before it was established that such treatment did more harm than good and that, as a result, some of the women who received this treatment had increased suffering and shortened lives. One comment stated that a patient should have some assurance that an investigational drug may be potentially life-saving that would outweigh any potential negative risks of using the drug. Some comments maintained that, until there is a certain threshold of data available, there should be no access whatsoever. One comment argued that there should no expanded access until the completion of phase 2 testing, and then only if the phase 2 data are compelling. Another comment recommended that there be no expanded access until evidence of a drug's safety and effectiveness has been demonstrated in clinical trials that will be submitted for approval, which would usually be data from phase 3 trials but may include phase 2 data. Other comments were concerned that the proposed rule required too much evidence to obtain an investigational drug for treatment use. Those comments believe that the evidentiary standards would inappropriately deny access to investigational drugs to some patients.

(Response) The assessment of the risks and benefits of investigational therapies in the absence of complete data about the safety and effectiveness of those therapies is challenging and subject to varied interpretations and viewpoints. FDA believes the proposed rule strikes an appropriate balance and sets forth a reasonable approach to balancing risks and benefits. That approach, as outlined in the discussion above, requires an assessment of risk and benefit based on the relative seriousness of the disease or condition and the size of the population to be treated under the expanded access IND or protocol—with the evidentiary requirements decreasing as seriousness increases and the size of the population decreases. Increasing the amount of evidence needed as the size of the population exposed increases is based on FDA's considerable experience with the clinical development of drugs that demonstrates the need to cautiously increase the size of exposure in order to detect serious toxicities that occur in small percentages of those exposed (and are thus not likely to be detected in a small population exposure). Decreasing the amount of evidence needed as the seriousness of the disease or condition increases simply acknowledges that patients in greater peril are willing to assume greater risks.

FDA recognizes that investigational drugs have risks, including unknown risks, and that it is likely that some drugs made available for treatment use will ultimately be shown to have no benefit, and in fact cause harm. As a result, there is the potential for some patients to be harmed by such drugs. However, FDA believes that, on balance, more patients are likely to gain some benefit from investigational drugs than be harmed by them and, therefore, patient interests are best served by making such drugs available under appropriate programs. FDA does not believe that a lesser evidentiary standard is warranted. FDA believes that to require less evidence would significantly increase the likelihood that patients would be more harmed than benefited by use of experimental therapies.

Conversely, FDA does not believe that there should categorically be a specified minimum amount of data, such as data from completed phase 2 or 3 trials, before any expanded access is permitted. As detailed in the preamble to the proposed rule (71 FR 75147 at 75168), FDA believes there needs to be flexibility in the evidentiary standards to be applied to the varied types of expanded access INDs and expanded access protocols that the agency is likely to receive. Moreover, even if a specified minimum amount of data for expanded access were desirable, FDA believes that completion of phase 2 or 3 testing is more than should be required for certain types of expanded access INDs and expanded access protocols.

(Comment 28) One comment argued that access has the potential to increase the risk to patients with the possibility of no commensurate benefit. The comment maintained that safety issues related to exposure to an investigational drug are best addressed in the context of clinical trials and asked FDA to require that access be provided only under a defined protocol, by a qualified investigator, with defined dosage range and adverse event monitoring procedures, and with specified time intervals for assessing response.

(Response) FDA agrees that access protocols should provide a detailed plan for the conduct of the protocol, including plans for data collection and patient monitoring commensurate with the size of the population to be treated and the nature of the use (e.g., short-term versus long-term). However, because of the broad range of potential populations for which access may be provided under an expanded access protocol—from an individual patient to many thousands of patients—and the wide range of potential risks and resulting need for variations in the intensity of monitoring, it would not be good policy to require the same level of detail and specificity for each protocol. The amount of detail and specificity required will increase with increasing size of the population, increasing complexity of the disease being treated, and greater risks associated with the use of the drug. For the same reasons, the amount of data to be collected and the potential utility of that data might vary. Accordingly, FDA believes it would not be useful to promulgate specific and uniform data collection and monitor

requirements for all expanded access protocols.

i. *Individual Patient Evidentiary Standard*

Proposed § 312.310(a)(1) provides that the physician seeking access for a patient 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. Concerning the evidence needed before treating an individual patient with an immediately life-threatening illness or disease or condition, the preamble to the proposed rule stated that 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. However, the preamble further stated that in some cases, 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 (71 FR 75147 at 75151).

(Comment 29) Several comments were concerned that the evidentiary standards applicable to individual patient expanded access allow for the possibility of making a drug available to a patient without evidence from clinical experience. One comment stated that ''it is wrong to permit use in the absence of evidence in humans and to present this scenario as 'treatment' even for desperately ill patients.'' Another comment stated that ''it seems inappropriate and possibly dangerous to permit this relatively uncontrolled access to an investigational drug to represent the first human exposure to a drug.'' Another comment recommended that there be at least preliminary clinical evidence (such as phase 1 safety testing) before there be any expanded access use regardless of the number of patients. One comment recommended that the final rule state that proceeding with treatment use in an individual patient should be a rare circumstance that requires, at a minimum, submission to FDA of robust evidence from nonclinical studies to show that it is reasonably safe to proceed with the proposed treatment use, and information forming the basis from nonclinical toxicokinetic studies and nonclinical pharmacology studies for selecting dosage, dosage interval, and duration of treatment for use in patients. One comment recommended that the evidentiary threshold for individual patient expanded access be evidence from the clinical trials intended to demonstrate safety and effectiveness for marketing approval (which would ordinarily be phase 3 studies but could include phase 2 studies that support approval). The comment added, however, that this category could be used to provide continuity of care for a patient who appeared to benefit from a drug during participation in an earlier clinical trial.

(Response) FDA agrees that making an investigational drug available to an individual patient in the absence of any clinical data to support the use may carry substantial risk. FDA does not believe, however, that access under such circumstances should be entirely foreclosed by the expanded access provisions. FDA believes—and our experience has demonstrated—that there are circumstances in which such use may be appropriate. These circumstances might involve a patient with an imminently life-threatening disease or condition, a novel therapy that has a plausible pharmacologic rationale suggesting it may potentially be beneficial for that disease or condition, and robust nonclinical safety data to support the use. FDA does agree that use of an investigational drug for treatment purposes in an individual patient in the absence of any clinical data should be extremely rare. FDA anticipates that authorizing an individual patient treatment use of a drug in the absence of clinical data on use of the drug for that indication would be more likely to occur when there was some clinical data on the drug (e.g., from a study for another use) but no clinical data in the population or disease for which treatment use is sought.

However, FDA does not agree that there should be no expanded access to an investigational drug for anyone until the evidence needed to support approval is developed, which ordinarily would not occur until the completion of phase 3 clinical testing. In addition, FDA does not believe the expanded access provisions in subpart I are necessary to provide continuity of care for patients who seemed to have responded to an investigational therapy during a clinical trial. A protocol amendment adding a continuation phase to the clinical trial would ordinarily be the preferred mechanism for providing an investigational therapy to clinical trial participants who wish to continue to receive the drug after the completion of the controlled phase of the clinical trial.

(Comment 30) Two comments recommended that FDA have different evidentiary standards for individual patient expanded access for patients with a serious disease or condition and the subset of those patients with an immediately life-threatening disease or condition. For immediately life-threatening diseases or conditions, one comment recommended that there be data from completed phase 1 testing at doses similar to those to be used in the treatment use and preliminary evidence suggesting possible effectiveness. The other comment recommended that the evidentiary standard that applies to treatment INDs for immediately life-threatening diseases or conditions apply to individual patient treatment use for such conditions (i.e., the available scientific evidence taken as 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). Such evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence. For individual patient treatment use for serious diseases or conditions, both comments recommended that there be evidence of safety and effectiveness from phase 3 trials, although in some circumstances compelling data from phase 2 trials may be sufficient (the same standard that applies to treatment INDs for serious diseases or conditions).

(Response) As discussed in the previous response, FDA believes that the suggested evidentiary requirements are too high a barrier to access for individual patient treatment use. Where the population exposed to an experimental therapy is small (in this case, a single individual), the amount of safety and effectiveness evidence needed to support the use is less than would be needed to allow exposure in the size population that might be treated under a treatment IND (often more than 1,000 patients).

In contrast to treatment INDs, which usually occur very late in a drug's development, individual patient treatment use may be sought quite early in a drug's development, and at any point during the development. Therefore, FDA also believes it is important to have flexibility in the evidentiary standards to permit it to respond appropriately to wide variations in the amount and nature of evidence that might be presented in support of an individual patient IND. Thus, FDA would prefer to avoid evidentiary standards pegged to data

from specific phases of drug development. FDA also believes a two-tiered evidentiary standard—one standard for serious diseases and conditions and a lower standard for immediately life-threatening diseases or conditions—is unnecessary for individual patient INDs because the relative seriousness of the disease or condition is an implicit component of the risk-benefit assessment for individual patient INDs, and the current evidentiary standard allows for considerable flexibility in the amount and nature of evidence needed to support an individual patient IND.

ii. *Intermediate-size patient population evidentiary requirements.*

Proposed § 312.315(b)(1) provides that, for expanded access under intermediate-size population INDs or protocols, FDA must determine that 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. Proposed § 312.315(b)(2) provides that FDA must determine that there is at least preliminary clinical evidence of effectiveness or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

(Comment 31) One comment recommended that FDA have different evidentiary standards for intermediate-size expanded access for serious diseases or conditions and intermediate-size expanded access for immediately life-threatening diseases or conditions. For INDs for immediately life-threatening diseases or conditions, the comment stated that there should be some preliminary evidence of clinical effectiveness. For INDs for serious diseases or conditions, the comment recommended that there be evidence of safety data from completed phase 1 testing at doses similar to those to be used in the treatment use and preliminary evidence suggesting possible effectiveness.

(Response) Because intermediate-size population INDs can occur earlier in drug development than treatment INDs and because there are three different intermediate-size population access scenarios (for a drug being developed, for a drug not being developed, and for an approved or related drug that is not available through marketing channels), FDA must have flexibility in the evidentiary standards to permit it to respond appropriately to variations in the amount and nature of evidence that might be presented in support of an intermediate-size population IND. Thus, FDA rejects the recommendation to have evidentiary standards pegged to data from a specific phase or phases of drug development. Again, because of the flexibility inherent in the evidentiary standards for intermediate-size patient population INDs, FDA does not believe it is necessary or useful to have different standards for serious diseases or conditions than for immediately life-threatening diseases or conditions.

iii. *Treatment IND or treatment protocol evidentiary standards.*

Proposed § 312.320(a)(3)(i) provides that for a treatment IND or treatment protocol for a serious disease or condition, there must be sufficient evidence of safety and effectiveness to support the use, which would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials. Section 312.320(a)(3)(ii) provides that, for an immediately life-threatening disease or condition, the available scientific evidence taken as whole must 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. Such evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

(Comment 32) Two comments were concerned that the proposed evidentiary standards for authorizing a treatment IND or treatment protocol were not sufficiently rigorous to protect patients. One comment recommended that, for treatment INDs or treatment protocols for serious diseases or conditions, only data from phase 3 clinical trials should be used to assess the potential benefits and risks of the drug. The comment also recommended that for a treatment IND or treatment protocol for immediately-life threatening diseases or conditions, only data from phase 3 clinical trials or compelling data from phase 2 trials should be considered. One comment objected to the proposed evidentiary standard for a treatment IND or a treatment protocol for an immediately life-threatening disease or condition because it would permit authorization of expanded access on the basis of clinical data more preliminary than phase 2 or 3 data.

Two comments were concerned that the evidentiary standards for a treatment IND were overly rigorous. One comment stated that requiring safety and effectiveness data from phase 3 or phase 2 studies limits the use of expanded access under treatment INDs to programs initiated very late in the drug development process. The comment noted that if phase 3 data are required, a treatment IND would typically only provide access to the investigational drug for a matter of months (i.e., the time between the initiation of a treatment IND and approval of a drug for marketing would be relatively short) and thus would not meet the needs of patients or substantially help small biotech companies. The comment argued that to be truly useful, either treatment INDs or treatment protocols need to be available based upon phase 1 data (at least in cases where appropriate because of the severity of the disease and a relatively benign safety profile for the drug), the intermediate population programs need to be able to go well above 100 patients (i.e., up to 500 or 1,000 patients), or there needs to a fourth category between the intermediate and the large populations programs. Another comment stated that the proposed rule's evidentiary requirements for a treatment IND raise the bar to a level effectively equivalent to the amount of data required to obtain marketing approval.

(Response) FDA believes that the proposed evidentiary requirements for authorizing treatment use under a treatment IND effectively balance making an investigational drug available to a substantial number of patients who might benefit from the drug with simultaneously protecting those patients from unreasonable risks associated with the drug. Our experience with this standard—spanning more than two decades—supports this assessment. Moreover, the evidentiary standards provide a certain amount of flexibility, particularly in the case of a treatment IND to treat an immediately life-threatening disease or condition, so that FDA can make investigational therapies available to substantial numbers of patients as early in the development process as is reasonably possible. FDA believes that more rigorous or inflexible standards would present an inappropriate barrier to obtaining a treatment IND in some cases. FDA also believes that relaxing these standards could potentially expose significant numbers of patients receiving investigational drugs under a treatment IND to unnecessary harm. A key tenet of drug development is to gradually increase the size of the population exposed to an investigational drug so as to be able to detect relatively low-frequency, serious toxicity as early as possible, and before very large numbers of patients have been exposed. This

principle applies with equal force to the use of investigational drugs for treatment use.

FDA wishes to emphasize that the evidentiary standards for a treatment IND are not the functional equivalent of the amount and type of data needed for marketing approval. The standards provide a degree of flexibility that enables FDA to authorize a treatment IND on the basis of data often well short of that needed to obtain marketing approval. FDA also does not believe that there needs to be a fourth category of treatment use in between an intermediate-size patient population IND and a treatment IND. As discussed elsewhere in this preamble, FDA intends that there be sufficient flexibility in the size of the population that might be treated under an intermediate-size population IND to enable treatment of as many patients as is supported by the available evidence of safety and effectiveness.

(Comment 33) One comment objected to the proposed rule's evidentiary standard for a treatment IND or treatment protocol for a serious disease, asserting that it was higher than both the statutory and current regulatory standards and thus further restricted access. The comment noted that section 561(c)(1) of the act only requires ''sufficient'' evidence of safety and effectiveness. The comment also noted that § 312.34(a) of FDA's current regulations allows drugs to be made available during Phase 2 ''in appropriate circumstances.'' The comment pointed out that § 312.320(a)(3) of the proposed rule provides that the evidence needed for a treatment IND or treatment protocol would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials. The comment stated that, under the proposed rule, phase 2 trials would have to be completed, not merely ongoing, thus raising the standard for expanded access for treatment INDs and treatment protocols. The comment also stated that FDA has also raised the standard because the data would have to be ''compelling'' The comment suggested that because of design limitations, many phase 2 trials could be considered not compelling. The comment suggested that the proposed rule may result in treatment INDs and treatment protocols being less frequent than under FDA's current regulations. The comment stated that the final rule should use the language in § 312.34(a) of FDA's current regulation instead of the new proposed language in § 312.320(a)(3).

(Response) FDA does not agree that the proposed rule articulates a more stringent evidentiary standard for a treatment IND or treatment protocol for a serious disease or condition than was contained in FDA's previous regulation in § 312.34. Section 312.34 was not specific about the nature of the evidence that would be needed to support a treatment IND for a serious, as opposed to immediately life-threatening, disease or condition. Rather, the general discussion in § 312.34(a) suggested an earliest point in time at which such a treatment IND could be allowed to proceed (''in appropriate circumstances, a drug may be made available during phase 2''). FDA has always interpreted that requirement to mean that a treatment IND for a serious, but non-life-threatening, disease or condition would have to be supported by some phase 2 data (controlled trial data on the disease of interest), but that phase 2 did not have to be completed. Or, to put it another way, at least one phase 2 trial would have to have been completed, but others could be ongoing. FDA has never interpreted this provision to mean that a treatment IND for a serious disease or condition could proceed without any phase 2 data. Therefore, FDA believes that stating in this final rule that data needed to support for a treatment IND for a serious disease or condition could consist of compelling data from phase 2 trials is consistent with the statement that a drug may be made available for treatment use during phase 2.

FDA also does not agree that characterizing the phase 2 data needed to support an treatment IND for a serious disease or condition as compelling raises the bar compared to that in § 312.34. That provision made clear that a treatment IND for a serious disease or condition would ordinarily not be permitted until some point during phase 3 or at a point when all controlled trials were completed. To permit a treatment IND to proceed during phase 2 was plainly intended to be an exceptional circumstance. FDA does not believe that ambiguous, inconclusive, or marginally statistically significant phase 2 data would justify the exceptional circumstance of permitting a treatment IND for a serious disease or condition based on phase 2 data. Therefore, FDA believes it is reasonable to characterize the phase 2 data needed as compelling. FDA also disputes the contention that the design of a typical phase 2 could not yield compelling data.

For the reasons stated previously, FDA also does not agree that there will be fewer treatment INDs and treatment protocols for serious disease or conditions because of the way FDA articulated the evidentiary standard for a treatment IND for a serious disease or condition in § 312.320(a)(3) of this final rule.

c. *Non-interference with drug development.*

Proposed § 312.305(a)(3) states that, for all expanded access uses, 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. For a treatment IND, proposed § 312.320(a)(1) also requires FDA to determine that the drug is being investigated in a controlled trial under an IND designed to support a marketing application for the expanded access use, or that all clinical trials of the drug have been completed, and that the sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence.

(Comment 34) Several comments expressed concern that the proposed rule would seriously impede the initiation and completion of clinical trials and drug development generally. A number of comments stated that, given a choice, patients would be more likely to try to obtain an investigational drug under an expanded access IND or protocol than to participate in a clinical trial of the drug (and, for example, risk randomization to another treatment). Two comments argued that making drugs more widely available under expanded access INDs would have a domino effect in which decreased enrollment in clinical trials would lead to less rigorous trial protocols, less useful data, and ultimately decrease the amount of safety and efficacy information on approved drugs.

(Response) FDA believes that the provisions in the proposed rule requiring that expanded access programs not impede clinical development of the investigational drug that is being made available for treatment use are adequate to mitigate the impact of expanded access on clinical development. In the case of individual patient expanded access INDs, an individual patient is not eligible to obtain access under an individual patient expanded access IND if the patient can participate in a clinical trial of the drug or obtain the drug under a larger access IND. In the case of an intermediate-size patient population IND for a drug being developed, the intent of such an IND is to make a drug available to patients who cannot enroll in a clinical trial; therefore, there would be no effect on

drug development. The other two intermediate-size patient population IND scenarios do not involve drugs that are being actively developed. In the case of a treatment IND, in FDA's experience, sponsors usually do not initiate treatment INDs until the clinical studies needed to support approval are completed or fully enrolled. However, it is possible to authorize a treatment IND before clinical trials needed to support marketing approval are fully enrolled. In such cases, it would be important for FDA to closely monitor the implications of the treatment IND on the rate of accrual of subjects into the clinical trial and other clinical development milestones.

(Comment 35) Some comments asked FDA to specify how it will determine that making an investigational drug available for treatment use will not interfere with clinical trials or drug development generally. One comment stated that the expanded access rule should contain more explicit criteria for determining that expanded access does not detrimentally affect clinical trials.

(Response) FDA believes the criteria are sufficiently explicit to enable FDA to meaningfully assess the impact of an expanded access program on development, and also provide FDA the flexibility to ask for varied types of assurances that access will not impede development, depending on the particular situation. For example, before authorizing a treatment IND for an investigational drug for which clinical trials are ongoing, FDA could seek specific assurances from the sponsor that the treatment IND would not interfere with accrual of patients in the clinical trial. FDA would likely request that the sponsor submit a comprehensive investigational plan with a timetable and milestones to its IND (if it had not done so already), so that FDA could periodically assess whether the treatment IND is having an effect on accrual or other parameters related to the pace of clinical development. If FDA determines that the treatment IND is slowing the pace of drug development or the sponsor is not actively pursuing marketing approval with due diligence, FDA can place the treatment IND on clinical hold. It is also worth noting that it is likely not in the sponsor's interest to delay development because it delays marketing approval and commercial sale of the drug. Therefore, sponsors are unlikely to provide expanded access in situations in which drug development would be impeded.

(Comment 36) One comment raised two objections to the provisions of the proposed rule relating to FDA's finding of noninterference with clinical trials. First, the comment asserted that with regard to ''widespread'' treatment INDs, the criteria imposed by § 312.305(a)(3) were broader than the authority in section 561(c)(5) of the act and impermissibly permitted FDA to refuse to approve requests for expanded access for reasons other than the proposed treatment use's effect on enrollment of clinical trials. The comment referred to the proposed rule's criterion that providing expanded access 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 (§ 312.305(a)(3)), and urged that the final rule use statutory language rather than that used in the proposed rule.

Second, in a section related to individual patient access to investigational drugs, the comment argued that FDA lacks statutory authority for the proposed rule's product development criteria. Specifically, the comment noted that in the case of the single patient IND, Congress gave FDA authority to authorize a single patient IND if 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.'' The comment objected to the phrase ''or otherwise compromise the potential development of the expanded access use'' in proposed § 312.305(a)(3).

(Response) FDA disagrees with the comment. Regarding the first assertion, that FDA has applied a more stringent provision on noninterference with clinical trials than is called for in the section of the act relating to expanded access for treatment INDs, FDA disagrees that the language in § 312.305(a)(3) impermissibly expands the grounds on which FDA may reject a proposed treatment IND. Section 312.305(a)(3) provides that, for all types of expanded access, 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.'' While admittedly much of this language matches terminology found in section 561(b)(3) of the act, which applies to individual patient treatment access and access by small groups of patients, it also generally describes the type of finding that FDA must make under section 561(c) of the act, which applies to treatment INDs.

The comment seems to be based on the mistaken assumption that under section 561(c)(5), the only determination that FDA must make is whether an investigational drug will ''interfere with the enrollment of patients in ongoing clinical investigations.'' However, under section 561(c)(4) of the act, FDA also must determine that the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence. Such active pursuit of marketing approval with due diligence implicitly includes a determination that the treatment use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval for the investigational drug, which is why FDA included those particular terms in the regulation. FDA could have simply restated the statutory language in the regulation, but since the regulation implementing the statute is aimed, in part, at shedding light on how FDA interprets the statute, the agency believes the proposed language provides more helpful guidance than merely restating the terms from the statute without more.

Regarding the argument that the statutory language does not allow FDA to require a determination that provision of the investigational drug for treatment use will not ''otherwise compromise the potential development of the expanded access use,'' FDA disagrees for reasons similar to those explained previously. In § 312.305(a)(3), which is applicable to all treatment uses, FDA included this term to generically address other criteria required under different sections of section 561, including section 561(b)(4), (c)(3) and (c)(4). FDA does not intend to use this catchall language as a limitless means to deny treatment use of investigational drugs. Rather, the intent is to endow the implementing regulation with sufficient flexibility to allow FDA to address situations where potential development of the treatment use would be compromised by a particular treatment proposal, for instance, where a proposed use would usurp the entire population of patients who might be studied in controlled clinical trials. This particular regulatory language is motivated by one of the core notions underlying the act—namely, recognition that the best form of access to a drug is full marketing approval.

d. *Impeding development of related drug products.*

(Comment 37) One comment expressed concern about the potential for expanded access to impede development of other drug products being developed for the same or a similar indication as the investigational drug being sought for treatment use. The comment recommended that requests for expanded access include a statement that the public list of clinical trials has been reviewed and the patient is not eligible or is otherwise unable to participate (e.g., because of distance) in available studies. Another comment cited an example of a situation in which enrollment in a clinical trial had decreased following accelerated approval of drugs for the same use under subpart H.

(Response) FDA acknowledges the possibility that a large expanded access IND for a given product could impede concurrent development of other products for the same or a similar indication because trials for those products would be competing with the access program for the same patient population. However, requiring that the sponsor of a proposed expanded access IND demonstrate that the expanded access use will not impede development of not only its drug but of any other drug in clinical development for the same use would seem to present an unreasonable obstacle to access. For example, it is not clear how a sponsor would be able to demonstrate no effect on the development of a related therapy absent some proprietary knowledge about the development plans of the related therapy. Because there is no obvious way that the sponsor of a proposed expanded access plan could provide proof that the plan would have no effect on another company's development program, such determinations would have to rely primarily on conjecture. For that reason, such a requirement would likely be applied inconsistently and, as a result, could unnecessarily deny access to patients in desperate circumstances. FDA also does not believe that the sponsor of a competing therapy under development should have the ability to cause an ongoing expanded access IND to be put on hold, as would be the case if FDA were to require a sponsor to show that the expanded access IND would not interfere with another company's development program, and the other company were to demonstrate such interference.

FDA also acknowledges the potential for marketing approval of a related product for the same or a similar indication to impede development of drugs for that indication. However, denial or delay of marketing approval because such approval would impede development of a competing product is clearly not in the best interests of the public health because it would deny patients access to a proven effective therapy. There do not appear to be any other regulatory options that could mitigate the impact on development or approval of a related drug.

(Comment 38) One comment stated that expanded access would be more likely to impede development in the early stages of drug development and the development of orphan drugs.

(Response) FDA agrees that expanded access has greater potential to impede development when a drug is available under an access IND early in development, particularly if the access is widespread. For this reason, FDA must determine that a patient seeking access to an investigational drug under an individual patient expanded access IND cannot participate in a clinical trial of the drug or obtain the drug under a larger expanded access IND or protocol (§ 312.310(a)(2)). Similarly, an intermediate-size patient population IND intended for a drug being developed is intended to make the drug available only to those who cannot participate in a clinical trial of the drug (§ 312.315(a)(2)). FDA believes that these provisions should minimize the potential for these types of expanded access INDs to impede drug development.

FDA also agrees that expanded access for drugs for orphan diseases has added potential to impede drug development due to the relatively smaller population from which clinical trial subjects can be drawn. FDA will carefully evaluate any expanded access submission for an orphan drug to ensure that the data needed to support approval of the orphan product will not be compromised by the expanded access use.

(Comment 39) One comment maintained that expanded access would be more likely to decrease clinical trial participation in more rural communities and that even if clinical trials were still able to accrue adequate numbers of subjects, the demographics of participation in clinical trials could be skewed toward more urban populations.

(Response) FDA disagrees. The agency believes that expanded access programs would have a neutral effect on clinical trial enrollment in rural areas because the same criteria apply in rural and more urban settings. Admittedly, patients in rural areas are more likely to be unable to enroll in a clinical trial because of geographical constraints, but providing access to those patients would have no effect on clinical trial enrollment or the demographics of the trial because those patients would not have been able to participate in the clinical trial because of geographical constraints.

(Comment 40) One comment asked whether there have ever been any investigational drugs made available through a treatment IND that were not subsequently approved for marketing.

(Response) Yes, there have been drugs that were made available under a treatment IND that did not obtain marketing approval. However, for these drugs, the failure to obtain marketing approved was not due to the treatment IND interfering with the clinical development program.

4. Expanded Access IND Submission Requirements

Section 312.305(b) describes the content of an IND submission or protocol amendment for expanded access. In the event that a licensed physician, as opposed to a commercial sponsor, is making the IND submission, it provides that the licensed physician may provide some of the required information by obtaining a right of reference to the content of the existing IND. Proposed § 312.305(b)(2) requires that an expanded access submission include:

- 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 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 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 the 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.

(Comment 41) One comment asked whether the proposed submission requirements for expanded access apply to both sponsors and sponsor-investigators. The comment also asked whether some of the required information could be incorporated into the protocol rather than provided as separate documents in the IND submission, including the rationale for the intended use of the investigational drug with a list of generally available treatment options and an explanation as to why they are not preferable, criteria for patient selection, a description of the patient's disease or condition (including recent medical history), and previous treatment use (for an individual patient submission).

(Response) The submission requirements are sponsor requirements and thus are intended to apply to both sponsors and sponsor-investigators. The listing of general submission requirements in § 312.305 is not intended to convey the impression that each element of the submission be contained in a separate document. As the comment points out, certain required submission elements are topics that are appropriate for inclusion in a single protocol. Other elements, such as pharmacology/toxicology and chemistry, manufacturing, and controls (CMC), may more typically be found in separate documentation. FDA's primary concern is not with the number of individual documents submitted, but that the required elements be submitted in a form that makes the information readily accessible and leaves no question that the submission contains the necessary information.

a. *Submissions for individual patient expanded access.*

(Comment 42) Several comments expressed concern that individual physicians would not be able to comply with the submission requirements for expanded access for an individual patient. The comments stated that most individual physicians will not have access to the drug's CMC or pharmacology and toxicology information. One comment stated that FDA sometimes raises difficult manufacturing, pharmacology, toxicology, pharmacokinetic, clinical, and statistical issues, and these issues sometimes result in physicians withdrawing expanded access requests. One comment opined that the submission requirements for individual patient expanded access may have the unintended effect of rendering the proposed rule relatively meaningless for the vast majority of the patient population if there is no existing IND or if the sponsor of the IND will not provide the information needed to support the expanded access request. The comment added that physicians may not know whether an IND exists or how to find that out.

(Response) In FDA's experience, the vast majority of expanded access INDs for individual patients are for investigational drugs in development, and submissions are made on behalf of patients unable to participate in clinical trials. In these situations, the submission requirements are not onerous. The commercial sponsor that is developing the drug may make a submission for individual patient access as a protocol amendment to its existing IND, in which case the licensed physician must only provide the sponsor with the required information about the individual patient. Alternatively, the commercial sponsor may elect only to provide the drug and require the physician to submit his or her own IND. In this situation, the commercial sponsor routinely permits the licensed physician to refer to any needed information in its existing IND, so, again, the licensed physician usually only has to provide the relevant information about the physician's patient. In each of these scenarios, the information the licensed physician must provide is ordinarily readily available in patient medical records.

In rare circumstances, a licensed physician may seek to obtain access for an individual patient to an investigational drug not being developed. If a drug is not being developed and has never been the subject of an IND, the submission requirements become more complex. There may be other sources that could provide some of the necessary information (e.g., materials data sheets) to minimize the burden on the physician to an extent. However, FDA must have reasonable assurances about the integrity and safety of the product, so the IND submission will require a significant amount of information concerning the manufacturing of the product and its pharmacology/toxicology profile for FDA to permit use of the drug for the expanded access use. FDA's guidance for industry entitled ''Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products,'' provides some insight into the amount and nature of the information that would be required in these situations. However, because these situations are rare, FDA does not believe that the submission requirements present an obstacle to the vast majority of patients who seek to obtain investigational drugs for treatment use under the expanded access regulations, and the agency is convinced that the requirements are an essential component of human subject protection.

(Comment 43) Two comments expressed the view that many parts of Form FDA 1571 may not be appropriate for use by an individual doctor for expanded access purposes. The comments asked that FDA provide a streamlined version of Form FDA 1571 that is specific to individual patient expanded access. One comment recommended that FDA encourage or require standard nomenclature on expanded access submissions so such submissions could be readily distinguished from non-expanded access submissions. The comment stated that for a treatment IND, the sponsor should make two entries to Item 11 of the 1571: Check the box for INITIAL INVESTIGATIONAL NEW DRUG APPLICATION, and enter ''OTHER: Treatment IND'' on the blank line. For an expanded access protocol under an existing IND, the comment suggested that the sponsor also make two entries to Item 11 of the 1571: Check the box for PROTOCOL AMENDMENT: NEW PROTOCOL, and enter ''OTHER: New Protocol for Expanded Access'' on the blank line.

(Response) FDA agrees that it is desirable to be able to readily distinguish expanded access submissions from non-expanded access submissions. FDA does not believe, however, that a new form specific to expanded access is necessary to accomplish this task. FDA believes that instructions for filling out Form FDA 1571 for expanded access purposes and standardized nomenclature will suffice, helping sponsors to complete the form appropriately and helping FDA to readily identify expanded access submissions. FDA may develop guidance to provide instructions for completing Form FDA 1571 and sample completed forms for each type of expanded access.

b. *Intermediate-size population IND submission requirements.*

In addition to the general submission requirements, proposed § 312.315(c) describes requirements specifically applicable to submissions for intermediate-size population expanded access INDs. Proposed § 312.315(c)(1) requires that the submission state whether the drug is being developed or not being developed. For a drug not being developed, proposed § 312.315(c)(2) requires that the sponsor

explain why the drug cannot currently be developed and under what circumstances the drug could be developed.

(Comment 44) One comment requested that the requirements in proposed § 312.315(c)(2) and (c)(3) be removed because they do not seem relevant to the determination of whether access is appropriate for the intermediate-size group.

(Response) FDA disagrees. One of FDA's primary concerns with making investigational drugs available for treatment use is the potential for treatment use to prevent the development of information necessary to demonstrate safety and effectiveness by usurping a population that could have been enrolled in a clinical trial. FDA believes that section 561 of the act contemplates that expanded access to investigational drugs is not appropriate when that access prevents the development of important safety and effectiveness information that could have been developed if there were no expanded access. Requiring a sponsor to explain why no development is possible when a drug is not being developed at all, or why a clinical trial cannot be conducted to study the treatment use when a drug is being developed for a use other than the treatment use, squarely addresses FDA's concerns.

(Comment 45) One comment recommended that before concluding that a patient or patient population is ineligible to enroll in a clinical trial for purposes of this requirement, the investigator, sponsor, and FDA should carefully consider whether the clinical study protocol could be amended to include the patient population contemplated for treatment use without affecting the safety of the subjects or the integrity of the study.

(Response) FDA agrees that the optimal solution would be to somehow incorporate the potential intermediate-size treatment use population in an ongoing clinical trial by modifying the inclusion/exclusion criteria while not compromising safety or study integrity, or to enroll that population in a new study. FDA expects that sponsors would have explored all reasonably possible avenues for studying the patient population before seeking an expanded access IND for treatment use in that population and that the submission would explain why those avenues were foreclosed. By requiring the sponsor to explain why the population for which an intermediate-size expanded access IND is sought is not eligible to be enrolled in a clinical trial, FDA is encouraging, at least implicitly, this thought process.

(Comment 46) One comment asked where in the electronic common technical document (eCTD) to include the submission information that is specific to intermediate-size patient population INDs.

(Response) The eCTD does not distinguish INDs of different-size patient populations. The information specific to an intermediate-size patient population IND would go in the same location as one for a treatment IND or a single patient treatment IND.

5. Safeguards for Expanded Access

Proposed § 312.305(c) explains how the responsibilities of sponsors and investigators set forth in subpart D (Responsibilities of Sponsors and Investigators) of part 312 apply to expanded access INDs. 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 is considered an investigator for purposes of part 312 and, therefore, must comply with the responsibilities for investigators set forth in subpart D to the extent they are applicable to the expanded access use. Proposed § 312.305(c)(2) states that an individual or entity that submits an expanded access IND or protocol 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 to the extent they are applicable to the expanded access use. Proposed § 312.305(c)(3) states that a licensed physician under whose direction an investigational drug is administered or dispensed, and who submits an expanded access IND, is considered a sponsor-investigator and must comply with the responsibilities of sponsors and investigators in subpart D to the extent applicable to the expanded access use.

Proposed § 312.305(c)(4) provides that for all expanded access INDs, investigators are responsible for reporting adverse events to the sponsor, ensuring that the informed consent requirements in part 50 (21 CFR part 50) are met, ensuring that an 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.

a. *''Person'' v. ''individual or entity.''*

(Comment 47) One comment recommended that proposed § 312.305(c)(2) (which states that an individual or entity that submits an expanded access IND or protocol under subpart I is considered a sponsor for purposes of part 312) use the term ''person'' rather than ''individual or entity.'' The comment pointed out that ''person'' is defined in the act and includes ''individual, partnership, corporation, and association.''

(Response) The term ''individual or entity'' is based on, and intended to be shorthand for, language in the definition of a ''sponsor'' in § 312.3(b) that states that a sponsor may be an ''individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.'' Because the term relates to an existing definition of sponsor in the IND regulations, and because in FDA's experience that definition has been clear and effective in describing who or what may be considered a sponsor for purposes of part 312, FDA prefers to retain the language in the proposed rule.

b. *Sponsor and investigator responsibilities.*

Proposed § 312.305(c)(5) provides that for all expanded access INDs, 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 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.

Proposed § 312.310(c)(3) further provides that FDA may also require sponsors to monitor an individual patient expanded access use if the use is for an extended duration. Proposed § 312.315(d)(2) states that the sponsor is responsible for monitoring the intermediate-size population expanded access protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators. Proposed § 312.320(c) states that the sponsor is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

(Comment 48) One comment stated that making physicians investigators for purposes of part 312 will be daunting and extremely time-consuming and that the typical gastroenterologist not affiliated with a large teaching or

research hospital will not be able to satisfy these requirements.

(Response) FDA disagrees. For a licensed physician providing access under an individual patient IND, the responsibilities of an investigator closely parallel those necessary for providing routine patient care. For example, the information about a patient that a physician is required to submit to obtain an IND would usually be derived from the patient history and progress notes. In most cases, the remaining IND submission requirements would be largely satisfied by obtaining a right of reference to an IND maintained by a commercial sponsor, which is usually easily obtained. Any required monitoring of the course of treatment with the investigational drug would be similar to the type of monitoring provided as part of routine patient care. The patient outcomes information required to be submitted after treatment with the investigational drug would closely parallel the content of a typical discharge summary. Therefore, FDA believes that, in most cases, the IND obligations imposed on licensed physicians by this final rule would not be significantly more burdensome than the recordkeeping and patient evaluation required in the course of routine clinical care of a patient.

c. *Adverse event reporting.*

(Comment 49) One comment from a pharmaceutical company asked whether licensed physicians who obtain an investigational drug for expanded access use under their own INDs are required to report adverse events to both the pharmaceutical company supplying the drug and FDA. The comment maintained that it is important for the pharmaceutical company developing the drug to be informed of any adverse events observed in expanded access use.

(Response) Because the physician IND holder is both investigator and sponsor in this scenario, the physician is not required by the IND regulations to report adverse events to the drug manufacturer who provided the drug to the physician. The regulations require only that adverse events observed by the investigator (the physician) be reported to the sponsor, who is also the physician in this scenario. The physician, in his or her capacity as a sponsor, is required to report adverse events to FDA and other investigators (not relevant for individual patient access), including reporting of serious and unexpected adverse events in an expedited manner. However, although there is no regulatory provision that would require physicians to report adverse events to the drug manufacturer/supplier, FDA sees no obstacle to the drug manufacturer/supplier requiring, as a condition of making the drug available to the physician, that the physician agree to provide the drug manufacturer/supplier with copies of all adverse event reports provided to FDA.

In addition, in the preamble to the proposed rule (71 FR 75147 at 75153), FDA expressed a strong preference for having commercial sponsors make investigational drugs available for treatment use under amendments to their INDs rather than requiring physicians to obtain their own INDs. In that scenario, the physician is required to report adverse events to the commercial sponsor under § 312.64.

(Comment 50) One comment suggested that adverse events for individual patient INDs should be addressed in a separate section of the NDA or biologics license application (BLA) instead of being included in the integrated summary of safety. The comment stated that this approach would help alleviate manufacturers' concerns that allowing individual patient INDs (typically involving especially sick patients) would exaggerate adverse events for the broader population.

(Response) FDA does not believe it is necessary or helpful to exclude adverse events information from individual patient INDs from the integrated summary of safety (ISS) in an NDA. The ISS is intended to evaluate adverse events information from the total population exposed to a drug. The analysis takes into account the relative strength of the data and the characteristics of subjects who experienced adverse events that may bear on causality. For example, data indicating that an adverse event occurred in multiple subjects in the drug treatment arm of a controlled trial is much more reliable than adverse events information from uncontrolled, individual patient expanded access exposures in patients who are very ill. The implication that inclusion of adverse events information from individual patient expanded access exposures over-emphasizes negative safety information is unfounded and plainly inconsistent with the methodology FDA uses to analyze drug safety.

(Comment 51) Two comments stated that, for investigational new molecular entities, adverse event reporting for expanded access use should be limited to serious adverse events and deaths unless there are specific adverse events that are identified a priori because they are related to an identified safety concern that may affect the risk-benefit assessment.

(Response) FDA strongly disagrees. FDA believes that all adverse events identified in expanded access uses should be reported to FDA in the manner described in §§ 312.32 and 312.33. FDA's primary interest is the expedited reporting of serious and unexpected events as required by § 312.32(c). Data collected on nonserious or expected events from expanded access use, in particular from exposure of an individual patient or small number of patients to a drug, is not as useful as data collected from controlled trials that may identity differences in event rates across treatment groups (e.g., control group, across different doses). Nonetheless, information from expanded access exposures on these types of adverse events can still contribute to the safety assessment of a new molecular entity (e.g., corroborate observations in other settings). In general, FDA believes it is important that a drug's safety assessment consider adverse events observed in the entire population exposed to a drug.

(Comment 52) One comment inquired about how to report adverse events for approved drugs made available under an expanded access IND.

(Response) For an approved drug made available under an expanded access IND (e.g., in a circumstance in which an approved drug is subject to a restricted distribution agreement that limits prescribing to a certain disease or condition, and a patient is seeking access to the drug for another use), adverse events must be reported to FDA under the IND in accordance with § 312.305(c)(5).

d. *Obtaining Informed Consent for Expanded Access Use.*

(Comment 53) Many comments from individual consumers stated that it is particularly important for patients receiving investigational drugs in expanded access programs to receive full disclosure of the risks, and to fully understand the risks, associated with the investigational therapy. Two comments were very concerned that patients receiving investigational drugs for treatment use not be misled about the likelihood that the treatment will be beneficial. One comment stated that many patients are led to believe that access to an investigational intervention is their best hope, but often it is a false hope. Another comment stated that patients with immediately life-threatening conditions are extremely vulnerable and may not fully comprehend the information they are provided about a drug by health care

practitioners. Another comment recommended that FDA provide guidance on how to obtain informed consent from patients who are candidates to receive an investigational drug for treatment use.

(Response) FDA agrees that patients who are candidates to receive investigational drugs under expanded access programs, because they have serious or immediately life-threatening diseases or conditions and have exhausted other treatment options, are a particularly vulnerable population. Therefore, they should be afforded a rigorous informed consent process that effectively communicates the risks and potential benefits of any investigational therapy to be used for treatment use in a way that does not raise false expectations about a positive outcome from treatment and makes clear what is unknown about the drug. Because of the vulnerable nature of expanded access patients, FDA encourages submission of informed consent documents intended to be used for expanded access programs to FDA for review. FDA will also consider whether guidance on how to obtain informed consent from such patients is needed.

(Comment 54) One comment stated that because expanded access does not technically involve ''research'' or a ''clinical investigation,'' the requirements and principles for obtaining the informed consent of subjects participating in clinical investigations in part 50 may not adequately address the range of issues that would arise in obtaining the informed consent of patients receiving investigational drugs under expanded access programs. The comment recommended that the expanded access regulations include requirements concerning the specific information that must be included in informed consent documents for expanded access programs.

(Response) Again, because of the vulnerable nature of the typical patient or population to receive an investigational drug under an expanded access program, FDA agrees that patients in expanded access programs should be afforded a rigorous informed consent process tailored to the unique issues that arise in the expanded access context. FDA does not believe, however, that it is necessary to add specific informed consent requirements to the expanded access regulations or to amend the informed consent regulations to incorporate specific requirements for expanded access. FDA believes that existing informed consent regulations adequately address the range of issues relevant to informed consent for expanded access problems, in particular issues concerning informed consent in vulnerable populations (see, e.g., parts 50 and 56).

(Comment 55) One comment stated that informed consent documents must reflect that patients cannot expect to personally benefit from the drug, but that the knowledge gained from the experiment will help other patients in the future.

(Response) FDA disagrees. The comment seems to misunderstand the overarching purpose of expanded access—to make investigational drugs available for treatment purposes to patients with serious or immediately life-threatening diseases or conditions and with no other treatment options because the investigational drugs could conceivably benefit these patients—not to systematically investigate the use of the drug for the disease or condition. Treatment use under an expanded access mechanism, in contrast to evaluation of an investigational drug in a clinical trial, is not intended primarily to develop data that could be used to benefit future patients. However, as FDA made clear in response to comment 54, patients receiving investigational drugs for treatment use should be afforded a rigorous informed consent process that is careful not to overstate the expected benefits of the investigational drug and is otherwise cognizant of the inherent vulnerabilities and information needs of patients seeking access to investigational drugs for treatment use.

(Comment 56) One comment recommended that before an IRB can be allowed to review expanded access programs, FDA should require the IRB to establish special criteria to ensure that physicians have discussed all treatment options with patients as part of the informed consent process and that patients and their families fully understand the experimental and investigational nature of a drug or other therapy, the types and degrees of unknown risks, and the potential positive and negative health outcomes.

(Response) Because patients seeking access to investigational drugs for treatment use are a particularly vulnerable group and the intent is treatment of a disease or condition, as opposed to a clinical investigation of the use, FDA believes it is important for IRB review to be particularly sensitive to the unique issues raised by use of investigational drugs in expanded access programs. FDA agrees that it would be useful for an IRB that is likely to review expanded access use to be familiar with the nature of expanded access protocols, the rules and processes related to obtaining access, and the particular concerns related to obtaining informed consent from patients receiving investigational drugs for treatment use. FDA does not believe, however, that it is necessary to require in regulation that IRBs have special processes and procedures for reviewing expanded access protocols. Existing regulations already require IRBs to consider the vulnerable nature of the population that will receive an investigational drug and to ensure that risks are minimized (which would necessarily involve some consideration of whether there are any lower-risk treatment options), and § 50.25(a)(4) requires that an informed consent disclose appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(Comment 57) One comment stated that a patient receiving expanded access should be competent to give informed consent.

(Response) While FDA agrees that valid informed consent is a necessary prerequisite to receiving an investigational product in an expanded access setting, FDA does not agree that access to investigational drugs under expanded access programs should be limited to only those who are competent to give their own informed consent, if that is the intended implication of the comment. FDA's regulations concerning protection of human subjects informed consent (part 50) recognize that a subject may not be competent to give informed consent and that valid informed consent may be given by the subject's legally authorized representative. Section 50.20 defines ''legally authorized representative'' as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. The same definition should apply to treatment with an investigational product under an expanded access program.

(Comment 58) One comment recommended requiring that IRBs establish criteria for the length and readability of informed consent documents.

(Response) This comment is beyond the scope of this rule. The rule does not address the requirements on IRBs and the comment raises a concern broader than expanded access.

e. *IRB review of expanded access use.*

(Comment 59) Some comments were concerned that the requirement for IRB review was a potential obstacle to making investigational drugs available

for treatment use under expanded access INDs, particularly for individual patient INDs. One comment maintained that the IRB review process is slow, tedious, cumbersome, and requires too much documentation, and that physicians are not familiar with the IRB process. The comment suggested that some type of centralized IRB may be needed for small- to medium-sized access programs. Another comment noted that in academic research settings, there is intensive IRB approval and oversight, and recommended that FDA explore standardizing expanded access program protocols so that some of the administrative work, in particular IRB submissions, can be lessened. One comment recommended that, for individual patient expanded access INDs, FDA reduce or limit the scope of the requirement for IRB review because of the time, difficulty, and, in some cases, the expense (e.g., when a commercial IRB must be used) of obtaining IRB review. The comment recommended that FDA permit review by a subset of the full IRB or waive IRB review if a drug has completed phase 1 safety testing (see response to comment 60 for discussion of why waiver of IRB review is not a viable option).

(Response) FDA recognizes that there are circumstances in which IRB review for an expanded access use, particularly an individual patient use, may be difficult to obtain because an institution's IRB cannot or will not provide a timely review or because the hospital or other clinical setting does not have an affiliated IRB. FDA recommends that IRBs affiliated with institutions that are likely to have patients seeking access to investigational drugs for treatment use under individual patient access INDs consider establishing processes or procedures to facilitate timely IRB review of these INDs. In addition, use of centralized IRB review and other cooperative arrangements could facilitate IRB review at these institutions as well as in settings that are not affiliated with IRBs. FDA fully supports centralized IRB review under appropriate circumstances and encourages sponsors to help make this option available where possible. FDA believes these mechanisms could ease the burdens associated with obtaining IRB review of individual patient INDs and limit the need to rely on commercial INDs. Therefore, FDA is not persuaded that obtaining IRB review is an excessive burden and potential obstacle to obtaining access to investigational therapies under expanded access INDs.

FDA does not believe that current regulations provide authority for IRB review of individual patient expanded access INDs by less than the full IRB. The IRB regulations provide for expedited review—under which an IRB review may be done by only one or a small number of IRB members—of new INDs or protocols only under minimal risk situations (§ 56.110(b)). Use of an investigational drug for treatment purposes would not be considered minimal risk and, therefore, does not meet the criteria for expedited review. Revising the IRB regulations to provide for a more limited IRB review of individual patient expanded access INDs involves significant human subject protections issues that were not considered in this rulemaking and, therefore, such revision is beyond the scope of this rulemaking.

(Comment 60) One comment stated that FDA should eliminate the proposed requirements for IRB review and obtaining informed consent for individual patient treatment use INDs. The comment maintained that the use of an investigational drug for treatment use is not part of a clinical investigation and therefore beyond the intended scope of parts 56 and 50. The comment further argued that these safeguards are unnecessary for individual patient treatment use because there is an established physician-patient relationship and, therefore, individual patient treatment use is analogous to the physician-patient relationship in a typical clinical setting in which such safeguards are unnecessary.

(Response) FDA does not agree that it lacks legal authority to require IRB review and informed consent for individual patient expanded access use or any other expanded access use. Expanded access use involves administration of unapproved products that have not yet been shown to be safe and effective, and raises sufficiently similar concerns to clinical research that informed consent and IRB review are warranted. Moreover, section 561 of the act contains numerous references to ''conditions determined by the Secretary'' and to protocol compliance with ''regulations promulgated under section 505(i)'' (which include informed consent and IRB regulations), indicating that Congress intended FDA to require conditions such as informed consent and IRB review, consistent with FDA's long-standing practice regarding treatment use with investigational products. In addition, FDA strongly believes that recipients of investigational products under any type of expanded access IND should be afforded the same human subject protections provided clinical trial participants by the IRB review process. FDA equally strongly believes that all patients considering treatment with an investigational therapy under an expanded access IND should be fully informed about the risks and potential benefits of the experimental therapy, including disclosure that safety and effectiveness have not been established, and give their informed consent prior to being treated with an investigational therapy. Patients seeking access to investigational therapies under expanded access programs often are in somewhat dire clinical circumstances and thus are a particularly vulnerable population. Therefore, such patients are, arguably, even more in need of the human subjects protections provided by IRB review and informed consent than many clinical trial participants.

(Comment 61) One comment recommended the elimination of the requirements for prior IRB review and approval in accordance with part 56 and the requirement for written informed consent in accordance with part 50 for individual patient expanded access use (but recommended the retention of these requirements for intermediate-size population and treatment INDs). The comment argued that use of an investigational drug for the emergency treatment of individual patients is not part of a clinical investigation and thus is not consistent with the scope of parts 50 and 56. The comment stated that eliminating the requirement would solve problems and avoid confusion related to differences between FDA's IRB regulations and IRB regulations applicable to Federal agencies and grantees under 45 CFR part 46 (the so-called ''Common Rule''). Current FDA regulations (§§ 56.104(c) and 50.23) allow for the emergency use of an investigational drug without prospective IRB review and approval and a waiver of the requirement for prospective informed consent of the involved patient-subject, but the Common Rule specifies that all research involving human subjects must be prospectively reviewed and approved by a convened IRB committee (with the exception of certain minimal risk categories of research, which do not include expanded access use). The comment maintained that the Common Rule applies unless the requested emergency use is considered ''treatment'' rather than ''research'' and thus is not subject to prior IRB review and approval under the Common Rule. The comment maintained that prior FDA review of individual patient expanded access would suffice to ensure patient safety

and compliance with the protocol and applicable regulations.

(Response) Although FDA agrees that it is accurate to characterize the use as ''expanded access'' or ''treatment use'' rather than a ''clinical investigation'' of the drug, which places individual patient INDs outside the scope of the Common Rule, FDA disagrees that prior FDA review, without additional review by a qualified third party, provides adequate safeguards. The types of patients that would typically be eligible to obtain investigational drugs under expanded access programs are vulnerable and have somewhat desperate clinical circumstances and, therefore, are in particular need of the protections afforded by IRB review and the informed consent process. FDA acknowledges that in emergency situations involving individual patient access, there is not always prospective IRB review. However, FDA believes that some type of retrospective IRB review is still important in most cases, especially if treatment with the investigational drug is ongoing. FDA also believes that informed consent is an important element of any treatment use, even in emergency situations. From a medical ethics perspective, the need for informed consent increases with the seriousness of the disease or condition and the exigency of the clinical situation, so it would be all the more important in emergency situations with individual patients. The purported advantages of eliminating any prospective third-party IRB review and informed consent are not enough to offset the potential harm.

f. *Investigator reporting responsibilities for individual patient INDs*.

Proposed § 312.310(c)(2) states that ''at the conclusion of treatment, the licensed physician or sponsor must provide a summary of the results of the expanded access use, including unexpected adverse effects.''

(Comment 62) One comment recommended that the licensed physician be required to provide a summary of ''all adverse effects possibly related to the investigational drug'' rather than only ''unexpected adverse effects.'' The comment stated that it is likely that many private practice physicians requesting expanded access for the emergency treatment of their individual patients will not be familiar with all of the current information related to the adverse event profile of the investigational drug and/or FDA's regulatory definition of ''unexpected adverse effects.'' The comment added that requiring physicians to report all adverse effects possibly related to the investigational drug would be consistent with the investigator reporting requirements in § 312.64(b).

(Response) FDA agrees that the licensed physician may be unaware of what events are expected or unexpected and, therefore, should be required to include information on all observed adverse events. Therefore, section 312.310(c)(2) has been revised to state that at the conclusion of treatment, the licensed physician or sponsor must provide FDA with a written summary of the results of the expanded access use, including adverse effects.

(Comment 63) One comment stated that adverse event reporting for expanded access use should take advantage of technological modernization in adverse event reporting, such as by using a centralized electronic database. The comment stated that such a database could provide access to basic tabulation and analysis of the voluminous serious adverse event reports that, in their present form, are virtually useless to individual site investigators and site IRBs.

(Response) FDA has no plans to implement an electronic data capture and analysis system for adverse events that is devoted exclusively to adverse events observed during expanded access use. FDA is actively involved in efforts to develop and implement electronic data systems for adverse event reporting generally, for both pre- and postmarketing adverse event reporting. FDA believes these systems will also contribute to improved data collection and analysis of adverse events information obtained from exposure to investigational drugs in expanded access programs.

g. *Qualifications of licensed physicians to participate in expanded access*.

Proposed § 312.305(c)(5) requires, among other things, that sponsors ensure that licensed physicians participating in expanded access programs are qualified to administer the investigational drug for the expanded access use.

(Comment 64) One comment recommended that FDA revise § 312.305(c)(5) to state: ''In general any licensed physician may participate in an expanded access protocol. Additional specific qualifications may be necessary in some situations.'' The comment recommended that FDA clarify its expectations about investigator qualifications for expanded access programs to reduce the burden for sponsors and facilitate broader physician participation in expanded access programs.

(Response) FDA does not believe the recommended language is necessary or desirable. Section 312.305(c)(5) requires simply that sponsors assure themselves that the licensed physicians who will be participating in an expanded access program are qualified to administer the drug for the expanded access use. FDA believes the requirement concerning the qualifications of the licensed physician-investigator is narrowly focused on the most germane issue—whether the physician is qualified to administer the drug for the expanded access use. FDA believes the language proposed in the comment minimizes the qualifications of the licensed physician to too great an extent because it eliminates even the cursory inquiry as to whether the physician is qualified to administer the drug.

h. *Investigator's brochure*.

Proposed § 312.305(c)(5) also requires the sponsor to provide the licensed physician with information needed to minimize the risk and maximize the potential benefits of the investigational drug, including ''providing the investigator brochure, if there is one.''

(Comment 65) One comment requested that this language be revised to state that the sponsor provide the investigator's brochure ''if required under § 312.55 (Informing investigators).''

(Response) FDA does not agree with the proposed change because it would appear to narrow the circumstances in which a sponsor would be required to provide an investigator's brochure. It could be interpreted as requiring that a sponsor make the investigator's brochure available only if the treatment use is the same use as is being developed (i.e., the use for which the investigator's brochure was written). FDA believes that the investigator's brochure would typically contain information that would be important for any proposed use of the investigational drug (e.g., information about adverse events associated with use of the drug) and, therefore, should be made available by the sponsor to licensed physicians in an expanded access program whenever an investigator's brochure exists. To more accurately express this intent, FDA has revised the provision in the final rule to state as follows: ''In all expanded access cases, sponsors are responsible for * * * providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (the investigator's brochure must be provided if one exists for the drug) * * *''

i. *Monitoring of expanded access INDs.*

The proposed rule makes the sponsor responsible for monitoring of expanded access INDs or protocols. Proposed § 312.305(c)(2) states that an individual or entity that submits an expanded access protocol or IND is a sponsor for purposes of part 312 and, therefore, must comply with the responsibilities for sponsors concerning the oversight of clinical investigations in subpart D of part 312, including monitoring of ongoing protocols (§ 312.56). Proposed § 312.310(c)(3) provides that FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration.

(Comment 66) One comment maintained that the requirement that sponsors monitor the conduct of individual patient expanded access protocols is impractical and burdensome and should be eliminated. Another comment objected to the requirement to monitor individual expanded access when the use is for an extended duration. The comment stated that this provision inappropriately interfered with the patient-physician relationship and implied that the individual physician may be incapable of monitoring the patient for an extended duration.

(Response) FDA does not believe the provision that gives FDA the option to require monitoring for an individual patient access protocol of extended duration is overly burdensome or impractical. The provision is intended to provide the option to monitor for relatively long-term use, such as chronic open-ended use that is likely to continue for many months. In FDA's experience, the majority of individual patient treatment uses do not go on for an extended duration, so the number of instances in which FDA is likely to require monitoring is small. Moreover, uses that go on for an extended duration are likely to have greater potential risk and, therefore, warrant higher scrutiny. Also, the monitoring need not be resource-intensive. Guidance concerning acceptable monitoring practice in the International Conference on Harmonisation guidance document entitled ''E6 Good Clinical Practice: Consolidated Guideline'' provides that the sponsor should determine the extent and nature of monitoring needed based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. These factors are either absent from an extended duration individual patient treatment use or favor low-intensity monitoring (e.g., n = 1), so minimal monitoring would likely suffice (e.g., may not need onsite monitoring). Therefore, it is reasonable to require monitoring for individual patient protocols of extended duration and necessary for appropriate patient protection.

(Comment 67) Two comments questioned why an industry sponsor should be required to monitor an individual patient IND when the licensed physician holds the IND.

(Response) Where the licensed physician is the IND holder for an individual patient expanded access IND, as opposed to the entity that is providing the investigational drug for the expanded access use, the entity providing the drug is not a sponsor with respect to that IND and, therefore, has no sponsor responsibilities under part 312.

Proposed § 312.315(d)(2) provides that the sponsor is responsible for monitoring the conduct of an intermediate-size patient population access protocol to ensure that licensed physicians who are providing the drug to their patients are complying with the protocol and applicable regulations.

(Comment 68) One comment requested that FDA eliminate the requirement for sponsor monitoring of intermediate-size access programs. The comment urged FDA to replace the monitoring requirement with additional information about the criteria for selection of investigators, the method for data collection by investigators, the circumstances under which a commercial IRB might be used to provide IRB oversight for investigators who practice in a setting without an IRB (and also in settings that have an IRB), and the sponsor's prospective plan for demonstrating due diligence in obtaining data from investigators.

(Response) FDA does not believe that the provisions the comment suggests adding to the intermediate-size patient population IND submission are adequate to replace real-time monitoring intended to determine whether investigators are complying with the protocol and their investigator responsibilities. FDA believes such monitoring is important to ensure appropriate use of the investigational drug and patient safety.

6. Issues Specific to Individual Patients, Including Emergency Use

(Comment 69) One comment recommended that FDA change the name of this expanded access category from ''individual patients, including for emergency use'' to ''individually identified patients for treatment use, including for emergency use'' to make it clear that this expanded access category is limited to the use of an investigational drug in an established physician-patient relationship.

(Response) FDA does not believe the name of the category needs to be changed. In FDA's experience, individual patient treatment use arises in the context of an established physician-patient relationship, so FDA does not think that point needs clarification. Moreover, FDA is uncertain how the recommended name change would clarify that issue.

Proposed § 312.310(a)(1) states that a licensed physician seeking to obtain an investigational drug for treatment use for a patient 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. FDA must also determine that 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 (proposed § 312.305(a)(2)).

(Comment 70) Some comments were concerned that the licensed physician would typically lack sufficient information about an investigational drug to make an informed decision about the risk to the patient from the investigational drug versus the risk from the disease or condition. One comment stated that the very nature of experimental drugs limits patients' and physicians' abilities to know and fully understand the risks and benefits of a particular drug. One comment maintained that it is also unlikely there would be any published literature or other sources of information available to physicians for drugs that are early in development. To address this problem, the comment requested that FDA revise the final rule to include a requirement that FDA provide information to the medical profession and patient advocacy organizations about the availability of investigational drugs for expanded access, including a full accounting of the scientific evidence supporting expanded access uses.

(Response) The requirement that the licensed physician determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition originates in Congress's mandate in FDAMA to expand access to investigational drugs for treatment use (section 561(b)(1) of the act) and is intended to provide greater autonomy to individual patients and their physicians in decisions about expanded access use. The underlying premise of the requirement is that physicians know more about the clinical situations of

their patients than does FDA and, therefore, should have considerable input into the assessment of risks and benefits. FDA acknowledges that there is often limited information available to physicians about the risks and benefits of an investigational drug and no practical way to provide the physician the information at FDA's disposal (information is typically proprietary and generally can only be disclosed to a member of the public on consent of the commercial sponsor).

That the physician will often have limited information does not, however, make access to investigational drugs for individual patients inherently dangerous. In these situations, in addition to the licensed physician's determination, FDA must determine that the potential benefit to the patient 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 has access to considerably more information about the investigational drug and can evaluate the potential benefits and risks of the therapy in light of the information provided by the physician about risks and benefits in relation to the individual patient's condition. FDA believes that its knowledge of the drug combined with the licensed physician's knowledge of the patient's clinical condition will lead to expanded access decisions for individual patients that are in the best interests of those patients.

Proposed § 312.310(a)(2) states that FDA must determine that the individual patient for whom expanded access use is sought cannot obtain the drug under another type of IND or protocol.

(Comment 71) One comment recommended that the word ''type'' be deleted from the language in § 312.310(a)(2) that ''FDA must determine that the patient cannot obtain the drug under another type of IND or protocol.''

(Response) FDA agrees that the intent of § 312.310(a) is accurately conveyed when the words ''type of'' are omitted and has revised the provision accordingly.

Section 312.310(c)(1) of the proposed rule states: ''Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy.''

(Comment 72) One comment recommended that the final rule describe submission requirements and processes to extend the treatment use in those instances where the initial authorization was for a single course of therapy, but additional courses are warranted.

(Response) FDA does not believe it is necessary to describe in the regulations specific requirements and processes for submissions to extend an expanded access treatment for an individual patient. FDA anticipates that, in most cases, the submission would require a minimal amount of information to demonstrate that the criteria for the expanded access use continue to be met and would focus primarily on the response to treatment to date, including any adverse events.

(Comment 73) One comment stated that the proposed rule's requirement that the duration of an individual patient treatment use generally be limited to a single course of therapy unless FDA expressly authorizes multiple courses or chronic therapy usurps the physician's role, restricts access, and therefore should be eliminated.

(Response) FDA disagrees. This rule provides for treatment use of an investigational drug in a vulnerable population, often on the basis of very little information about effectiveness and safety. To fairly weigh the risks and benefits of an investigational drug for use in this setting, FDA believes there has to be a clear understanding between the treating physician and FDA about the planned course of therapy. For example, to fairly evaluate the risks, it will usually be necessary to consider the planned dose and duration of therapy in relation to what is known about the occurrence of toxicity for that dose and duration of therapy. For the same reason, it will usually be necessary to consider the extent of prior exposure and the planned duration of subsequent therapy before authorizing additional courses of an investigational drug beyond the original treatment plan. Therefore, FDA does not believe it is reasonable or wise to authorize access of unspecified duration at the discretion of the treating physician. FDA also does not believe this provision unreasonably restricts access. FDA believes that subsequent courses of therapy will routinely be permitted where appropriate.

Proposed § 312.310(c)(2) requires, among other things, that ''the licensed physician or sponsor must provide a written summary of the results of the expanded access use.''

(Comment 74) One comment stated that the proposed rule should make clear to whom—presumably FDA—the written summary of the results of treatment use must be submitted.

(Response) FDA agrees. The written summary should be submitted to FDA, specifically to the IND. FDA has revised the language to clarify who should receive this summary as follows: ''At the conclusion of treatment, the licensed physician or sponsor must provide FDA with a written summary of the results of the expanded access use, including adverse effects.''

Proposed § 312.310(c)(4) provides that 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.

(Comment 75) One comment objected to this provision because it may increase the amount of time it takes for an individual to obtain access and, because there is a higher evidentiary standard for authorizing an intermediate-size population IND than for an individual patient IND, may make a drug less accessible for treatment use.

(Response) FDA does not believe that § 312.310(c)(4) will increase the amount of time it takes for an individual patient to obtain access. The intent of this provision is to make access more efficient at the point it becomes apparent that there will be more than a few isolated requests for expanded access by individual patients. By obtaining a submission for an expanded access IND that can enroll multiple patients, FDA believes this provision will decrease the amount of time needed to get an investigational drug to any patient seeking access under the multi-patient IND because it avoids the submission and review of many individual patient INDs. In addition, even at the point FDA believes it is appropriate to request a submission of a multi-patient access IND under § 312.315 or § 312.320, FDA does not intend to delay responding to individual patient submissions that are received during the time it takes a sponsor to prepare a submission for an intermediate-size population expanded access IND.

FDA agrees that the evidentiary requirement is somewhat higher as the size of the population to be treated under the access IND increases (e.g., from individual patient to intermediate-size population IND). However, FDA does not foresee that this will be an obstacle to obtaining access. FDA will not request submission of an expanded access IND that can enroll multiple patients until there has been some volume of experience under several individual patient INDs. Therefore, at the time FDA requests submission of a multi-patient expanded access IND under § 312.315 or § 312.320, FDA will have probably already concluded that

there is enough patient experience under individual patient INDs and other evidence to justify broader exposure under an IND that can enroll multiple patients (e.g., to permit treatment of 10 patients under an intermediate-size population IND).

(Comment 76) One comment pointed out an apparent discrepancy between the codified language in § 312.310(c)(4) of the proposed rule and the preamble discussion of the section. Section 312.310(c)(4) states that ''* * * FDA may ask the sponsor to submit an IND or protocol for use under § 312.315 or § 312.320.'' However, the preamble states that ''* * * 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.'' The comment stated that it appears that the preamble goes beyond the language of the regulation and asks what is meant by ''conduct a clinical trial of expanded access use'' in the preamble.

(Response) FDA does not believe there is an inconsistency between the two statements in the preamble and proposed § 312.310(c)(4). If FDA asks the sponsor to submit an IND or protocol for use under § 312.315 for a drug being developed, that submission would have to address why the patients to be treated under the intermediate-size expanded access IND cannot be enrolled in a clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients. Based on the information submitted, FDA must conclude that enrollment in a clinical trial is not possible before the intermediate-size population expanded access protocol can begin. However, FDA might reasonably conclude, based on that information, that a clinical trial in the intended treatment population is possible and ask the sponsor to conduct a clinical trial of the treatment use, either in lieu of, or in addition to, an intermediate-size population expanded access IND.

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 use of the drug without a written submission. The proposed rule provides that emergency use can be authorized by telephone.

(Comment 77) One comment was concerned that emergency use might be too narrowly defined and thus unnecessarily restrict access in a true emergency.

(Response) FDA's intent in articulating criteria for when it is appropriate to consider authorizing access without a written submission is intended to differentiate true emergency situations in which treatment must occur within a fairly narrow time frame from situations in which there is sufficient time to make a written submission. The emergency process is, by its exigent nature, not as deliberative and thorough a consideration of the risks and benefits of a proposed treatment use in an individual patient as is afforded by a review of a written submission. Therefore, the emergency procedures may expose patients to somewhat higher risk than a more deliberative, non-time-sensitive review and, therefore, should be used only in true emergencies. FDA is confident, however, that the rule as proposed will permit evaluation of all true emergency treatment use requests using the emergency procedures.

(Comment 78) One comment noted that the proposed regulations on emergency INDs require that licensed physicians obtaining an IND take on responsibilities more commonly associated with commercial sponsors such as monitoring, reporting adverse events, and submitting annual reports (where applicable). The comment was concerned that these responsibilities may make physicians less willing to obtain investigational drugs for their patients.

(Response) The agency recognizes that the licensed physician who must obtain his or her own IND to make a drug available for treatment use to an individual patient, whether or not in an emergency situation, is subject to regulatory obligations usually applicable to commercial sponsors and with which the physician may not be familiar. However, the agency believes that for an individual patient IND, these obligations will not be too onerous because they closely parallel the type of monitoring and documentation that are routine in a clinical practice (e.g., routine patient care, progress notes, discharge summary) and, therefore, are not a substantial added burden. FDA also believes these obligations are essential elements of human subject protection. In addition, FDA can provide assistance to licensed physicians in complying with their expanded access IND regulatory requirements (e.g., FDA's Office of Special Health Issues is a good resource for physicians concerning expanded access (see *http://www.fda.gov/oashi/home.html*)).

Proposed § 312.310(d)(2) requires, as a condition for authorizing emergency use without a written submission, that the licensed physician or sponsor explain how the expanded access use will meet the requirements of §§ 312.305(a) and 312.310(a) and, further, that the licensed physician or sponsor make a written submission that complies with the requirements of §§ 312.205(b) and 312.310(b) within 5 working days of the onset of the use.

(Comment 79) Two comments expressed concern about the requirement to make a written submission within 5 working days in situations in which a commercial sponsor has agreed to make the drug available under its own IND (as opposed to making the licensed physician obtain an IND). These comments stated that in these situations the commercial sponsor is dependent on the licensed physician to obtain the information needed to make a written submission and, in their experience, it takes approximately 30 days to obtain all the information needed to complete the written submission from the licensed physician. They ask that FDA provide a longer time period in which to make a submission.

(Response) FDA acknowledges that in situations in which a commercial sponsor makes an investigational drug available for treatment use under its own IND, it is dependent, to a certain extent, on the patient's physician to obtain the information needed to make the submission. Therefore, FDA agrees that the time to make a written submission should be extended. FDA believes that 15 working days should be sufficient time to obtain whatever information is needed to make a written submission. FDA is concerned that providing a longer period of time, such as 30 days, may reduce compliance with the written submission requirement and may negatively impact patient safety. FDA also believes it is inefficient and potentially confusing to have different time frames for making a written submission for a commercial sponsor who must obtain information from a patient's physician to complete a submission and a licensed physician who must complete his or her own IND submission. Therefore, 15 working days will be the time for making a written submission for each of these situations. Accordingly, the § 312.310(d)(2) has been revised to provide 15 working days for making a written submission following emergency authorization to treat an individual patient with an investigational drug.

(Comment 80) One comment stated that there were a number of administrative steps FDA should take to make expanded access for individual patients easier to obtain. The comment

stated that different divisions at FDA had different requirements concerning expanded access. The comment suggested that FDA make its internal requirements for individual patient expanded access consistent among the divisions. The comment also stated that FDA should post the name and contact information of the person in each division who is responsible for helping physicians submit individual patient expanded access requests.

(Response) One of the purposes that will be served by this final rule is to improve consistency in the way expanded access INDs are handled within FDA. FDA believes that including clear criteria and submission requirements in the regulations should help improve consistency in the individual patient expanded access process. In addition, FDA intends to educate reviewers and other review division staff on these new rules. FDA also plans to assess the implementation of these rules and will determine at a later time whether additional guidance is needed.

7. Issues Specific to Intermediate-Size Patient Populations

Proposed § 312.315 provides for expanded access use for multiple patients under a single IND or protocol for patient populations smaller than those typical in treatment INDs or treatment protocols, and sets forth the criteria, submission requirements, and safeguards specific to expanded access INDs for intermediate-size patient populations. The primary purpose of the intermediate-size patient population IND or protocol is to consolidate expanded access under a single IND to promote better monitoring, oversight, and ease of administration for an expanded access use compared to multiple individual patient INDs.

a. *General comments.*

(Comments 81) Several comments expressed approval for the creation of the intermediate-size patient population IND to formally bridge the gap between individual patient access and large population access under treatment INDs late in development. One comment agreed that this category would promote greater efficiency by aggregating various types of individual requests. Another comment stated that creation of this category might diminish the burdens of individual physicians in complying with the expanded access submission requirements for individual patient INDs, presumably because individual physicians would not have to make submissions once the individual patient INDs have been consolidated under an intermediate-size population IND.

(Response) FDA agrees that a potential advantage is to reduce the burdens of individual physicians trying to obtain access for individual patients. Ideally, only a limited number of physicians would make submissions for individual patients before patients receiving the investigational drug for the expanded access use could be consolidated under an intermediate-size population IND. That consolidation would ease the burden considerably for subsequent physicians seeking the drug for treatment use because they would not have to make their own IND submissions.

(Comment 82) One comment recommended that this expanded access category be renamed from ''Intermediate-size patient populations'' to ''Limited patient populations for treatment use.'' The comment maintained this change would clarify that the intent of this expanded access category is to provide ''compassionate'' treatment use of the investigational drug and involves only a limited number of prospective patients.

(Response) FDA does not believe it is necessary to further clarify the intent of this category of expanded access or of expanded access generally. Section 312.300(a) plainly describes the intent of expanded access. It states that ''[t]his 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.'' Moreover, it is apparent throughout the various requirements set forth in this subpart that the intent is treatment rather than assessment of the safety and effectiveness of an investigational drug in a controlled setting. In addition, FDA believes the term ''intermediate-size population'' better reflects the intent to describe an expanded access category intended to accommodate populations in between individual patients and the large populations that are typical of access to investigational drugs under treatment INDs or treatment protocols.

(Comment 83) One comment stated that the proposed rule does not address the situation in which an investigational drug being made available under a treatment IND would no longer be available under a treatment IND because of new information about the drug, but could still be made available under an intermediate-size patient population IND. The comment was concerned that, in that situation, the evidentiary threshold for expanded access would actually be lower than for the treatment IND.

(Response) FDA agrees that the proposed rule was not specifically intended to address a situation in which an investigational drug once available under a treatment IND would no longer be available under a treatment IND, but would then become available under an intermediate-size patient population expanded access IND. FDA believes this would be an unusual circumstance, but a foreseeable one, and that the rule as proposed could accommodate that circumstance. For example, clinical trials of an investigational drug available under a treatment IND might demonstrate lack of effectiveness on a primary endpoint that is compatible with the expanded access use under the treatment IND, but also provide preliminary evidence of effectiveness on secondary endpoints or in subset analyses, and such evidence could support a different expanded access use (e.g., a more narrowly defined population within a disease or a different indication) under an intermediate-size population expanded access IND. In this circumstance, some of the patients who were receiving the drug under the treatment IND might be eligible to receive the drug under the intermediate-size population IND on the basis of lesser evidence than supported the treatment IND. However, FDA does not see why this would be a problem (e.g., expose any patient to unreasonable risk), provided the evidence is adequate to support the size population to be treated under the intermediate-size population IND.

b. *Number of patients.*

The preamble to the proposed rule stated that FDA anticipates that the typical intermediate-size patient population treatment use IND or protocol will provide access to between 10 and 100 patients.

(Comments 84) Some comments were concerned that FDA's estimated range for the number of patients that could be enrolled in an intermediate-size patient population IND was too narrow. One comment stated that FDA substantially underestimated the sizes of the potential populations that would need access to an investigational drug under an intermediate-size patient population, and that the estimated range (between 10 and 100 patients) leaves a significant gap between the intermediate-size population IND and the treatment IND. The comment recommended the creation of a fourth category of expanded access IND to bridge this gap. One comment asked FDA to clarify the difference in size of population between the intermediate category and larger populations under treatment INDs or protocols because FDA did not provide any estimate of the lower end of the range for a treatment IND. Two

comments stated that, although the proposed rule contemplated that § 312.315(a)(3)(i) and (a)(3)(ii) would be for an intermediate-size population of 10 to 100 patients, the situations described in these subsections could easily involve much larger numbers of patients.

(Response) The population range (10 to 100) for the intermediate-size patient population IND identified in the preamble to the proposed rule is simply an estimate and is not intended to exclude the possibility that more (or fewer) patients could be treated under an intermediate-size patient population IND. For a drug being developed, it is possible that more than 100 patients could be treated under an intermediate-size population IND. However, our experience suggests that programs substantially larger than this are best administered under a treatment IND. FDA expects that there would ordinarily be a seamless transition from intermediate-size population IND to treatment IND at the point when there was adequate evidence to support the treatment IND, adequate progress with drug development, a sponsor willing to make the drug available to a larger population under a treatment IND, and sufficient numbers of patients who need the drug to justify a treatment IND.

For a drug not being developed, there is also the possibility that greater than 100 patients will need access to an investigational drug under an intermediate-size patient population IND. Although FDA anticipates that a relatively small number of patients would be receiving access at any given point in time under such an IND, it is foreseeable that, for some drugs in this category, conditions will never be right for development, and over a period of years the IND will provide access to more than 100 patients. However, if substantially more than 100 patients seek or continue to need access under this category within a fairly narrow time frame, FDA believes there would likely be an adequate number of potential subjects to initiate a clinical trial and formal development of the drug.

When a drug has been withdrawn for safety reasons or in a drug shortage situation, it is also foreseeable that there will be greater than 100 patients who may need access to the drug—for patients in whom the benefits of the withdrawn drug continue to exceed the risks associated with the drug or patients who need to rely on a drug not approved for marketing in the United States to substitute for an approved drug in short supply. In those cases, the intermediate-size population IND could be used to provide access to greater than 100 patients.

Because there is a need for flexibility to provide access to greater than 100 patients under an intermediate-size population IND in some circumstances, FDA has elected not to provide a specific estimate of the population range for this category in this final rule. FDA continues to believe that the population range identified in the proposed rule—10 to 100 patients—would accommodate most intermediate-size population INDs. However, FDA believes foremost that the size population that can be treated under an intermediate-size population IND should be dictated by the available evidence—the amount of exposure that the evidence will support—and the circumstances of a given case, rather than by a somewhat arbitrary estimate of the size of the upper bound of the population.

c. *Sub-categories of intermediate-size patient population expanded access.*

Proposed § 312.315 provides for access to an intermediate-size population in four situations:

- To provide a drug that is not being developed to patients who may benefit from the drug (typically patients with a rare disease or condition) (§ 312.315(a)(1))
- To make a drug that is being developed available to patients who cannot participate in clinical trials of the drug (§ 312.315(a)(2))
- To provide an approved drug that has been withdrawn for safety reasons, or cannot be marketed due to failure to meet the conditions of the approved application (usually a manufacturing problem) to a limited number of patients who are dependent on the drug (§ 312.315(a)(3)(i))
- To provide a drug that is related to an approved drug, but is not approved for marketing in the United States, in situations where there is a shortage of the approved drug or the approved drug is unavailable due to failure to meet the conditions of the approved application (§ 312.315(a)(3)(ii))

(Comment 85) One comment objected to the range of situations in this category, stating that the situations are too diverse to be accommodated in a single expanded access category.

(Response) FDA disagrees. Because the amount of evidence needed to make an investigational drug available under an intermediate-size population IND is based on the size of population anticipated to be treated under the IND, the category can accommodate situations with significant variations in the size of the treatment population (see also preceding comment response). FDA believes, therefore, that the criteria set forth in § 312.315 are adequate to ensure that the risks associated with use of drugs made available in each of these four situations are minimized and the potential benefits maximized across a variety of different treatment use situations and size populations.

(Comment 86) One comment recommended deleting the option to make an investigational drug available under an intermediate-size population IND when the drug is not being developed. The comment argued that because the disease is so rare that it is not possible to recruit patients for a clinical trial, the sponsor would not ordinarily maintain an active IND, nor would the sponsor be manufacturing investigational drug supplies (so, presumably, there is no reason for the category). The comment stated that the proposed rule also implies that this situation may be an open-ended commitment to expanded access, which is likely to further deter commercial sponsors. One comment asked how FDA would determine that the drug is the only promising therapy for the people with a rare condition without clinical data to support the use. The comment stated that this provision of the proposed rule would further erode the possibility of conducting a controlled clinical trial in this situation.

(Response) This category of expanded access use is based on FDA's experience with situations in which there has been no alternative but to make a drug not being developed available under an IND to a small number of patients who could benefit from it. In FDA's experience, it has not been difficult to determine that a drug is the treatment of choice for a discrete group of patients with a particular rare disease or condition. For example, some antivenins and drugs for tropical diseases are not commercially marketed in the United States because there is simply not a large enough market to develop the product for marketing, but these products are nonetheless needed on occasion by readily identifiable patients. FDA has made other products available to treat obscure conditions when the population is seemingly too small for even orphan drug development. For example, thalidomide was made available for a variety of conditions under several of these types of INDs before there was sufficient data to approve it. Currently, there are INDs for products not being actively developed that are ongoing, and FDA anticipates that it will encounter situations in the future in which this type of IND is needed. Because these types of INDs exist, and because one of FDA's goals with this rulemaking to

make the agency's various mechanisms for expanded access transparent and thereby make investigational drugs more widely available to those who might benefit, the agency believes it is important to describe this type of expanded access in the regulations.

FDA recognizes that a commercial sponsor might not be inclined to be a sponsor for this type of IND or to make a potentially open-ended commitment to manufacture products to provide to another sponsor under this type of IND. In FDA's experience, these types of INDs are not usually held by commercial sponsors. They are more commonly held by government agencies and academic institutions. So the fact that this type of IND is of little interest to a commercial sponsor is no reason to remove it from the expanded access regulations, particularly when it meets a demonstrated public health need.

FDA also recognizes that this type of access could potentially usurp the entire population that could possibly be enrolled in a clinical trial of a drug. However, FDA thinks this situation is not very likely because drugs are rarely developed (at least not in the United States) for the types of indications for which drugs are made available under this category. Nonetheless, where appropriate, FDA intends to make every effort to encourage potential sponsors to study such a drug in a clinical trial rather than provide it under an expanded access IND.

(Comment 87) One comment stated that there was no reason to have an intermediate-size population expanded access IND for a drug being developed. The comment stated that there is no justification for allowing access under such an IND for a disease different from the one being studied in the clinical trials. For the other situations in which a patient is unable to participate in the clinical trial (different disease stage, patient otherwise fails to meet enrollment criteria, enrollment is closed, or the trial site is not geographically accessible), the comment stated that the treatment IND would be the appropriate vehicle for expanded access.

(Response) FDA believes there is adequate justification for allowing expanded access under an intermediate-size patient population IND for a disease different from the one being studied in the clinical development program. For an oncology drug, for example, the characteristic of a cancer that is the target of a given chemotherapeutic agent (e.g., specific receptor or enzyme) may be present in other types of cancers. In that situation, it may be appropriate to make an investigational drug being studied for one cancer available to treat patients with another type of cancer before there is definitive evidence of effectiveness in the other type of cancer. As discussed above, FDA also believes it is important to be able to provide access to multiple patients in a controlled manner under an intermediate-size patient population IND at a point in time in which the use for which the drug is being made available would not yet meet the criteria for a treatment IND. In FDA's experience, it has been helpful from an administrative, clinical safety, and monitoring perspective to provide for a multi-patient expanded access IND to bridge the gap between individual patient INDs and treatment INDs.

(Comment 88) One comment stated that it is not clear why patients should receive expanded access to a drug that is no longer marketed for safety reasons. The comment stated that a clinical trial is the appropriate setting to identify patients for whom the potential benefits of a drug outweigh the risks. One comment agreed that, when a drug is withdrawn from marketing because of safety reasons, there may be a subset of patients for whom the benefits of treatment would outweigh the risks. The comment also pointed out that by stating in the preamble to the proposed rule that those patients for whom the benefits of treatment are believed to outweigh the risks ''could continue to receive the drug under an intermediate-size patient population IND,'' FDA implied that only patients who were already receiving the drug when marketing ceased could obtain the drug under such an IND. The comment asked FDA to clarify whether this provision is intended to make a drug available only to patients who were receiving the drug when it was withdrawn for safety reasons or if it would also be possible to provide the drug to patients who had not yet received it.

(Response) In FDA's experience, there are multiple examples of situations in which a drug has been withdrawn from the market for safety reasons and there has been a need to make the drug available to a subset of patients in whom the benefits of treatment outweigh the risks. Although those who receive the drug will ordinarily be those who were already receiving the drug at the time of withdrawal and appear to have benefited, it was not FDA's intent to absolutely foreclose the possibility that new patients could receive a drug that had been withdrawn from marketing for safety reasons. It is possible that a population in whom benefits continue to outweigh risks could be characterized in a way that would permit access to patients who have not previously been treated with the drug, even though the drug is unsafe for marketing. However, a manufacturer may be reluctant to make an open-ended commitment to provide a drug that has been withdrawn for safety reasons to a subset of patients when there is no commercial benefit to the manufacturer. This reluctance could also affect whether new patients would be able to obtain the drug.

(Comment 89) One comment recommended that the final rule clarify that some situations in which a marketed drug is found to benefit only a subset of the population for which it was approved can be addressed through a restricted distribution program of the FDA-approved product in accordance with subpart H of part 314, rather than through withdrawal of the drug for safety reasons and use of an intermediate-size patient population IND to make the drug available to the subset population.

(Response) FDA agrees that, in situations in which a drug is found to be beneficial in only a subset of the population in which it was originally approved, it may be possible to allow continued marketing of the drug under a restricted distribution program (Lotronex was originally marketed without restrictions and is now marketed under a restricted distribution program). In these situations, there would usually be more compelling data to support the use in the subset population than would be needed for an expanded access IND (i.e., a more rigorously defined subset population). The appropriate mechanism for making a drug available to the subset of patients in whom the benefits continue to outweigh the risks would depend on the circumstances of the particular case. FDA is always willing to explore the full range of options with the manufacturer of such a drug.

d. *Drug shortage.*

(Comment 90) One comment stated that it is not clear that the expanded access rule would be the right mechanism for access in a drug shortage situation because the numbers of patients needing access could be well in excess of the 100 patients that the preamble suggests are the upper bound of the intermediate-size population IND category.

(Response) FDA is retracting a statement in the preamble to the proposed rule suggesting that there is a 100-patient upper bound on the population for an intermediate-size expanded access IND. FDA agrees that a drug shortage situation could result in a need for access in more than 100

patients and more patients than could reasonably be accommodated by an intermediate-size expanded access IND. In such situations, FDA would be more likely to exercise its enforcement discretion, the effect of which would be to permit marketing of a related product that did not meet the FDA approval requirements to substitute for the drug in short supply until supply issues for the FDA-approved product were resolved. FDA included the drug shortage provision in the expanded access regulations to address a situation in which there is a relatively small, discrete population affected by a drug shortage. Which mechanism would be appropriate to make a related drug available in a drug shortage situation—an intermediate-size population IND or enforcement discretion—would depend on the circumstances of that situation.

e. *Good manufacturing practices (GMP) issues.*

(Comment 91) One comment suggested that expanded access was not the appropriate vehicle for providing access to a drug that is approved but is not being manufactured in a manner consistent with the approval. The comment stated that because the drug is not investigational, access should be handled under a different mechanism. The comment added that there should be assurance of close oversight of the manufacturer to minimize harm to patients. Another comment asked how it would be determined that the risk due to manufacturing problems is acceptable. The comment pointed out that the IND would have to cross-reference the NDA for CMC information and also describe the good manufacturing practices (GMP) issues.

(Response) As in the case of a drug shortage, GMP issues for a product could create a need for access in a population too large to be accommodated under an intermediate-size expanded access IND. As with a drug shortage, in these situations FDA would be more likely to use enforcement discretion to make the drug available to a very large number of patients. FDA agrees that, whether enforcement discretion or an expanded access IND is used, there must be careful consideration of the safety implications of the manufacturing concerns, including possible monitoring mechanisms to ensure that patients are not being harmed by a product that has GMP concerns but is nonetheless being made available to patients.

8. Issues Specific to Treatment IND and Treatment Protocol

The proposed rule specifically solicited comment on FDA's decision to continue to describe the type of expanded access for treatment use that makes investigational drugs available to large populations as the ''treatment IND'' or ''treatment protocol.''

(Comment 92) One comment expressed the view that, despite 20 years of use, these terms are confusing. The comment recommended that the terminology be changed to ''large-size patient populations'' to be consistent with the names of the other two categories of expanded access.

(Response) FDA continues to believe that it would be preferable to retain the terms ''treatment IND'' and ''treatment protocol.'' Because these terms have been in use for more than 20 years, FDA believes they have become so strongly associated with making investigational drugs available to large populations that to replace the terms would generate needless confusion. FDA recognizes that the term ''treatment use'' is now widely used to refer generically to use of an investigational drug for treatment purposes outside of a clinical trial, and not just to use under a treatment IND or protocol. However, FDA believes the confusion that would result from changing the name of the treatment IND outweighs any potential confusion resulting from use of the word ''treatment'' in the title of the large population expanded access IND but not in the other expanded access categories.

(Comment 93) One comment noted that FDA's current regulation concerning the submission requirements for a treatment protocol (§ 312.35(a)(ii)) provides that a submission for a treatment protocol must explain why the use of the investigational drug is preferable to the use of available marketed treatments. The comment pointed out that § 312.305(b)(2)(ii) of the proposed rule provides that submissions for all expanded access uses must explain why the use of the investigational drug is preferable to the use of available therapeutic options. The comment interpreted this provision of the proposed rule as permitting expanded access for a treatment protocol only when the treatment protocol explains why the use of the investigational drug is preferable to any approved or unapproved therapies, not just preferable to any available marketed treatment. The comment contended that this provision could be interpreted to require companies to show that the product to be used for treatment use is better than both approved and unapproved therapies because the preamble states that ''available therapy'' includes not just FDA-approved products for that indication, but also includes (1) treatments not FDA-regulated (e.g., surgery) and (2) off-label use (i.e., not labeled for use for the relevant condition or disease, but supported by compelling literature reference) (71 FR 75147 at 75151). To avoid this perceived problem, the comment suggested that FDA take one of three steps: (1) Put the definition of ''available therapy'' stated in FDA's guidance for industry entitled ''Available Therapy'' in a formally issued rule, (2) revert back to the requirement that the investigational new drug must only be measured against other FDA-approved marketed products, or (3) approve the unapproved therapy for the new indication so that its use becomes ''on-label.''

(Response) The Available Therapy guidance (p. 4) states that ''available therapy (and the terms existing treatments and existing therapy) should be interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions.'' This guidance was intended to apply to the use of the term in § 312.34(b)(1)(ii) of FDA's current regulations concerning treatment INDs and treatment protocols. That regulation includes the criterion that ''[t]here is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population.'' Section 312.34(b)(1)(ii) is intended to apply equally to the use of the term in new subpart I. FDA believes this guidance has effectively addressed confusion associated with use of the term ''available therapy'' in the varied contexts in which it is used in FDA's regulations. Therefore, FDA does not believe it is necessary at this time to promulgate a regulation defining the term or revise the guidance so that only approved therapies could be considered available therapy. Nor would it be appropriate to simply approve the unapproved therapy for the new indication for use, apparently without regard to the evidence supporting the use, so that its use becomes ''on-label.''

9. Clinical Holds of Expanded Access INDs

Proposed § 312.42(b)(3) specifies the conditions under which FDA may place an expanded access IND or protocol on clinical hold. Proposed § 312.42(b)(3)(i) allows FDA to place a proposed expanded access use on clinical hold if the pertinent criteria in subpart I for authorizing the use are not met (e.g., non-serious disease or condition, satisfactory or comparable therapies are available, insufficient evidence to support the use) or the IND does not comply with the pertinent submission

requirements in subpart I. Proposed § 312.42(b)(3)(ii) allows FDA to place an ongoing expanded access IND on clinical hold if the agency determines that the pertinent criteria in subpart I are no longer satisfied.

(Comment 94) One comment emphasized the importance of providing a high degree of clarity about the reasons for imposing a clinical hold on an access program to assure that other studies of the investigational drug are not unintentionally affected. The comment stated that lack of clarity could shut down an entire development program and suggested that in the final rule, FDA cite specific reasons for imposing a clinical hold on an access program. The comment asserted that FDA should apply the same level of rigor for imposing holds on access programs as is applied to clinical holds of clinical trials. Another comment suggested that FDA propose an approach for supplying drugs to patients who are clearly benefiting from treatment and are participating in an expanded access program that is put on clinical hold.

(Response) FDA does not believe it is necessary or desirable to cite in the regulations specific potential reasons for a clinical hold of an expanded access IND. Section 312.42(b)(3) makes clear that failure to meet any of the criteria or submission requirements pertinent to authorizing any of the expanded access IND categories may be a basis for a clinical hold. It also makes clear that if any of the criteria that were the basis for authorizing an expanded access IND are no longer satisfied, FDA may place an ongoing expanded access IND on clinical hold. If FDA were to cite specific potential reasons for a hold, it could give the misimpression that failure to meet criteria or submission requirements not expressly mentioned would not be a basis for a hold.

FDA anticipates that clinical holds for expanded access INDs will be handled in the same manner as for INDs for clinical trials. That is, the clinical hold letter will cite the relevant regulation and explain in detail how the criteria that are the basis for the hold are not met. FDA further anticipates that, in the event that the basis for a clinical hold is relevant only to an expanded access IND and not to the clinical development program, the relevant clinical hold documentation will make this abundantly clear.

In addition, in situations in which an ongoing expanded access IND is placed on hold, FDA will carefully consider the needs of patients already receiving the drug. FDA will not hesitate to use a partial clinical hold (which permits patients already being treated with a drug to continue treatment) where appropriate.

10. Comments on Analysis of Impacts

(Comment 95) Three comments from pharmaceutical companies and a trade association stated that the rule would likely increase sponsors' administrative, medical, and regulatory burdens associated with expanded access. The comments specifically mentioned the costs of providing the investigational drug, conducting clinical laboratory tests, and monitoring, collecting, processing, analyzing, and summarizing data.

(Response) Based on our analysis, we conclude that the final rule will not have a substantial economic impact. The final rule clarifies and expands on regulations in place since 1986 but does not substantially change those regulations; therefore, the overall economic impact should be small. Treatment use of investigational drugs is relatively uncommon and a particular sponsor would be expected to submit a treatment use request only infrequently. Therefore any additional regulatory burden is expected to be small and widely dispersed among affected entities. Most treatment use requests are for individuals or single patients for which the drug, clinical laboratory testing, monitoring, data processing, and reporting costs are expected to be small. The proposed rule does not require sponsors to make investigational drugs available for treatment use. Such a decision is the sponsor's alone and will presumably be based on a number of factors, including cost. If the sponsor can demonstrate that the clinical trial could not be conducted unless the sponsor is able to charge for the investigational drug, the sponsor may request permission to charge patients and recover the direct costs associated with the treatment use.

(Comment 96) A comment from an insurance company provided an estimate of the costs to enrollees in commercial private health plans associated with the expanded access rule that indicates the costs to be much larger than those stated in the proposed rule. The comment assumed that physicians would request access to investigational drugs only when available therapies have failed or when conventional therapies do not exist. Additional information related to the comment and submitted to the docket at FDA's request indicated that ''* * * the grand total number of patients projected to utilize INDs under these proposals each year is approximately 67,500.'' The comment also stated its belief that investigational drugs will be used as first-line therapy, second-line therapy, monotherapy, and combined therapy with FDA-approved medications. The comment stated that the aggregate additive cost per year to all U.S. private-sector payers would be $273,600,000. The comment maintained that these estimates actually understate the burden to private-sector payers because they exclude potential annual costs to Medicare Advantage plans.

(Response) Based on our analysis, we concluded that the costs of this final rule should be small. The cost estimate provided in the comment appears to include costs for investigational drugs under provisions of the charging final rule published elsewhere in this issue of the **Federal Register**. In response to the comment, we have included estimates of the number of individual patients with access to investigational drugs under current rules and the number of additional patients we expect to gain expanded access to investigational drugs under this final rule. FDA's estimates indicate that, on average, as many as 53,159 patients per year have access to investigational drugs under current rules. In addition, we estimate that as many as 3,095 additional patients will gain expanded access to investigational drugs under this final rule. These estimates are based on assumptions used in our Analysis of Impacts for the proposed rule that were not substantively challenged in any comments received. It appears that the estimate of 67,500 patients per year in the comment draws no distinction between patients receiving investigational drugs under current rules and the additional patients who will have expanded access under this final rule. In assessing the impact of the final rule, it is the incremental effect, or additional patients that will gain expanded access, that must be considered. Patients with access to investigational drugs under current rules are not relevant to an analysis of impacts for this final rule. The only direct costs that are relevant to this final rule are the costs to drug sponsors to prepare and submit expanded access requests. The comment did not provide an estimate of these costs.

(Comment 97) A comment from a capital fund disagreed with the proposed rule's assertion that the rule would not have a significant economic impact on a substantial number of small entities. The comment stated that FDA had overlooked the extensive role of small biotech companies in developing novel kinds of investigational drugs that are often the most sought-after therapies for expanded access. The comment also

stated that small biotech companies severely lack funding and also face special difficulties in getting their therapies to the stage where they are able to obtain significant partnering arrangements. The comment stated that such companies could be substantially helped by expanded access programs by permitting them to reach larger numbers of patients sooner and to generate larger amounts of supporting data sooner. The comment stated that the most powerful boost for small biotech companies and the patients seeking their new therapies would come from combining expanded access programs with policies allowing cost recovery and reimbursement (the subject of the charging proposed rule). The comment also advocated minimal efficacy requirements for expanded access and stated that such a policy would not impose substantial costs on society or the healthcare system because sponsors would be paying for the costs of producing and supplying the therapy in most expanded access programs. The comment added that if such programs enable a product to reach marketing approval sooner than otherwise, that would greatly reduce the costs that sponsors must recoup in pricing products for commercial sale.

(Response) The comment suggests that investigational drugs produced by small biotech companies are often the most sought-after therapies for expanded access, but provides no examples. While small biotech companies may face a number of difficulties—including a lack of funding and partnering opportunities—such obstacles are neither the subject of this final rule nor the responsibility of FDA. The purpose of the proposed expanded access rule is not to help sponsors reach larger numbers of patients and generate larger amounts of supporting data sooner. The agency believes that these goals are best pursued through the normal drug development process. FDA believes that cost recovery for expanded access—the subject of the charging proposed rule—is appropriate only in limited circumstances. Further, the agency has determined that the amount to be charged should be limited to the direct costs of providing the investigational drug for the treatment use. Cost recovery through charging is not intended as a mechanism through which sponsors may generate funds to support drug development generally. The agency agrees with the comment that the proposed rule would not impose substantial costs on society or the healthcare system.

(Comment 98) One comment stated that the estimates of increased expanded use in the Analysis of Impacts appeared overly optimistic because **Federal Register** notices are not the best way of disseminating information to the lay public or their physicians and the proposed rule did not mention any additional efforts to disseminate information about expanded access.

(Response) Issuance of the final rule is not the only way FDA plans to disseminate information on expanded access programs to the lay public and physicians. FDA intends to develop and engage in a broad range of publicity and educational efforts in a variety of forums and media to increase awareness of the mechanisms for obtaining investigational drugs for treatment use.

IV. 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, 701(a) (21 U.S.C. 371(a)), and 505–1(f)(6).

Section 505(i) of the act directs the agency[1] 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 final rule 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 final 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 final 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 must submit a clinical protocol consistent with the provisions of section 505 of the act (21 U.S.C. 355) describing the use of the investigational drug in a single patient or a small group of patients. The final 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 the 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 will not expose patients to an unreasonable and significant risk of illness and injury. The

[1] 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.''

final 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 final rule sets forth the conditions under which FDA will place an expanded access use on clinical hold.

This final rule establishes 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 final 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 final rule is expected to aid in the efficient enforcement of the act.

Finally, section 505–1(f)(6) of the act, added by FDAAA, states that ''[t]he mechanisms under section 561 to provide for expanded access for patients with serious or life-threatening diseases or conditions may be used to provide access for patients with a serious or life-threatening disease or condition, the treatment of which is not an approved use for the drug, to a drug that is subject to elements to assure safe use under this subsection.'' FDA ''shall promulgate regulations for how a physician may provide the drug under the mechanisms of section 561.'' Because the expanded access mechanisms in this final rule may be used by patients seeking access to a drug that is subject to elements to assure safe use, this rule fulfills the FDAAA requirement.

V. 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.

VI. Analysis of Economic Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and 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 final rule is not an economically significant regulatory action under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Our economic analysis for the proposed rule did not indicate any significant new regulatory burden, and we did not receive any comments that would cause us to reconsider this determination. Therefore, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small 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 $133 million, using the most current (2008) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that will meet or exceed this amount.

The agency estimates that the total costs to drug sponsors and physicians to submit the additional expanded access submissions expected under this final rule will be between $1.5 million and $3.0 million per year. Because a typical sponsor will submit an expanded access use request only infrequently, these costs are expected to be widely dispersed among affected entities. The benefits of the final rule are expected to result from increased patient access to investigational drugs generally and from expanded access being made available for a broader variety of disease conditions and treatment settings. Private benefits will accrue to individual patients receiving drugs for expanded access use, whereas social benefits will accrue if information obtained contributes to the development of new therapies generally. Due to uncertainty with respect to the potential magnitude of such benefits, and a lack of necessary data, FDA did not generate quantitative estimates of expected benefits.

A. Objectives of the Final 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 final 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 final rule will 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.

B. Nature of the Problem Being Addressed

The fundamental problem addressed by the final 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 final rule is also intended to address concerns that, historically, cancer and Acquired Immunodeficiency Syndrome (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 final rule, the agency seeks to correct these shortcomings.

The final 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 discussed in section III.C.3 of this document. The final 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.

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 (0.0022 = 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 the regulations, 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 will be considered intermediate-size patient population expanded access submissions, FDA experts believe that most of the 55 other submissions each year will fall under this category.

Thus, approximately 2.7 percent (0.0269 = 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 previously is summarized in table 1 of this document.

TABLE 1.—BASELINE DATA FOR THE NO. OF INDS AND EXPANDED ACCESS REQUESTS BY CATEGORY

Category	Total INDs	Individual Patient or Emergency IND	Treatment IND or Protocol	Other
Number	2046.6	659	4.6	55
Percent of all INDs	100	32.2	0.2	2.7

One comment submitted in response to the proposed rule provided an estimate of the number of patients that might be affected by this rule. As part of our response, we have generated estimates of the number receiving investigational drugs under current expanded access programs, in place since 1986.

Based on the information presented previously, FDA currently receives an average of 659 individual patient or emergency INDs per year. Thus, approximately 659 individuals per year currently receive investigational drugs under single patient or emergency INDs. FDA believes that it is reasonable to assume that a typical expanded access submission for an intermediate-size patient population will affect between 10 and 100 individuals. Given that FDA currently receives an average of 55 such submissions per year, we estimate that between 550 and 5,500 individuals currently receive investigational drugs under intermediate-size patient population or other expanded access programs. A treatment IND or protocol can vary significantly in size and may include between 100 and 10,000 patients. Thus, an average of 4.6 treatment IND or protocol submissions could affect between 460 and 46,000 individuals. Based on this information, FDA estimates that between 1,669 and 52,159 individuals currently receive investigational drugs through expanded access programs. The wide range of these estimates reflects significant variation in the number of patients in intermediate-size patient populations, and treatment INDs or protocols. These estimates are summarized in table 2 of this document.

TABLE 2.—APPROXIMATE NO. OF INDIVIDUALS AFFECTED BY EXPANDED ACCESS PROGRAMS IN PLACE SINCE 1986

Category	Average No. of Submissions	No. of Patients	Minimum No. of Individuals	Maximum No. of Individuals
Individual Patient or Emergency IND	659	1	659	659
Small Patient Population/Other	55	10 to 100	550	5,500
Treatment IND or Protocol	4.6	100 to 10,000	460	46,000
Total			1,669	52,159

D. Nature of the Impact

The final rule will 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 in the preamble of the proposed rule (71 FR 75147 at 75149 to 75150), a major purpose of this 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 final rule will increase the number of patients who obtain access to investigational drugs for treatment use. This increase in volume will lead to more expanded access

submissions from sponsors and physicians seeking investigational drugs for their patients and, as a consequence, will require FDA to review more submissions. Given the relatively small burden associated with expanded access use submissions under the previous regulations (although such submissions are approximately one-third of all IND submissions, the vast majority of those are for individual patients and do not typically require substantial agency resources to review), and the small additional burden associated with the expanded access provisions in this final rule, FDA expects that the economic impact of the final rule will be small.

The final rule also attempts to minimize the potential administrative burdens for physicians, sponsors, and FDA that will result from an increased volume of patients obtaining investigational drugs for expanded access use. The final rule encourages the consolidation of multiple individual patient INDs or protocols for a given use under an intermediate-size patient population IND or protocol. By reducing the total volume of submissions that will 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 final 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 will 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 final rule does not significantly change the existing regulations 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 final rule should increase the number of individual patients seeking access to investigational drugs. FDA anticipates that this increase in individual patient expanded access submissions will be greatest in the years immediately following implementation of the final rule and will at some point level off or possibly even decline. This leveling off or decline will 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 final rule will 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 following issuance of this final rule, because of these uncertainties the agency can provide only an estimate of the range of potential increase. FDA believes that, after publication of the final rule, 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 will be most rapid in the years immediately following publication of the final rule and will 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 3 of this document.

TABLE 3.—EXPECTED PERCENT INCREASE AND ESTIMATED NO. OF INDIVIDUAL PATIENT EXPANDED ACCESS SUBMISSIONS

Year After Implementation of Final Rule	Expected Percent Increase in Individual Patient Submissions	Expected No. 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 1054
4	0	923 to 1054
5	0	923 to 1054

[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 the regulations, 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 final rule. The agency anticipates that this final rule will increase the number of such submissions. Because this previously informal mechanism will be described in the regulations 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 final 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 final 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 will 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 with 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 4 of this document.

TABLE 4.—EXPECTED PERCENT INCREASE AND ESTIMATED NO. OF INTERMEDIATE-SIZE PATIENT POPULATION EXPANDED ACCESS SUBMISSIONS

Year After Implementation of Final Rule	Expected Percent Increase in Intermediate-Size Patient Population Submissions	Expected No. 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 final 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 stated in the preamble of the proposed rule (71 FR 75147 at 75155), sponsors have instituted large expanded access programs under treatment INDs or treatment protocols or under less formal open-label (also referred to as open-access) protocols. 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 may, in certain circumstances, be required to list those programs at *http://www.clinicaltrials.gov*, a Web site maintained by the NIH 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 will 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 will be some economies of scale, so that the incremental costs will be relatively small on a per-patient basis. FDA believes any added costs will be justified by the potentially greater number of patients who will benefit from access to investigational drugs.

E. Benefits of the Final Rule

Because FDA currently has no data that will allow us to predict the extent to which the amendments to existing IND regulations will 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 will benefit from access to these drugs. Thus, the following discussion describes, in general terms, the nature of the potential benefits associated with the final rule.

The benefits of the final 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 will 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 will accrue to individual patients receiving drugs for expanded access use, whereas social benefits will 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 final 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 final rule, will improve access to investigational drugs and result in making expanded access use more widely available to patients regardless of treatment setting.

In formulating the final rule, FDA considered its statutory mandate and 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). 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 reduce the patient population available for 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 will experience diminished social benefits due to the reduced or delayed availability of new therapies approved for marketing by FDA.

The final 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 final rule effectively balances the interests of those patient populations who will 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 final 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 final rule will 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 will adequately protect the safety and welfare of patients who will seek, and may benefit from, expanded access to investigational drugs.

F. Costs of the Final Rule

To the extent that the final 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 final rule does not include any new, 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 final 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 will require a total of approximately 8 hours. This time burden will 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,[2] total employer costs per hour worked for employee compensation for registered nurses in the health care and social assistance sector was $44.21 as of March 2008. Thus, the cost of the estimated 6.8 hours of nurse time required to prepare and submit an individual patient expanded access submission will be approximately $301 ($300.62 = $44.21 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

[2] See *http://www.bls.gov/news.release/ecec.toc.htm*, last viewed July 11, 2008. (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**.)

that the median expected total compensation for a physician in the hematology/oncology specialty category was $387,739 as of March 2008.[3] This median total compensation figure corresponds to approximately $186 per hour ($186.41 = $387,739 / 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 $224 ($223.69 = $186.41 per hour x 1.2 hours). Therefore, the agency estimates that the total cost to prepare and submit an individual patient expanded access submission will be about $525 ($525 = $301 + $224). 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 5 of this document.

TABLE 5.—NO. OF ADDITIONAL INDIVIDUAL PATIENT EXPANDED ACCESS SUBMISSIONS AND ESTIMATED ANNUAL COSTS

Year After Implementation of Final Rule	Expected Increase in the No. of Individual Patient Submissions[1]	Expected Cost of Additional Individual Patient Submissions[2]
1	132–264	$69,300 to $138,600
2	198–329	$103,950 to $172,725
3	264–395	$138,600 to $207,375
4	264–395	$138,600 to $207,375
5	264–395	$138,600 to $207,375

[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 $525 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 will be divided between a Medical Director or Director of Clinical Research, typically a medical doctor (approximately 50 percent or 60 hours), a Regulatory Affairs Director (approximately 20 percent or 24 hours), and a Clinical Research Associate (approximately 30 percent or 36 hours).

Information available on the Internet suggests that the median total compensation for a physician serving as a Medical Director is about $316,134 per year.[4] This translates into an estimated hourly total compensation figure of about $152 ($151.98 = $316,134 / 2,080 hours). Thus, the cost associated with the 60 hours of Medical Director time required to prepare and submit an intermediate-size patient population expanded access submission is approximately $9,120 ($9,120 = 60 hours x $152).

Information available on the Internet also indicates that the median total compensation for a Regulatory Affairs Director is approximately $235,149 per year.[5] This translates into an estimated hourly total compensation figure of about $113 ($113.05 = $235,149 / 2,080 hours). Thus, the cost associated with the 24 hours of Regulatory Affairs Director time required to prepare and submit an intermediate-size patient population expanded access submission is approximately $2,712 ($2,712 = 24 hours x $113).

Finally, information available on the Internet indicates that the median total compensation for a Clinical Research Associate is approximately $86,890 per year.[6] This translates into an estimated hourly total compensation figure of about $42 ($41.77 = $86,890 / 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 $1,512 ($1,512 = 36 hours x $42).

Based on the information presented, the agency estimates that the total cost to prepare and submit an intermediate-size patient population expanded access submission will be approximately $13,350 ($13,344 = $9,120 + $2,712 + $1,512). 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 6 of this document.

TABLE 6.—NO. OF ADDITIONAL INTERMEDIATE-SIZE PATIENT POPULATION EXPANDED ACCESS SUBMISSIONS AND ESTIMATED ANNUAL COSTS

Year After Implementation After Final Rule	Expected Increase in the No. of Intermediate-Size Patient Population Submissions[1]	Expected Cost of Additional Intermediate-Size Patient Population Submissions[2]
1	3 to 6	$40,050 to $80,100
2	5 to 11	$66,750 to $146,850
3	11 to 22	$146,850 to $293,700

[3] See *http://swz.salary.com/salarywizard/layoutscripts/swzl_newsearch.asp*, last viewed July 11, 2008. (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**).

[4] See *http://swz.salary.com/salarywizard/layoutscripts/swzl_newsearch.asp*, last viewed July 11, 2008. (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**.)

[5] See footnote 4 of this document.

[6] See footnote 4 of this document.

TABLE 6.—NO. OF ADDITIONAL INTERMEDIATE-SIZE PATIENT POPULATION EXPANDED ACCESS SUBMISSIONS AND ESTIMATED ANNUAL COSTS—Continued

Year After Implementation After Final Rule	Expected Increase in the No. of Intermediate-Size Patient Population Submissions[1]	Expected Cost of Additional Intermediate-Size Patient Population Submissions[2]
4	14 to 27	$186,900 to $360,450
5	14 to 27	$186,900 to $360,450

[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 final rule will have an impact on the overall number of treatment INDs or treatment protocols. Therefore, FDA does not expect the provisions of this final rule regarding treatment INDs or treatment protocols to impose any incremental cost burden. The total estimated variable and annual cost burdens associated with this final rule are summarized in table 7 of this document.

TABLE 7.—COST SUMMARY

Year After Implementation of Final Rule	One-Time Fixed Cost	Variable Cost	Annual Cost[1]
1	$0	$109,350 to $218,700	$109,350 to $218,700
2	$0	$170,700 to $319,575	$170,700 to $319,575
3	$0	$285,450 to $501,075	$285,450 to $501,075
4	$0	$325,500 to $567,825	$325,500 to $567,825
5	$0	$325,500 to $567,825	$325,500 to $567,825

[1] Since estimated one-time fixed costs are negligible, annual costs equal variable costs.

For reasons discussed previously in this document, the agency expects that the total one-time costs of the final rule will be negligible. FDA expects that the annual costs of this final rule will range from a low of about $109,000 to $219,000 in the first year following publication of the final rule, to a high of about $325,000 to $568,000 in the fourth and fifth years. These estimates suggest total annual costs for the final rule of between $1.2 and $2.2 million for the 5-year period following implementation of the final rule.

The agency expects that the estimated incremental cost burdens associated with this final 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—will submit a request for expanded access to investigational drugs fairly infrequently. Second, as noted previously, the final 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 final rule are designed to minimize the amount of information and paperwork required to support a particular expanded access request. Physicians and drug sponsors will 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 will have such a right of reference, either because the sponsor is also the drug developer or the developer will generally be willing to grant the request. To the extent that these provisions minimize the informational burden on potential sponsors or physicians, the final rule will enhance both efficiency and cost effectiveness.

One comment submitted in response to the proposed rule provided an estimate of the number of patients that might be affected by this final rule. As part of our response, we have generated estimates of the number additional individuals that will gain access to investigational drugs as a result of the final rule.

Information presented in table 5 of this document indicates that FDA expects this final rule to generate between 132 and 395 additional individual patient or emergency INDs per year. Thus, we estimate that between 132 and 395 additional individuals per year will have expanded access to investigational drugs under single patient or emergency INDs as a result of this final rule. Information presented in table 6 of this document indicates that FDA expects this final rule to generate between 3 and 27 additional expanded access submissions for intermediate-size patient populations. As discussed previously,

we believe that an intermediate-size patient population or other expanded access program will generally include between 10 and 100 individuals. Therefore, we estimate that between 30 (30 = 3 x 10) and 2,700 (2,700 = 27 x 100) additional individuals per year will have expanded access to investigational drugs under intermediate-size patient populations. Finally, because FDA expects this final rule to have no impact on the number of treatment INDs or protocols, the number of patients with access to investigational drugs will be unaffected. Based on this information, FDA estimates that between 162 (162 = 132 + 30) and 3,095 (3,095 = 395 + 2,700) additional individuals will receive investigational drugs through expanded access programs as a result of this final rule. The range of these estimates reflects significant variation in the number of patients in intermediate-size patient populations. These estimates are summarized in table 8 of this document.

TABLE 8.—APPROXIMATE NO. OF ADDITIONAL INDIVIDUALS AFFECTED BY EXPANDED ACCESS PROGRAMS UNDER THE FINAL RULE

Category	Expected No. of Additional Submissions	No. of Patients	Minimum No. of Additional Individuals	Maximum No. of Additional Individuals
Individual Patient or Emergency IND	132 to 395	1	132	395
Small Patient Population/Other	3 to 27	10 to 100	30	2,700
Treatment IND or Protocol	0	100 to 10,000	0	0
Total			162	3,095

G. Minimizing the Impact on Small Entities

The agency does not believe the final rule will have a significant economic impact on a substantial number of small entities. Nevertheless, in the proposed rule, we recognized our uncertainty regarding the number and size distribution of affected entities, as well as the economic impact of the final rule on those entities, and requested detailed comment on these important issues. We received no comments that would cause us to change our determination that the final rule will not have a significant economic impact on a substantial number of small entities.

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) will 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 will 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 will 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 will allow the agency to identify the number of sponsors in this category that will qualify as small entities.

Thus, while highly uncertain, the agency believes that at least some of the entities submitting expanded access requests will qualify as small entities. As discussed in section VI.F of this document, the agency expects that any incremental burden associated with the final rule will be small and widely dispersed among affected entities.

H. Alternatives

FDA considered several alternatives to the final 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 will 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 final 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 has been used in situations in which both: (1) The expanded access use did not meet the criteria for a treatment IND under the previous regulation and (2) it would have been excessively burdensome for sponsors and FDA to require large numbers of individual patient INDs for the same use. The agency concluded that, consistent with the terminology of section 561(b)(4) of the act, it is preferable to establish an intermediate category for expanded access, with additional criteria and monitoring requirements, that will 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 the regulations 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 the regulations 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 will 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 final 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.

VII. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520) (the PRA). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting burden. Our estimate includes the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Expanded Access to Investigational Drugs for Treatment Use

Description: The final rule clarifies existing regulations and revises them by adding new types of expanded access for treatment use. Under the final rule, expanded access to investigational drugs will be available to individual patients, including in emergencies; to intermediate-size patient populations; and to larger populations under a treatment protocol or IND. The final 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 Final Rule

1. Submission Requirements for All Expanded Access Uses

Section 312.305(b) describes the submission requirements applicable to all types of expanded access.

Section 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.

Section 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 will 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 for expanded access use (ordinarily, information that will 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

Section 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:

- 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
- FDA must determine that the patient cannot obtain the drug under another type of IND.

Section 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.

Section 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.

Section 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

Section 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. Section 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 will conduct a clinical trial in these patients.

4. Treatment IND or Protocol

Section 312.320 describes the treatment IND or treatment protocol currently codified in §§ 312.34 and 312.35. Section 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 will 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 will not expose patients to an unreasonable and significant risk of illness or injury. This evidence will 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

Our 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. We expect an increase in the number of submissions for expanded access for individual patients and for intermediate-size patient populations as a result of this final rule.

1. Individual Patient Expanded Access

From 1997 to 2005, we received on average approximately 659 submissions for the treatment use of investigational drugs by individual patients per year. This estimate is based on our records of the number of individual patient IND submissions (primarily from physicians) and a survey of our review divisions on the prevalence of individual patient protocol exception submissions received from commercial drug sponsors. As indicated in the table below, we expect an increase in the number of individual patient expanded access submissions because the final rule will increase awareness of the option for individual patients to gain access to investigational drugs and decrease the perceived difficulty of obtaining such access. We anticipate that the increase in individual patient expanded access INDs or protocols will be greatest in the years immediately following implementation of the final rule and will at some point level off or possibly even decline. This leveling off or decline will 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.

We estimate that preparation and submission of an individual patient expanded access IND or protocol submission will 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 our review divisions, we estimate that, for the period 2000 through 2002, we received approximately 55 submissions per year that we consider expanded access for an intermediate-size patient population under the final rule. As indicated in table 9, we anticipate that this number will increase under the final rule 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 final rule encourages the consolidation of multiple individual patient INDs or protocols for a given expanded access use.

Information provided by our review divisions indicates that preparation and

submission of an intermediate-size patient population IND will require a total of approximately 120 hours.

3. Treatment IND or Treatment Protocol

We do not expect the final rule to have an impact on the overall number of treatment INDs or treatment protocols because this type of expanded access is already established in FDA regulations at §§ 312.34 and 312.35. Therefore, we do not expect the provisions of this final rule regarding treatment INDs or treatment protocols to impose any increased paperwork burden. The burden for these submissions, as currently required under § 312.35, is already approved by OMB under OMB control number 0910–0014.

Description of Respondents: Licensed physicians and manufacturers, including small business manufacturers.

Table 9 of this document presents the annualized reporting burden for the total number of expanded access submissions by type of expanded access use. The estimates in the table are based on data from section VI of this document and are calculated by averaging the projected number of submissions for the first 3 years after implementation of this final rule.

TABLE 9.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Responses	Hours per Response	Total Hours
§§ 312.305 and 312.310(b)	988	1	988	8	7,904
§§ 312.305(b) and 312.315(c)	68	1	68	120	8,160
Total					16,064

[1] There are no capital costs or operating and maintenance costs associated with this collection.

The information collection provisions in this final rule have been submitted to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VIII. Federalism

FDA has analyzed this final 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

21 CFR Part 312

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

21 CFR Part 316

Administrative practice and procedure, Drugs, Investigations, Medical research, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 312 and 316 are 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.

■ 2. Section 312.30 is amended by revising paragraph (c) to read as follows:

§ 312.30 Protocol amendments.

* * * * *

(c) *New investigator.* A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under § 312.315 or § 312.320. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

* * * * *

§ 312.34 [Removed]

■ 3. Section 312.34 is removed.

§ 312.35 [Removed]

■ 4. Section 312.35 is removed.

§ 312.36 [Removed]

■ 5. Section 312.36 is removed.

■ 6. 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) *Final 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.

* * * * *

■ 7. 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.

Subpart I—Expanded Access to Investigational Drugs for Treatment Use

§ 312.300 General.

(a) *Scope.* This subpart contains the requirements for the use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) 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 such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

(b) *Definitions.* The following definitions of terms apply to this subpart:

Immediately life-threatening disease or condition 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.

Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

§ 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 events 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 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 (the investigator's brochure must be provided if one exists for the drug), 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 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 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 FDA with a written summary of the results of the expanded access use, including 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, Outreach and Development, Center for Biologics Evaluation and Research, 301–827–1800 or 1–800–835–4709, e-mail: *ocod@fda.hhs.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, 301–796–3400, e-mail: *druginfo@fda.hhs.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 15 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.

PART 316—ORPHAN DRUGS

■ 8. The authority citation for 21 CFR part 316 continues to read as follows:

Authority: 21 U.S.C. 360aa, 360bb, 360cc, 360dd, 371.

■ 9. Section 316.40 is revised to read as follows:

§ 316.40 Treatment use of a designated orphan drug.

Prospective investigators seeking to obtain treatment use of designated orphan drugs may do so as provided in subpart I of this chapter.

Dated: July 20, 2009.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

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