DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 312

[Docket No. FDA–2006–N–0237] (formerly Docket No. 2006N–0061)

RIN 0910–AF13

Charging for Investigational Drugs Under an Investigational New Drug Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its investigational new drug application (IND) regulation concerning charging patients for investigational new drugs. This final rule revises the charging regulation to clarify the circumstances in which charging for an investigational drug in a clinical trial is appropriate, to set forth criteria for charging for an investigational drug for the different types of expanded access for treatment use described in the agency's final rule on expanded access for treatment use of investigational drugs published elsewhere in this issue of the **Federal Register**, and to clarify what costs can be recovered for an investigational drug. This final rule will permit charging for a broader range of uses than was explicitly permitted previously.

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 75168) (proposed rule), we proposed to amend our IND regulation concerning charging patients for investigational new drugs (former § 312.7(d) (21 CFR 312.7(d))) and to add new § 312.8 (charging for investigational drugs). Under FDA's previous § 312.7(d), FDA could authorize charging for an investigational drug used in a clinical trial under an IND and for an investigational drug used in a treatment protocol or treatment IND:

- Former § 312.7(d)(1) provided that a sponsor that wished to charge for an investigational drug in a clinical trial needed to provide a full written explanation of why charging was necessary for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered part of the normal cost of doing business.
- Former § 312.7(d)(2) described several conditions that needed to be met to charge for an investigational drug used under a treatment protocol or treatment IND.
- Former § 312.7(d)(3) provided that a sponsor could not commercialize an investigational drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug.
- Former § 312.7(d)(4) provided that FDA could withdraw authorization to charge if it determined that the conditions underlying the authorization were no longer being met.

In the preamble to the proposed rule, we identified three principal reasons for revising the previous charging regulation (the 1987 charging rule) (52 FR 19466, May 22, 1987).

First, the provisions of the 1987 charging rule concerning charging for investigational drugs in a clinical trial needed to be revised to take into account circumstances that were not anticipated when that original rule was adopted in 1987. FDA expected that requests to charge in a clinical trial would be limited to requests to charge for the sponsor's drug being tested in the trial. In fact, the agency received few such requests.

Far more common have been requests to charge for approved drugs in trials when the drugs needed to be obtained from another entity. These approved drugs may have been used in a trial of the sponsor's drug as an active control or in combination with the sponsor's drug. Even more common were requests to charge for approved drugs used in trials by a third party (not the holder of the approved application) that were intended to study new uses of the approved drug or to compare two drugs. FDA concluded that requests to charge for investigational drugs in these

situations may be appropriate, but that the criteria for evaluation of such requests are different from those that apply when the request to charge is for the sponsor's own drug being tested in a clinical trial. Accordingly, the agency concluded that the 1987 charging rule needed to be revised to provide criteria for charging for approved drugs used in clinical trials.

Second, the provisions of the 1987 charging rule related to treatment use allowed charging patients for investigational drugs only when those drugs were provided under a treatment IND or treatment protocol. Elsewhere in this issue of the **Federal Register**, FDA is publishing a final rule that adds to part 312 (21 CFR part 312) a new subpart I concerning ''Expanded Access to Investigational Drugs for Treatment Use'' (referred to in this document as the ''expanded access final rule'' or ''subpart I''). The expanded access final rule retains the treatment IND and treatment protocol provisions in the 1987 charging rule with minor modifications, and provides for two additional types of expanded access for treatment use: Expanded access for individual patients and expanded access for intermediate-size patient populations. The 1987 charging rule needed to be revised to provide authority to charge for investigational drugs for these two new categories of expanded access.

Third, the 1987 charging rule needed to be revised to specify the types of costs that can be recovered. The language of the 1987 charging rule was not very specific and did not provide sufficient guidance to sponsors on the costs that could be recovered. Moreover, because of the justifications for charging in a clinical trial differ from the justifications for charging for expanded access use, the agency believed that the costs appropriate for recovery would also differ.

The reasons FDA believed the 1987 charging rule needed to be revised are described more fully in the sections II.B, C, and D of the preamble to the proposed rule (71 FR 75168 at 75170 through 75171).

Accordingly, we proposed to remove paragraph (d) of former § 312.7 (paragraph (d) discussed charging for and commercialization of investigational drugs). We proposed to add new § 312.8 containing the following:

- General requirements for charging for investigational drugs,
- Specific requirements pertaining to charging for investigational drugs in a clinical trial,
- Requirements for charging for investigational drugs for treatment use under proposed subpart I (described in the proposed rule on expanded access to investigational drugs for treatment use (expanded access proposed rule) (71 FR 75147, December 14, 2006)), and
- Requirements for determining what costs can be recovered when charging for an investigational drug.

We received 40 comments on the charging proposed rule, which we address in section III of this document.

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

The final rule revises the charging regulation at § 312.7(d) and adds new § 312.8 to clarify the circumstances in which charging for an investigational drug in a clinical trial is appropriate, to set forth criteria for charging for an investigational drug for the different categories of expanded access for treatment use described in the expanded access final rule, and to clarify what costs can be recovered for an investigational drug. This final rule specifies the types of investigational uses of a drug in a clinical trial under part 312 that require prior authorization to charge and provides criteria to authorize charging for each of the uses described in the expanded access final rule.

A. General Requirements for Charging

New § 312.8(a) describes the general requirements and conditions for charging for investigational new drugs. Except for sponsors charging for a drug obtained from another entity (as described below), a sponsor who wishes to charge for an investigational drug must do the following:

- Comply with the applicable requirements for the type of use for which charging is requested (either in a clinical trial or for expanded access) (§ 312.8(a)(1)),
- Provide justification that the amount to be charged reflects only those costs that are permitted to be recovered (§ 312.8(a)(2)), and
- Obtain prior written authorization from FDA (§ 312.8(a)(3)).

Section 312.8(a)(4) provides that FDA will withdraw authorization to charge if it determines that charging is interfering with the development of a drug for marketing approval or that the criteria for the authorization are no longer being met.

In response to comments, the final rule does not require sponsors who must obtain an approved drug from another entity for use in a clinical trial to obtain FDA approval to charge for the drug or be otherwise subject to the requirements in new § 312.8.

B. Charging in Clinical Trials

Section 312.8(b) of the final rule describes specific requirements pertaining to charging for an investigational drug in a clinical trial, including investigational use of the sponsor's approved drug. The cost of an investigational drug used in a clinical trial is an anticipated cost of drug development and should ordinarily be borne by the sponsor. Therefore, FDA believes that charging should be permitted only when three circumstances are present, as described in § 312.8(b)(1) and as follows:

First, charging should be allowed only to facilitate development of a promising new drug or indication that might not otherwise be developed, or to obtain important safety information that might not otherwise be obtained. The preamble to the 1987 charging rule made clear that there should be compelling justification for taking the unusual step of allowing charging for unproven therapy during its development, stating that ''cost recovery is justified in clinical trials only when necessary to further the study and development of promising drugs that might otherwise be lost to the medical armamentarium.'' (52 FR 19466 at 19472). FDA believes that philosophy should continue to apply to charging in a clinical trial in this final rule. Accordingly, § 312.8(b)(1)(i) requires that a sponsor wishing to charge for its investigational drug in a clinical trial provide some evidence of potential clinical benefit that, if demonstrated in clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition. Products that are likely to meet this criterion are also likely to be eligible for fast track development programs and priority review (see FDA's guidance for industry on ''Fast Track Drug Development Programs—Designation, Development, and Application Review'' (January 2006), including the priority review policies for the Centers for Drug Evaluation and Research and Biologics Evaluation and Research in Appendix 3 of that guidance (available on the Internet at *http://www.fda.gov/cder/guidance/index.htm*)).

Second, charging should be permitted only for a trial that is necessary for the development of the drug. Therefore, § 312.8(b)(1)(ii) requires that the sponsor demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective

or safe for the purpose of obtaining initial marketing approval of the drug, or that it would support a significant change in the labeling of the sponsor's approved drug. For example, the trial could be designed to provide data that would support approval of a new indication or generate important comparative safety information.

Third, charging must be necessary to the conduct of the clinical trial. Under § 312.8(b)(1)(iii), a sponsor is required to demonstrate that clinical development of the drug could not be continued without charging because the cost of the drug is extraordinary. The cost of the drug may be extraordinary because of manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed (e.g., due to the size or duration of the trial) or some combination of these or other circumstances. In response to comments, this extraordinary cost criterion for charging for the sponsor's drug in a clinical trial has been revised to clarify that the resources of an individual sponsor are considered in determining whether cost is extraordinary.

Section 312.8(b)(2) provides that the authorization to charge for a drug in a clinical trial would ordinarily continue for the duration of the clinical trial because it is unlikely that the need for charging would change during the course of the trial. However, § 312.8(b)(2) gives FDA the discretion to specify a duration shorter than the length of the trial. FDA may specify a shorter duration if, for example, there is a particular concern that the authorization to charge has the potential to delay the development of a drug for marketing approval.

C. Charging for Expanded Access to Investigational Drugs for Treatment Use

Section 312.8(c) sets forth the criteria for charging for the three types of expanded access to investigational drugs for treatment use described in subpart I of part 312 (the expanded access final rule). Part 312, subpart I describes two types of treatment use (expanded access for individual patients and expanded access for intermediate-size patient populations) not previously described in FDA's regulations and, therefore, not specifically contemplated by the 1987 charging rule. FDA's goal in permitting charging for the treatment uses described in subpart I is to facilitate access to investigational drugs in situations in which a sponsor might not be able to provide a drug for such use absent charging, or to facilitate broader access to an investigational drug for treatment use than would be possible absent charging.

The agency's principal concern with charging patients in expanded access settings for investigational drugs is that charging not interfere with the development of drugs for commercial marketing. Accordingly, § 312.8(c)(1) requires a sponsor wishing to charge for an investigational drug for any of the three types of expanded access under part 312, subpart I to provide reasonable assurance that charging will not interfere with developing the drug for marketing approval.

For the types of expanded access to investigational drugs described in proposed subpart I, FDA believes it is less likely that the limited numbers of patients who might obtain individual patient expanded access to an investigational drug (§ 312.310) or intermediate-size patient population expanded access (§ 312.315) would impede development of a drug or indication. The potential to interfere with drug development is greatest for treatment use under a treatment IND or treatment protocol (§ 312.320). Treatment INDs or treatment protocols can attract large numbers of patients and thus have the potential to significantly affect enrollment in the clinical trials needed to establish safety and effectiveness. Accordingly, § 312.8(c)(2) sets forth specific information that would be required to reasonably assure FDA that charging for an investigational drug under a treatment IND or treatment protocol will not interfere with drug development. Sponsors are required to provide evidence of sufficient enrollment in any ongoing clinical trials needed for marketing approval to reasonably assure FDA that the trials will be completed as planned (§ 312.8(c)(2)(i)). Sponsors are also required to provide evidence of adequate progress in the development of the drug for marketing approval (§ 312.8(c)(2)(ii)). Such evidence could include successful meetings with FDA before submission of a new drug application (NDA), submission of an NDA, or completion of other significant drug development milestones. Sponsors are also required to submit information under their general investigational plans (§ 312.23(a)(3)(iv)) specifying the drug development milestones they plan to meet in the coming year (§ 312.8(c)(2)(iii)).

Section 312.8(c)(3) specifies that the authorization to charge be limited to the number of patients authorized to receive the drug for treatment use, if there is a limitation. For example, the authorization to charge for an investigational drug under an individual patient expanded access submission is limited to a single patient. Similarly, the authorization to charge under an intermediate-size patient population expanded access submission is limited to the number of patients permitted to receive the drug under that particular intermediate-size patient population expanded access IND or protocol.

Section 312.8(c)(4) provides that FDA will ordinarily authorize charging for expanded access for treatment use under part 312, subpart I to continue for 1 year from the time of FDA authorization and that FDA may reauthorize charging for additional periods upon request. It also provides FDA the discretion to specify a shorter authorization. The final rule limits the authorization to charge to a period of 1 year or less to permit the agency to periodically assess whether the criteria for charging continue to be met. FDA anticipates that it will exercise its discretion to specify a shorter duration when there is a particular concern that charging could interfere with drug development.

D. Recoverable Costs

Section 312.8(d) describes the kinds of costs that are recoverable when charging for an investigational drug in a clinical trial and for expanded access for treatment use under part 312, subpart I. The purpose of permitting charging for an investigational drug in a clinical trial is to permit a sponsor to recover the costs of making a drug available to study subjects when those costs are extraordinary. Thus, § 312.8(d)(1) limits cost recovery to the direct costs of making the investigational drug available in these situations. Indirect costs can not be recovered.

Section 312.8(d)(1)(i) describes direct costs as costs incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery. Direct costs include costs per unit to manufacture the drug (e.g., raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging is authorized) or costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug.

Indirect costs are costs that are not attributable solely to making the drug available for the investigational use for which charging is requested (for example, expenditures for physical plant and equipment that are incurred primarily for the purpose of producing large quantities of the drug for commercial sale after approval, or for

making the drug available for a variety of investigational uses). Indirect costs are not appropriate for cost recovery for investigational uses because these costs would be incurred even if the clinical trial or expanded access use for which charging is authorized did not occur. Section § 312.8(d)(1)(ii) states that indirect costs include costs incurred primarily to produce the drug for commercial sale (e.g., costs for facilities and equipment used to manufacture the supply of investigational drug, but that are primarily intended to produce large quantities of the drug for eventual commercial sale) and research and development, administrative, labor, or other costs that would be incurred even if the clinical trial or treatment use for which charging is authorized did not occur.

Sponsors who provide investigational drugs for expanded access for treatment use for intermediate-size patient populations and for treatment INDs and treatment protocols incur costs in addition to the anticipated and ordinary costs of drug development. The purpose of permitting cost recovery for expanded access use is to encourage sponsors to make investigational drugs available for treatment use. Thus, § 312.8(d)(2) permits a sponsor to recover the costs of administering treatment use programs for intermediate-size patient populations and for treatment INDs and treatment protocols, as well as the direct costs of the drug. The final rule does not authorize sponsors to recover administrative costs associated with expanded access for individual patients because these costs would be so minor. Section 312.8(d)(2) provides that in addition to the direct costs of the drug described in § 312.8(d)(1), a sponsor may recover the costs of monitoring the expanded access use, complying with IND reporting requirements, and other administrative costs directly associated with making a drug available for treatment use under §§ 312.315 and 312.320.

Section 312.8(d)(3) provides that, to support its calculation for cost recovery, a sponsor must provide supporting documentation to show that the cost calculation is consistent with the relevant requirements in § 312.8(d). The proposed rule has been revised to state that the documentation must be accompanied by a statement that a certified public accountant has reviewed and approved the calculations.

III. Comments on the Proposed Rule

A. Overview of Comments

The agency received 40 comments on the proposed rule. Comments were received from individuals (persons with serious diseases,[1] persons with family members with serious diseases, and other interested persons), health care and consumer advocacy organizations, pharmaceutical and biotechnology companies, health insurance companies, trade organizations, a State government, an academic medical center, and a venture capital company.

Some comments from individuals were supportive of the charging regulation to the extent that it may make it easier to develop drugs for serious diseases in some cases and make investigational drugs more broadly available for treatment use under expanded access programs. Other comments from individuals were concerned that charging, in the absence of reimbursement for investigational drugs by health insurance companies, would limit enrollment in clinical trials and expanded access programs to those who can afford to pay for the drug.

Health care and consumer advocacy organizations were generally supportive of the proposed rule. Some stated that the rule struck the appropriate balance between facilitating development of costly therapies, including drugs for rare diseases, and increasing access to investigational drugs for treatment use. One advocacy organization expressed concern about the effects of charging on equitable access across different economic strata, arguing that the ability to enroll in clinical trials and expanded access programs may be restricted to wealthier individuals. One organization was skeptical of the agency's assertion that facilitating charging for investigational drugs made available under expanded access programs would increase access.

FDA believes this final rule will facilitate development of some costly therapies that might not have been developed absent cost recovery and will encourage expanded access programs. FDA also acknowledges, however, that the rule has the potential to create certain inequities. Issues related to equitable access are discussed in greater detail in responses to comments 36 through 39.

The major concerns of pharmaceutical and biotechnology companies and their trade organizations were the requirements pertaining to charging for approved drugs being evaluated in a clinical trial under an IND. These companies were most concerned with the requirements pertaining to charging for approved drugs that must be obtained from another entity for use in a trial. An academic medical center was very supportive of FDA's efforts to clarify the charging requirements pertaining to approved drugs used in a trial under an IND. As discussed in greater detail in responses to comments 27 and 31, FDA has revised the proposed rule so that sponsors need not obtain authorization from FDA to charge for approved drugs obtained from another entity not affiliated with the sponsor.

The primary concern of health insurance companies and their trade organization was that the new charging regulation may create pressure on third-party payers to reimburse, or lead to legislation requiring them to reimburse, for investigational drugs. Reimbursement issues are discussed in greater detail in comments 63 through 65.

A major concern for a small biotechnology company, a venture capital firm, and a State health agency was the narrowing of the cost recovery provision in the proposed rule to permit recovery of direct costs only for an investigational drug used in a clinical trial, and to specifically exclude recovery of substantial capital expenditures incurred for purposes of large-scale manufacturing and general research and development costs. These comments were concerned that this narrowing would make it more difficult for entities with limited resources to develop expensive new therapies. FDA continues to believe that these expenditures are not appropriate for cost recovery during the development of a new drug. These concerns are discussed in greater detail in responses to comments 1 and 46.

B. General Comments

(Comment 1) Two comments stated that charging for investigational drugs to treat rare diseases or conditions (orphan drugs) should be subject to less stringent criteria than charging for drugs to treat non-orphan diseases. The comments maintained that drugs to treat orphan diseases are commonly developed by small companies or not-for-profit entities that have limited or no ability to raise money from capital markets. Therefore, less restrictive charging criteria are needed to permit these entities to recover their development costs.

(Response) FDA does not believe there is justification for different and less stringent cost recovery criteria for investigational drugs for orphan diseases than non-orphan diseases. As stated in the preamble to the proposed rule, FDA does not believe that charging

[1] Unless otherwise indicated, ''serious diseases'' in this final rule refers to serious or immediately life-threatening diseases or conditions.

for an investigational drug in clinical studies intended to support approval of the drug is the appropriate mechanism to recoup research and development costs beyond those costs directly associated with making the drug available under criteria described in this charging rule (71 FR 75168 at 75171) (see response to comment 46 for further discussion). FDA believes sponsors intending to develop orphan products should pursue orphan product designation from FDA to assist with development and recovery of investment (21 CFR part 316). Such designation provides for tax credits for the costs of clinical research associated with development of an orphan drug and 7 years of marketing exclusivity after an orphan drug is approved. In addition, sponsors that obtain orphan designation may be eligible to receive grants from FDA of up to $350,000 per year for 4 years to defray directly the costs of clinical research (for more information, see Office of Orphan Products Development, *http://www.fda.gov/orphan/index.htm*). Moreover, orphan designation and grant funds from FDA often provide incentives for additional investment from other sources. This final rule is intended only to address the situation in which the cost of the drug itself is so high that a sponsor needs to recover costs associated with making the drug available to be able to conduct or continue the trial.

(Comment 2) One comment mentioned that it is not clear if the rule applies to both unapproved drugs and approved drugs under investigation for new indications.

(Response) The rule applies to both unapproved drugs and, in certain situations, approved drugs under investigation for new indications (see also response to comment 4).

(Comment 3) One comment suggested that to improve the readability of the proposed rule, the rule should have different provisions for company-sponsored expanded access programs than for investigator-sponsored expanded access programs. The comment also suggested that there should be different provisions for new molecular entities than for approved products being studied for new indications.

(Response) FDA does not believe there is a need for separate provisions for expanded access depending on whether the sponsor of the IND is a manufacturer or a noncommercial sponsor such as an individual physician. In either case, FDA's primary concern is whether the IND would somehow interfere with drug development, so the criteria would be the same for both groups. We also do not believe that separate provisions are needed regarding the amount charged because, in both cases, the amount charged would be limited to costs.

Based on changes made to the proposed rule, FDA also does not believe there is any need to divide the rule into requirements applicable to charging for new molecular entities and requirements applicable to charging for approved drugs under investigation for new uses. FDA has revised the proposed rule to eliminate the requirement that a sponsor who obtains an approved drug from another source to use in a trial as an active control or in a trial intended to obtain additional information about the approved drug (e.g., to study a new indication, to study a safety endpoint) must obtain prior authorization to charge for the approved drug when used for an investigational purpose (see comments 27 and 31). FDA has retained the requirement that a sponsor obtain permission to charge for its own approved drug in a trial of that drug. In this scenario, FDA believes the same criteria as would apply to charging for an unapproved drug should apply. Therefore, a separate provision is not needed.

(Comment 4) One comment stated that the proposed rule's restrictions on charging should not apply to approved drugs and that investigators and others charging for approved drugs should be permitted to charge their usual amounts and to receive the customary insurance reimbursement. The comment also noted that restricting charges for approved drugs in clinical trials would be administratively burdensome to investigators.

(Response) FDA agrees in part and disagrees in part. FDA agrees that a sponsor that is not the marketer of an approved drug (i.e., is not the entity that holds the approved application) should not be required to obtain FDA approval to charge for the drug when it is used in a clinical trial for any purpose—e.g., used for its approved indication as an active control or in a trial of a new indication for the drug (see comments 27 and 31 discussing in greater detail the revision to the final rule to accommodate this change). Accordingly, the provisions in the proposed rule requiring prior authorization to charge in these situations have been deleted from this final rule. However, FDA believes a sponsor seeking to charge for its own approved drug in a trial of a new use or to obtain important safety information about the drug should be treated differently. In these situations, the sponsor is ordinarily conducting the trial to enhance or preserve the commercial value of the drug. Therefore, as is the case with a request to charge for a new molecular entity, the sponsor should be required to overcome the presumption that the cost of the drug is a normal cost of the business of drug development, a cost that should ordinarily be borne by the sponsor of the trial. Therefore, FDA believes the sponsor should be required to obtain prior authorization to charge and should meet the same burden for charging for the approved drug in a clinical trial as it would be required to meet for charging for a new molecular entity. That is, the requirements in § 312.8(b)(1) apply with equal force to charging for the sponsor's unapproved drug and charging for the sponsor's approved drug in a trial of a new use or a trial that could otherwise result in an important labeling change. It is beyond the scope of the regulation and FDA's authority to regulate insurance reimbursement with respect to clinical trials involving approved drugs.

C. General Criteria for Charging

Proposed § 312.8(a) set forth the general requirements and conditions for charging for investigational drugs. A sponsor that wishes to charge for an investigational drug must:

- Comply with the applicable requirements for the type of use for which charging is requested (either in a clinical trial or for expanded access) (proposed § 312.8(a)(1)),
- Provide justification that the amount to be charged reflects only those costs that are permitted to be recovered (proposed § 312.8(a)(2)), and
- Obtain prior written authorization from FDA (proposed § 312.8(a)(3)).

1. Justification for the Amount To Be Charged

(Comment 5) One comment asked that the following language be added at the end of § 312.8(a)(2) and (c)(1) of the proposed rule: ''Any such charges found to be recoverable costs as determined under [§ 312.8(d)] shall be minimized and/or terminated to the greatest degree or at the earliest opportunity possible consistent with the criteria in this rule. If circumstances supporting charging under this rule are no longer met, charging shall terminate.''

(Response) FDA does not believe it is necessary to insert additional language concerning how long and how much to charge because the language essentially repeats the requirements that are already in other parts of the rule. Section 312.8(b)(2) and (c)(4) of the final rule specify how long it is permissible to charge in a clinical trial and for an

expanded access use, respectively. Section 312.8(a)(4) permits FDA to withdraw the authorization to charge at any time if it determines that charging is interfering with the development of a drug for marketing approval or that the criteria for the authorization are otherwise no longer being met. Section 312.8(d) specifies what costs can be recovered during whatever time period charging is authorized.

2. Prior Written Authorization to Charge

The requirement in the proposed rule to obtain prior written authorization from FDA to charge for any investigational drug is a change from the requirements under the 1987 charging rule. Under the 1987 charging rule, a sponsor was required to obtain prior written authorization to charge for an investigational drug in a clinical trial (§ 312.7(d)(1)), but a sponsor of a treatment IND or a treatment protocol under § 312.34 was permitted to commence charging 30 days after receipt by FDA of an information amendment concerning charging, unless FDA notified the sponsor to the contrary (§ 312.7(d)(2)).

(Comment 6) One comment requested that FDA retain the provision in the 1987 charging rule (§ 312.7(d)(2)) that allowed authorization to charge for an investigational drug under a treatment IND or treatment protocol to go into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary by FDA (§ 312.7(d)(2)), and further, that FDA make this provision applicable to all expanded access uses. The comment argued that the requirement for prior authorization would result in delay in the availability of investigational drugs for expanded access uses. One comment requested that FDA add the following language after the provision requiring prior written authorization to charge for an investigational drug: ''Such authorization shall not be unreasonably withheld.'' Two comments agreed with FDA's decision to require prior written authorization from FDA to charge for drugs obtained through expanded access programs.

(Response) FDA does not agree that charging for expanded access uses should be permitted without prior written authorization to charge from FDA. FDA believes it is important to determine, in advance of any patient being charged, that the criteria for charging are met (in particular, the requirement that charging not interfere with drug development) and that the amount to be charged is consistent with the cost recovery requirements.

FDA also does not believe that this provision will delay access to investigational therapies by patients with serious diseases who lack therapeutic alternatives. When there is a pressing need for cost recovery to make an investigational therapy available, FDA will ordinarily be able to expedite review of a charging request. For a new IND, FDA anticipates that, in most cases, it will be able to make a charging determination at the same time it makes a determination on the underlying expanded access IND. When the need to charge becomes evident after an expanded access IND is ongoing, FDA anticipates that a sponsor would be able to foresee the need to charge sufficiently far in advance of that need to be able to make a charging submission and obtain a timely FDA determination.

FDA also does not believe it is necessary to specify that the authorization to charge ''shall not be unreasonably withheld.'' The Administrative Procedure Act provides that an agency decision may be set aside by the courts if found to be ''arbitrary, capricious an abuse of discretion, or otherwise not in accordance with law'' (5 U.S.C. 706(2)(A)). The agency believes this language provides the appropriate standard for FDA's decision of whether to allow charging for an investigational drug.

3. Withdrawal of Authorization to Charge

Proposed § 312.8(a)(4) specified that FDA will withdraw the authorization to charge if it determines that charging is interfering with the development of a drug for marketing approval or that the criteria for the authorization are otherwise no longer being met.

(Comment 7) One comment recommended that the rule include an additional requirement specifying that FDA notify the sponsor of a proposal to withdraw authorization to charge and that FDA provide the sponsor an opportunity to respond.

(Response) FDA expects in most cases to provide reasonable notice before withdrawing an authorization to charge to allow sponsors an opportunity to address the agency's concerns. We are not amending the proposed rule as requested, however, because the agency believes we should have the flexibility, when warranted, to withdraw an authorization to charge without providing advance notice to the sponsor. Sponsors can request review of FDA's withdrawal of an authorization to charge using dispute resolution processes.

4. Lack of Timeframe for FDA Response

(Comment 8) Two comments recommended that the final rule include a general timeframe for FDA to decide whether to permit charging. One of the comments recommended that FDA decide all charging requests within 30 to 60 days.

(Response) FDA does not believe it should commit to a specified time period for review that would apply to all charging requests. In many cases, FDA anticipates being able to make a determination on a request to charge at the same time it responds to the underlying IND submission (when the submissions are made at the same time). However, in FDA's experience, charging requests can present challenging issues that require some discussion between FDA and the sponsor. Thus, it is difficult to estimate reliably a time period for making a charging request determination that would apply uniformly to all charging requests. For this reason, FDA is not prepared to commit to a 30-day timeframe for making charging request determinations. FDA also does not foresee the need for a 60-day maximum review time.

D. Charging in a Clinical Trial

Proposed § 312.8(b) described specific requirements pertaining to charging for an investigational drug in a clinical trial. This provision described criteria for charging for an investigational drug in three situations:

- Charging for the sponsor's own drug in a clinical trial (§ 312.8(b)(1)),
- Charging for an approved drug that a sponsor must obtain from another entity for use as an active control or in combination with another drug in a clinical trial designed to evaluate the safety and effectiveness of the sponsor's investigational drug (§ 312.8(b)(2)), and
- Charging for an approved drug that must be obtained from another entity in a clinical trial designed to evaluate the approved drug (e.g., for another indication) (§ 312.8(b)(3)).

1. General Comments

(Comment 9) Several comments stated that permitting charging for the investigational drug in clinical trials would make it even more difficult to enroll subjects into clinical trials and, therefore, could increase the time to complete trials and delay bringing new drugs to market. Three comments stated that charging could discourage enrollment by patients who lack the resources to pay for the investigational drug. One comment stated that charging for nonreimbursed, investigational

therapies could discourage physicians from recommending enrollment in trials to their patients who are eligible.

(Response) As was the case with the prior charging rule, the provisions concerning charging for the sponsor's investigational drug in this final rule are intended to help sponsors develop important new therapies that would be very difficult or impossible to develop absent charging. In FDA's experience, sponsors have rarely found it necessary to charge for such therapies in clinical trials to develop a drug for marketing approval. FDA anticipates that charging for the sponsor's drug in a clinical trial will continue to be an unusual circumstance. FDA recognizes that charging could make it difficult to enroll subjects in clinical trials and may have a disproportionate impact on enrollment of patients who cannot afford to pay for the investigational drug. FDA expects, however, that sponsors will monitor clinical trial accrual rates and take whatever steps are necessary to ensure that subjects are able to enroll. For example, in FDA's experience, sponsors who have charged for an investigational drug in a clinical trial have made provision to enroll subjects unable to pay.

(Comment 10) Two comments stated that the financial burden for conducting clinical trials, including supplying the investigational drug, should be carried by the sponsors, who stand to benefit from the drug if commercialized.

(Response) FDA agrees that, in most circumstances, sponsors should bear the costs of making an investigational drug available in a clinical trial. The preamble to the proposed rule stated: ''Generally, the costs of conducting a clinical trial are costs that the sponsor should bear. Conducting a clinical trial is part of the drug development process, and drug development is an ordinary business expense for a commercial sponsor'' (71 FR 75168 at 75170). The preamble to the proposed rule also clarified that the philosophy underlying the 1987 charging rule—that charging for an investigational drug in a clinical trial should be an exceptional circumstance and justified only when necessary to further the study of a promising drug that might otherwise not be developed—was intended to apply to this charging rule (71 FR 75168 at 75170).

(Comment 11) One comment stated that FDA should include in the codified portion of the rule the language from the preamble of the 1987 charging rule that: ''FDA * * * [presumes] that supplying investigational drugs to subjects participating in clinical trials without charge is part of the normal cost of doing business.''

(Response) FDA does not believe it is necessary to include the suggested language in this final rule. The preamble to the proposed rule contained language similar to the language in the preamble to the 1987 charging rule, stating that: ''Generally, the costs of conducting a clinical trial are costs that the sponsor should bear. Conducting a clinical trial is part of the drug development process, and drug development is an ordinary business expense for a commercial sponsor'' (71 FR 75168 at 75170). Thus it is clear that FDA intends that the presumption that the cost of an investigational drug should ordinarily be borne by the sponsor and charging is justified only in exceptional circumstances be carried forward to this rule. That presumption is implicit in the stringent criteria in § 312.8(b)(1) for allowing charging for a sponsor's drug in a clinical trial. FDA does not believe it is necessary to state the presumption in the codified language.

(Comment 12) One comment stated that FDA should consider working with pharmaceutical firms to develop better ways of funding clinical trials of investigational drugs. The comment recommended that FDA evaluate practical ways the pharmaceutical industry can fund patient expenses for investigational drugs used in clinical studies and that one option would be for FDA to evaluate the viability of establishing a common patient pool funded by pharmaceutical firms on a voluntary or required basis.

(Response) The agency believes that the comment raises a valid concern. This charging rule is intended to allow a sponsor to recover its costs associated with making an investigational drug available to clinical trial subjects when the cost of the drug is so high that the study could not be conducted without charging. The rule is not intended to help defray other costs associated with the conduct of a trial. However, in FDA's experience, the drug cost is usually not the largest expense associated with clinical trials. Typically, the costs of administering and monitoring a clinical trial are much greater than the cost of the drug. At present, FDA is focusing its collaborative efforts with industry on improving the efficiency of the clinical trial process through various Critical Path programs (e.g., Clinical Trial Transformation Initiative, *http://www.fda.gov/oc/initiatives/criticalpath/clinicaltrials.html*). FDA encourages efforts to develop alternative mechanisms to finance important clinical research by private sector interests or nonregulatory governmental bodies, but believes such efforts would be best administered by private sector interests or nonregulatory governmental bodies.

(Comment 13) One comment recommended that the title of the rule be changed from ''Charging for Investigational Drugs'' to ''Charging for Drugs Used in Clinical Trials'' because the rule also would permit sponsors to charge for approved drugs, which, the comment asserts, are not investigational.

(Response) FDA disagrees. The rule addresses charging for investigational drugs both in clinical trials and in expanded access programs under new subpart I. Because the recommended title would seem to exclude expanded access uses, that title is too narrow. Moreover, the use of an approved drug in a trial of a new use is an investigational use and thus clearly covered by the rule and its title. See response to comment 15 for discussion of a minor change to the section's title.

(Comment 14) Two comments stated that permitting charging for an investigational drug in a clinical trial—because it might exclude economically disadvantaged persons from trial participation—could exacerbate existing problems with underrepresentation of economically disadvantaged and minorities in such trials, and thus may limit generalizability of trial results.

(Response) FDA does not believe that inability to participate in a clinical trial because a subject cannot pay for the drug will have a meaningful effect on generalizability of trial results. Many factors affect participation in clinical trials, including geographic location, ability to qualify for the trial, demographic representation at trial sites, and an insufficient number of slots for all who might like to participate. The effects of charging on the nature of the trial population would probably be of limited significance relative to other factors that could affect generalizability. In addition, in FDA's experience, sponsors that charge subjects for investigational drug in a clinical trial typically make provision for subjects who are unable to pay for the drug, thus mitigating any potential effect on generalizability due to underrepresentation of individuals from lower economic strata.

(Comment 15) Two comments recommended that the rule include a provision stating that the rule does not apply to clinical trials that are exempt from the requirement to have an IND.

(Response) FDA did not intend that the charging regulation apply to clinical trials that are exempt from the IND requirements under § 312.2(b). To make

this clearer, FDA has changed the title of § 312.8 to ''Charging for investigational drugs under an IND.''

(Comment 16) Two comments stated that permitting charging for unapproved drugs in clinical trials has the potential to adversely affect FDA resources.

(Response) As discussed in greater detail in section I of this document, FDA believes it is important to provide an option to charge for investigational drugs in certain circumstances and, also, that is it is important for FDA to regulate charging to prevent commercialization of unapproved drugs and unapproved indications. In FDA's years of experience reviewing charging requests under the 1987 charging rule, such requests have been infrequent and the resources required to conduct such reviews did not have a negative effect on FDA's mission to ensure the safety and effectiveness of new drugs. The proposed rule expanded the scope of INDs for which sponsors may seek cost recovery to include the three types of expanded access INDs under new subpart I. However, in response to comments, the final rule no longer requires sponsors that must obtain an approved drug from another entity to obtain FDA authorization to charge for that approved drug. Thus, FDA anticipates only a modest increase in the number of requests to charge due to this final rule.

In addition, the cost calculation was perhaps the most time-consuming aspect of preparing and reviewing charging requests under the 1987 charging rule. This final rule clarifies and simplifies the scope of recoverable costs. Thus, FDA anticipates that it will typically take less time to prepare and review a charging submission under the new rule than under the 1987 charging rule.

(Comment 17) One comment stated that the rule should differentiate between different phases of testing of an unapproved drug because the justification for allowing recovery and the supporting evidence will vary for different clinical trials in different phases of drug development.

(Response) FDA believes the criteria described in § 312.8(b)(1) concerning charging for a sponsor's drug provide sufficient flexibility to evaluate requests to charge for a drug in clinical trials in different phases of drug development (also see response to comment 19 discussing the variable basis for assessing whether a drug has a potential clinical benefit that would be a significant advantage over available products and response to comment 20 discussing when a clinical trial would be considered essential to establishing that the drug is effective and safe).

2. Charging for the Sponsor's Own Drug in a Clinical Trial

Proposed § 312.8(b)(1) set forth three criteria, in addition to the general criteria in § 312.8(a), that needed to be met to permit a sponsor to charge for its own investigational drug in a clinical trial.

a. *Significant advantage over available therapy.* Section 312.8(b)(1)(i) of the proposed rule provided that a sponsor who wishes to charge for its investigational drug, including investigational use of its approved drug, must provide evidence that the drug has a potential clinical benefit that, if demonstrated in the clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition.

(Comment 18) One comment stated that this criterion is not meaningful as it would apply to all drugs that are selected to be developed by pharmaceutical and biotechnology companies.

(Response) FDA does not agree that all drugs selected to be developed for marketing offer a potential significant advantage over available therapy. Companies often deliberately develop drugs that offer only modest advantages over existing therapy or appear to be similar to existing therapy. There may be good commercial and clinical reasons to pursue such development. For example, there is likely to be variation in response to a pharmacologic intervention, both in desired treatment effect and incidence of adverse effects, in different individuals. Thus, the availability of similar therapies can provide alternatives for those who have inadequate responses to a drug or experience an adverse reaction even if a significant advantage has not been clinically shown for any of the therapies. This criterion is intended to distinguish those types of drugs from those for which there are preliminary clinical data suggesting a significant advantage in the therapy for a given disease and for which the development program is geared toward establishing that advantage.

(Comment 19) One comment asked for clarification about the type and degree of evidence needed to show a significant advantage, especially at the beginning of large phase 3 trials. Another comment recommended that this criterion concerning a significant advantage be replaced with ''evidence of potential advantage over available therapy.'' The comment stated that the significant advantage standard would be likely to prevent a sponsor from charging for its own drug because the standard presumes that comparative studies have been conducted against all the other products.

(Response) The amount and type of data needed to demonstrate a potential clinical benefit that would be a significant advantage over existing therapy will vary with the stage of development. For a request to charge for a large phase 3 trial, ordinarily the clinical data developed in phase 2 will need to confirm or be consistent with a potential significant advantage to satisfy this criterion. For a request to charge for a trial in an earlier phase of development, more preliminary data consistent with a potential significant advantage will suffice. FDA does not agree that comparative data will always be necessary to demonstrate a potential significant advantage over existing therapy. The agency believes that the need to provide comparative data is a matter of judgment. For example, there may be noncomparative phase 2 data and a plausible pharmacologic basis that suggest a significant advantage over existing therapy, and the phase 3 trial for which charging is requested may be a comparative design intended to demonstrate that advantage. Similarly, comparative data are not needed if the drug is intended to treat a disease or subpopulation with a disease, for which there is no satisfactory existing therapy (see also FDA guidance for industry entitled ''Fast Track Development Programs—Designation, Development, and Application Review'' (June 2006), especially section III.B.2, discussing demonstrating a drug's potential at various stages of development).

FDA also does not agree that charging for an investigational drug in a clinical trial should be permitted on the basis of only a potential advantage over existing therapy, without regard to the significance of the advantage. FDA continues to believe that, as was articulated in the preamble to the proposed rule (71 FR 75168 at 75171), the cost of making a drug available to study subjects during development should ordinarily be borne by the sponsor. Charging for drugs in this situation should be reserved for the exceptional circumstance in which it is necessary to continue development of a drug that offers a potential significant advantage over existing therapy.

b. *Essential to safety or effectiveness.* Section 312.8(b)(1)(ii) of the proposed rule provided that a sponsor that wishes to charge for its investigational drug, including investigational use of its

approved drug, must demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is safe or effective for the purpose of obtaining initial approval of a drug, or would support a significant change in the labeling of an approved drug (e.g., new indication, inclusion of comparative safety information).

(Comment 20) One comment stated that the criterion to show that data obtained from the clinical trial are essential to show safety or effectiveness or make a significant labeling change would make it unreasonably difficult for a sponsor to obtain authorization to charge because it would require a sponsor to show that all other trial components of the development program have been identified and marketing approval could not be obtained without completion of the trial for which charging is requested. The comment recommended that, instead, the criterion should be that the study is a phase 2 or 3 protocol that was not put on hold by FDA (§ 312.42) or the trial was agreed to by FDA through the special protocol assessment process (see FDA guidance for industry entitled ''Special Protocol Assessment'' (May 2002)). Another comment stated that this criterion is vague and overly broad because, arguably, all clinical trials conducted in a drug development program would be essential to show safety and effectiveness.

(Response) FDA does not agree that this provision is too restrictive. The phrase ''essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of a drug'' is intended to limit charging—whether in comparative trials, trials of a new use of an approved drug, or other trials—to those trials that will generate effectiveness or safety data on the endpoint or endpoints intended to establish safety or effectiveness (e.g., clinical outcome on the disease of interest), trials that would provide direct corroborative support for such trials, and trials that were necessary prerequisites to the major safety and effectiveness trials (e.g., essential to refining the study design). Such trials would include later phase (e.g., phase 2 and 3) controlled clinical trials evaluating the clinical endpoints that would establish safety and effectiveness (e.g., trials designed to demonstrate the drug's the potential clinical advantage), but could also include important clinical pharmacology studies (e.g., thorough QT prolongation studies, drug-drug interaction studies), safety studies, and other types of studies that would provide essential corroboration for the data from the major safety and effectiveness trials, or aid in the design of those trials.

FDA does agree that its determination, pursuant to a special protocol assessment, that a phase 3 study design and protocol are adequate to provide effectiveness data that would support approval of a marketing application would, in most cases, mean that the clinical trial is essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of the drug.

FDA does not agree that this provision is overly broad. FDA acknowledges that the trials conducted as part of a clinical development program typically build on one another. However, it is very unlikely that all such trials would be considered essential because they provide the data on the endpoints that establish safety and effectiveness, essential corroboration for those data, or are essential prerequisites to the major safety and effectiveness studies (e.g., because they enable the design to be refined so that the data will support approval).

c. *Extraordinary cost.* Section 312.8(b)(1)(iii) of the proposed rule provided that a sponsor that wishes to charge for its investigational drug, including investigational use of its approved drug, must demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary. The proposed rule stated that the cost may be extraordinary due to manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed (e.g., due to the size or duration of the trial), or some combination of these or other extraordinary circumstances.

(Comment 21) Several comments had significant concerns about the extraordinary cost criterion. Two comments maintained that this provision is too vague and subjective for a regulatory requirement. They argued that whether a cost is extraordinary depends to a certain extent on the resources and perspective of the sponsor, i.e., what may be an extraordinary cost for a small company with limited resources may not be so for a larger company with more resources. One of these comments requested additional guidance, either in the rule or in a separate guidance document, on the meaning of extraordinary cost. Two comments stated that this requirement is more stringent than the 1987 charging rule, which requires only that the sponsor provide a written explanation for why charging is necessary for the sponsor to undertake or continue the trial. These comments recommended that FDA delete the extraordinary cost criterion and replace it with the requirement from previous § 312.7(d)(1) requiring a full written explanation of the reasons charging is necessary for the sponsor to undertake or continue the clinical trial or expanded access. One comment requested that FDA clarify how extraordinary cost is to be determined for a large company with numerous corporate affiliates, each with separate budgets.

(Response) In the proposed rule, FDA attempted to describe the concept of extraordinary cost in a way that would make the determination independent of the relative resources of a sponsor. FDA perceived that this approach would be fairer than an approach based on sponsor resources, arguably making cost recovery equally accessible to all sponsors. FDA continues to believe that there are potential scenarios in which a drug cost would be so great that it would be considered extraordinary for any sponsor no matter how great a sponsor's resources. And FDA believes that the parameters set forth in the final rule—that the cost may be extraordinary due to manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed (e.g., due to the size or duration of the trial), or some combination of these or other extraordinary circumstances—provide a functional objective test for whether a cost is extraordinary.

However, FDA also acknowledges that, as a practical matter, whether a drug cost is extraordinary in any given case will often be a function of the resources of a given sponsor. FDA believes that the rule should reflect the reality that a sponsor seeking cost recovery for a drug used in a clinical trial will more often be a sponsor with relatively fewer resources compared to the larger, established pharmaceutical and biotechnology companies. Accordingly, FDA has revised the extraordinary cost criterion in § 312.8(b)(1)(iii) to clarify that a sponsor can demonstrate a cost is extraordinary relative to the resources available to that sponsor. This revision is also responsive to the comments suggesting that we retain the requirement in the previous regulation that a sponsor provide a written explanation of why charging is necessary to conduct the study. The sponsor would be able to provide such an explanation to demonstrate that the cost is extraordinary for that sponsor.

(Comment 22) One comment stated that extraordinary cost is not a meaningful distinguishing criterion in the current environment as, arguably, most new therapies have extraordinary costs.

(Response) FDA does not agree that the concept of extraordinary drug cost is meaningless in the current environment. Extraordinary cost in this rule does not refer to the amount that would eventually be charged for a marketed drug in a commercial setting. Arguably, such costs are often extraordinary compared to historical pricing. Extraordinary cost in this rule refers only to the actual cost of the drug product in the clinical trial. This rule is primarily intended to provide cost recovery in clinical trials in cases in which the drug product itself is expensive to provide because of difficulty in manufacturing costs, scarcity of a natural resource needed to manufacture the drug, the large quantity of clinical supply needed to conduct studies, or other extraordinary circumstances, and therefore represents a substantial added cost above and beyond the routine costs associated with the conduct of the study.

(Comment 23) Two comments stated that FDA lacked the expertise to decide whether the cost of a drug is extraordinary and would need to review factual analyses about the sponsor's costs, comparative costs of other treatments, and arguments about what costs are ordinary versus extraordinary.

(Response) FDA does not believe that it will be difficult to differentiate drugs that are truly extraordinarily costly by objective measures from those that are not, or that such determinations will require special expertise. FDA believes it has enough accumulated experience with the vast array of drugs within its purview to have the ability to make such determinations about the relative costs of various drugs.

(Comment 24) Two comments expressed concerns with the requirement in § 312.8(b)(1)(iii) that a sponsor ''[d]emonstrate that the trial *could* not be conducted without charging because the cost of the drug is extraordinary'' (emphasis added). The comments stated that the more appropriate inquiry is whether a sponsor *would* not conduct a trial absent cost recovery because the cost is extraordinary, so, presumably, it would not be in the sponsor's commercial interest to conduct the trial. Similarly, another comment stated that companies may choose not to develop a drug because it would not be lucrative, but that does not mean the drug could not be developed.

(Response) The charging regulation is not intended to provide a mechanism to subsidize drug development generally or to provide an incentive to reconsider development of a drug that a sponsor has elected not to develop because it was not predicted to be profitable (e.g., would not generate enough revenue to recoup development costs and provide a profit). The intent of the final rule is to address the situation in which the very high, near-term cost of making the drug available to subjects in a clinical trial is a deterrent to development, not the drug's long-term, potential profitability. Therefore, FDA believes that the appropriate inquiry is whether a trial *could not* be conducted without charging because the cost of the drug is extraordinary.

(Comment 25) One comment stated that the need to charge could be for reasons other than extraordinarily high manufacturing costs. The comment maintained that small biotechnology companies have difficulty obtaining funding for clinical trials even when the product is promising and the rule should recognize a sponsor's inability to obtain funding as a reason for charging in a clinical trial.

(Response) As discussed in the preceding comment response, charging for investigational drugs under this rule is not intended to provide funding for clinical trials or drug development generally. The intent is to address the situation in which there is a very high cost associated with making a drug available to clinical trial subjects and that drug cost prevents continued development unless the cost of the drug can be recouped during development. Therefore general development costs, such as costs associated with conducting and monitoring a clinical trial, should not be incorporated in the amount charged for the investigational drug and the lack of funding for such costs is not an independent basis for permitting charging for the study drug (but could be a factor in assessing whether the cost is extraordinary for a given sponsor under § 312.8(b)(1)(iii)).

FDA recognizes that in most drug development scenarios, the costs associated with the conduct of clinical trials and drug development generally are greater than the costs of the investigational drug product, and the development costs may be a deterrent to continuing development of a drug. However, FDA does not believe that incorporating those costs into an amount charged for the investigational drug is the appropriate mechanism to address that situation. If a sponsor wishes to recover from trial subjects other costs associated with the conduct of a clinical trial (e.g., the costs of medical care necessitated by participation in a clinical trial), FDA believes that recovery should occur independent of any charge for the drug product.

(Comment 26) One comment maintained that the extraordinary cost requirement, when applied to charging for the sponsor's approved drug in a trial evaluating a new use of that drug, would discourage manufacturers from developing new uses for approved products.

(Response) FDA believes that the criteria for permitting charging should be the same for charging for the sponsor's investigational drug in trials to support initial marketing approval as for charging in trials of a sponsor's approved drug for a new indication. In each, the cost of the drug is a routine business expense that would ordinarily be recouped after approval of the drug or new indication, and subjects are being asked to pay for an unapproved product or unapproved use in a setting in which charging for the drug is not the norm. The agency is aware that there are many factors that a sponsor weighs in determining whether to develop an approved drug for a new use. FDA does not believe that limiting charging for the sponsor's approved drug in a clinical trial to situations in which the cost of the drug is extraordinary would, in most cases, be the deciding factor in a sponsor's decision to develop or not develop a new indication.

3. Charging for an Approved Drug Obtained From Another Entity for Use as an Active Control or in Combination With Another Drug

Proposed § 312.8(b)(2) described the criteria for charging for an approved drug obtained from another entity for use as an active control or in combination with another drug. To charge in this situation a sponsor must:

- Demonstrate that the clinical trial is adequately designed to evaluate the safety and effectiveness of the sponsor's drug and
- Demonstrate that the holder of the approved application is not providing the drug to the sponsor free of charge.

(Comment 27) Many comments expressed concerns with the provisions in the proposed rule concerning charging for approved drugs obtained from another entity for use as an active control or in combination with another drug. Three comments stated that FDA approval should not be required to charge for approved drugs when the drugs are used for their approved or medically accepted indications and at approved or medically accepted doses and dose regimens. One comment opined that the cost of approved drugs used in a trial for medically accepted purposes is not a drug development expense that should be borne by the sponsor. Two comments stated that the

rule should not distinguish between an approved drug obtained from another entity and an approved drug that is the sponsor's own drug and charging should be permitted for both. Another comment noted that the rationale that trial subjects should not be charged for exposing themselves to the risks of an unproven drug does not apply to approved drugs used for a medically accepted purpose. One comment stated that pharmaceutical companies seldom charge patients for the cost of an approved drug used in a clinical trial. Two comments stated that the investigator commonly buys approved drugs and bills the patient's health insurance or the investigator writes a prescription for the patient, who fills the prescription at a pharmacy that bills the patient's insurance.

Several comments also raised concerns that the charging regulation might interfere with routine reimbursement by third-party payers for approved drugs used for their approved indications in clinical trials. Some comments stated that, when approved drugs used as comparators are charged for in a clinical trial, they are ordinarily dispensed through the normal distribution channel—either an inpatient or outpatient pharmacy—and third-party payers routinely reimburse for such uses. One comment asked FDA to clarify that the proposed rule does not apply to a situation in which the sponsor is not involved in directly supplying approved drugs used as comparators or in combination and does not incur direct acquisition or handling costs that it then seeks to pass on to trial subjects, such as when the drug is dispensed from a pharmacy.

One comment stated that requiring sponsors to seek authorization to charge in cases in which the sponsor is not directly acquiring an approved drug from another entity, such as cases in which the approved drug is obtained or prescribed by investigators and subjects are billed by the investigator or pharmacy, would dramatically alter existing practice without benefiting trial subjects. The comment stated that a large number of clinical studies would need to be submitted for FDA review, dramatically increasing the administrative burden on FDA to review charging requests for affected trials and on sponsors in making submissions.

(Response) The agency agrees that requiring sponsors to obtain authorization to charge for approved drugs obtained from another entity for use as active controls or in combination with another drug, or for other uses is not necessary. We recognize that one of the major rationales for limiting charging—that the safety and effectiveness of the drug is unproven—is often not present in this situation. Moreover, FDA believes there would almost never be a basis to deny a request to charge for an approved drug for use as active control or in combination with another drug under the criteria in the proposed rule. FDA also acknowledges the potential for significant administrative burdens associated with complying with the proposed charging requirements if, as the comments stated, the current practice in many cases is simply to have the approved drug dispensed from a pharmacy and have patients or third parties pay the usual cost for the drug. Moreover, FDA does not want to impose a regulatory requirement that might somehow interfere with the way in which drug costs are reimbursed by third-party payers. Accordingly, in the final rule, FDA has revised proposed § 312.8(a) and deleted proposed § 312.8(a)(2) and (a)(3), to clarify that a sponsor need not obtain authorization to charge for an approved drug used for an approved indication in a clinical trial done under an IND.

(Comment 28) Three comments stated that approved drugs used as active controls or in combination with another drug are not investigational because they are approved and are not being ''investigated'' in the clinical trial.

(Response) FDA disagrees. When an approved drug is used as an active control or in combination with another drug (e.g., as standard therapy in a study comparing standard therapy to standard therapy plus a new investigational therapy), the treatment effect of the active control or the standard therapy is being measured and compared to the new therapy. Therefore, the approved drug is part of the clinical investigation, and hence an investigational drug for purposes of part 312. Notwithstanding that such use is subject to part 312, FDA has revised the proposed charging rule so that sponsors are no longer required to obtain authorization to charge for approved drugs obtained from another entity for use as active controls or in combination with another therapy (as discussed in the preceding comment response).

(Comment 29) One comment argued that sponsors should be able to charge for approved drugs without FDA authorization when used in clinical trials for ''medically accepted'' uses, which the comment defined as uses supported by a recognized compendium such as U.S. Pharmacopeia Drug Information (USP DI).

(Response) As discussed in the responses to comments 27 and 31, FDA has revised the proposed rule to remove the requirement that a sponsor obtain prior approval to charge for an approved drug that the sponsor must obtain from another source for use as an active control or in combination with another drug, or in a trial evaluating the approved drug for a new use or to obtain important safety information. However, the final rule retains the requirement that a sponsor studying its own approved drug for a new indication or to support another type of significant labeling change must obtain approval to charge for the drug in the study. FDA does not agree that whether the use of the drug is ''medically accepted'' by a recognized compendium should be a distinguishing criterion for determining whether the sponsor should be required to obtain authorization to charge for its drug in that situation.

(Comment 30) One comment asked how a trial blind could be maintained if there is charging for a competitor's product used as an active control, but not for the sponsor's investigational drug.

(Response) We note that the final rule removes the requirement of the proposed rule that sponsors seek FDA authorization to charge for a competitor's product used as an active control. In general, FDA believes that maintaining the trial blind is the responsibility of the sponsor.

4. Charging for an Approved Drug Obtained From Another Entity in a Clinical Trial of the Drug

Proposed § 312.8(b)(3) provided that, for a sponsor to charge for an approved drug obtained from another source in a clinical trial to evaluate that drug, it must:

- Demonstrate that the clinical trial is adequately designed to evaluate the safety or effectiveness of a new indication or to provide important safety information related to an approved indication and
- Demonstrate that the holder of the approved application is not providing the drug to the sponsor free of charge.

(Comment 31) Two comments stated that the requirement that a sponsor seeking to charge for an approved drug obtained from another source must demonstrate that the trial design is adequate to evaluate the effectiveness of the new indication is unnecessary because it essentially duplicates what a sponsor is required to demonstrate to be allowed to proceed with the trial under the IND review process. The comments argue that the fact that FDA has not placed the trial on clinical hold (§ 312.42) should be enough evidence that FDA considers the trial of adequate

design. One comment stated that whether the drug is available without charge does not require FDA review. One comment asked FDA to clarify what constitutes sufficient evidence that the sponsor charging for a drug has not received the drug free of charge. Another comment suggested that additional criteria be added as a safeguard to ensure that drug is not being made available free of charge, such as representation by the sponsor that the manufacturer is not funding or supporting the trial in any way.

(Response) FDA acknowledges that the proposed criteria for obtaining authorization to charge for an approved drug that the sponsor must obtain from another entity in a trial of a new use of that drug, or to obtain important new safety information, do not present a significant barrier to obtaining cost recovery. FDA intended to present a relatively low barrier to encourage the kinds of trials that might not be of commercial interest to the drug manufacturer or to otherwise encourage trials that would further elucidate the characteristics of approved drugs. FDA agrees that, for phase 2 and 3 trials, the fact that the trial has not been placed on clinical hold would ordinarily be sufficient to satisfy the criterion that the trial is adequately designed to evaluate the unapproved drug for a new indication. FDA also acknowledges that it intended to rely primarily on the representations of the sponsor for assurance that the drug was not being made available free of charge.

In light of these comments, FDA now recognizes that, based on the criteria in the proposed rule, there would seldom be a basis to deny a request to charge for an approved drug that a sponsor must obtain from another source to study a new use or to obtain important new safety information. FDA also recognizes that the cost recovery calculation for this type of use would usually be very straightforward—ordinarily, the sponsor's acquisition cost if the sponsor purchases the drug directly or the cost of the drug when dispensed from a pharmacy. Therefore, FDA concludes that to require submission of a request to charge for an approved drug obtained from another source would often be a needless administrative burden for the sponsor and FDA. Accordingly, we have decided not to finalize proposed § 312.8(b)(3) in this final rule.

(Comment 32) One comment stated that the ability to charge for an investigational drug obtained from another entity for use in a clinical trial of the drug should be limited to nonprofit organizations. The comment further recommended that the organization be required to demonstrate that it sought grant funds for the trial and any denial of such funds was not due to lack of merit in the research plan.

(Response) FDA does not agree that the ability to charge for an approved drug obtained from another entity should be limited to nonprofit organizations. As discussed in the previous response, FDA has removed from this final rule the proposed requirement that a sponsor obtain prior approval to charge for an approved drug obtained from another entity for use in a trial of the approved drug. Thus, any type of sponsor can charge for such drugs without obtaining authorization from FDA.

FDA hopes that sponsors that must obtain a drug from another entity would ordinarily explore all reasonable financing options (e.g., grants from various sources, funding from the drug manufacturer, a drug supply from the drug manufacturer) before seeking to charge trial subjects for the drug. However, FDA does not believe that it is necessary to specify in regulation that a sponsor exhaust all available alternative financing options before charging for the study drug.

5. Duration of Charging in a Clinical Trial

(Comment 33) One comment interpreted the provision stating that the authorization to charge for a drug in a clinical trial will usually last for the duration of the trial, unless FDA specifies a shorter period, to mean that FDA's approval of the IND (after 30 days) constitutes authorization to charge for an approved drug in a trial of a new indication for the drug as long as the protocol states that the sponsor or investigators may charge for the drug.

(Response) FDA disagrees with this interpretation. Section 312.8(a)(3), which applies to all requests to charge, requires that a sponsor obtain prior written authorization from FDA to charge for an investigational drug. A sponsor must specifically request to charge under the applicable paragraph in § 312.8 and obtain authorization to charge pursuant to that request before it can charge for a trial drug. No provision in this final rule should be construed to mean that FDA's failure to place a protocol on clinical hold constitutes implicit authorization to charge for an investigational drug, notwithstanding that the protocol contains a provision stating that the sponsor intends to charge.

E. Charging for Expanded Access to Investigational Drugs for Treatment Use

Proposed § 312.8(c) set forth criteria for charging for the three types of expanded access to investigational drugs for treatment use described in new subpart I of part 312—individual patient INDs, intermediate-size patient population INDs, and treatment INDs (see the expanded access final rule published elsewhere in this issue of the **Federal Register**). FDA's primary concern with charging patients in expanded access settings is that charging not interfere with the development of investigational drugs for commercial marketing. Therefore, under proposed § 312.8(c)(1), a sponsor seeking to charge for expanded access use must provide reasonable assurance that charging will not interfere with developing the drug for marketing approval. To provide such assurance for a treatment IND or protocol under § 312.320, a sponsor must include evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval to reasonably assure FDA that the trials will be successfully completed as planned (§ 312.8(c)(2)(i)); evidence of adequate progress in the development of the drug for marketing approval (§ 312.8(c)(2)(ii)); and information submitted under a sponsor's general investigational plan specifying the drug development milestones the sponsor plans to meet in the next year (§ 312.8(c)(2)(iii)).

Proposed § 312.8(c)(3) provided that the authorization to charge for an expanded access use is limited to the number of patients authorized to receive the drug under the treatment use protocol or IND, if there is a limitation.

Proposed § 312.8(c)(4) provided that the authorization to charge for expanded access may continue for 1 year from the time of FDA authorization and that sponsors may request that FDA reauthorize charging for additional time periods.

1. General Comments

(Comment 34) One comment objected to the idea that sponsors could only charge for expanded access if the cost was extraordinary.

(Response) FDA believes this comment misread the proposed rule. The cost of an investigational drug need not be extraordinary for a sponsor to be able to charge for the drug under an expanded access IND or protocol in subpart I. That extraordinary cost criterion in the proposed § 312.8(b)(1)(iii) applied only to charging for a sponsor's investigational drug in a clinical trial of that drug under

proposed § 312.8(b)(1). Moreover, this criterion has now been eliminated in the final rule (see comments 21 through 26).

(Comment 35) One comment stated that there is a conflict between the proposed rule on charging and the proposed rule on expanded access because the charging rule would not permit charging for expanded access for individual patients or intermediate-size patient populations if there were no ongoing or planned clinical trial that would support marketing approval. One comment asked that charging for individual patient expanded access be permitted. The comment also stated that it was not clear if charging was permitted for intermediate-size patient population expanded access. One comment stated that sponsors should be permitted to charge for investigational drugs for all types of expanded access programs, provided that charging will not impede drug development.

(Response) FDA believes these comments misread the proposed rule. Proposed § 312.8(c)(1) stated that a sponsor who wishes to charge for an investigational drug for any treatment use under subpart I of part 312 must provide reasonable assurance that charging will not interfere with developing the drug for marketing approval. Moreover, the preamble to the proposed rule specifically stated that one of the major reasons that FDA was revising the 1987 charging rule was to provide authority to charge for investigational drugs under the two new categories of expanded access for treatment use—individual patient and intermediate-size population expanded access INDs (71 FR 75168 at 75169 through 75170). For expanded access under a treatment IND or treatment protocol, the proposed rule stated that such assurance must also include the specific types of evidence in § 312.8(c)(2), including evidence of sufficient enrollment in any ongoing clinical trials needed for marketing approval. However, the specific types of evidence identified apply only to requests to charge for expanded access use under new § 312.320 (treatment IND or treatment protocol) (see § 312.8(c)(2)). Because individual patient INDs (new § 312.310) and intermediate-size patient population INDs can occur earlier in drug development and typically involve much smaller numbers of patients, FDA did not think it would be helpful to specify in the rule how to provide reasonable assurance that charging will not interfere with developing the drug for marketing approval for those types of expanded access program. To clarify that the evidentiary requirements apply only to treatment INDs or treatment protocols, we have revised § 312.8(c)(2) to describe § 312.320 as covering treatment INDs and treatment protocols, rather than merely citing to the section as the proposed rules had done.

2. Increasing Access

In the preamble to the proposed rule, FDA identified the costs associated with making investigational drugs available for treatment use under expanded access programs as a potential obstacle to the availability of such drugs (section II.C of the proposed rule). By facilitating charging for such use, FDA stated that it hoped there would be greater access to investigational drugs (section VI.E of the proposed rule).

(Comment 36) Several comments expressed concerns about the implications of permitting charging for investigational drugs for treatment use under expanded access programs on how such drugs are allocated. Some comments stated that the proposed rule may not increase expanded access because third-party payers are not likely to reimburse for investigational therapies, thus depriving patients not able to afford such drugs. One comment added that neither patients nor insurers should pay for investigational drugs or treatments and that the proposed rule will significantly exacerbate the current problems of access to, and affordability of, health care. Another comment stated that, although the poor may qualify for company-sponsored assistance to pay for investigational drugs, middle-class patients may not be eligible for such programs yet still be unable to afford such drugs. Two comments stated that permitting charging only for direct costs may not increase access because it will not provide enough financial incentive for companies to offer access. One comment agreed that permitting charging for investigational drugs made available under expanded access programs will result in greater access to investigational drugs.

(Response) FDA recognizes that permitting cost recovery for expanded access to investigational drugs for treatment use will not remove all barriers to access. The agency shares the concerns about equitable access to such drugs among patients with varying financial resources. FDA's goal, with this cost recovery provision, is to enable willing sponsors to make a drug available that could not otherwise be made available or to make a drug more widely available than would be possible absent cost recovery, thus potentially benefiting more individuals than would have benefited absent charging. FDA has no control over reimbursement policy. FDA hopes that sponsors that charge for investigational drugs under expanded access programs will also make provision for those who cannot afford such therapies.

FDA believes that permitting sponsors to recover all costs associated with making an investigational drug available and administering an expanded access program provides a reasonable incentive for sponsors to make investigational drugs available for treatment use. As discussed in greater detail in comment 46, FDA believes the cost recovery provision, to the extent it allows companies to recover all the direct costs associated with making the drug available and administering the expanded access program, removes a significant obstacle to making drugs available for treatment use for some sponsors (e.g., sponsors with limited resources for expanded access programs) while preventing commercialization of investigational drugs.

(Comment 37) One comment stated that FDA should closely monitor expanded access programs for which it permits cost recovery to ensure that sponsors honor any commitments to make drugs available to those who cannot afford them.

(Response) FDA hopes that sponsors would, of their own initiative, honor their commitments to make investigational drugs available to those who cannot afford them. However, FDA cannot require a sponsor to honor a commitment to provide a drug to those who cannot afford it, or otherwise compel a sponsor to provide expanded access. FDA also recognizes that circumstances may change such that a sponsor is no longer able to honor a commitment to make investigational drugs available to those who cannot afford to pay for them.

(Comment 38) One comment stated that permitting charging for investigational drugs for expanded access under subpart I will create a dichotomy between rich and poor because patients who can afford to pay for investigational drugs can be guaranteed access under treatment use protocols, but those who cannot will be forced to enroll in clinical trials with only a chance that they will receive the investigational drug in question.

(Response) FDA does not agree that this rule will lead to a situation in which those with fewer resources disproportionately bear the burdens of participating in clinical trials. A sponsor cannot charge for an investigational drug under a treatment IND unless there is evidence of sufficient enrollment in any ongoing clinical trials needed for marketing approval to provide FDA

reasonable assurance that the trials will be successfully completed (§ 312.8(c)(2)(i)). FDA anticipates, therefore, that in most cases, the majority of subjects needed to be enrolled in a trial will have been enrolled before the drug is available under a treatment IND in which the sponsor charges for the drug, so the trial will be fully enrolled. In addition, access to investigational drugs under an individual patient or intermediate-size population expanded access program is usually limited to individuals who are ineligible to enroll in controlled clinical trials. Section 312.310(a)(2) provides that FDA must determine that a patient seeking access to a drug under an individual patient IND cannot obtain the drug under another IND or protocol, which would include a clinical trial or a larger expanded access IND. Section 312.315(a)(2) explains that the intermediate-size patient population IND for a drug being developed is intended to address the situation in which patients requesting access to a drug are unable to participate in a clinical trial of the drug because, for example, they do not meet enrollment criteria, enrollment is closed, or the trial site is not geographically accessible. For these reasons, FDA believes this charging rule will not have a significant impact on the distribution of individuals participating in clinical trials and expanded access programs based on relative wealth.

(Comment 39) One comment stated that poor and lower- to middle-class patients should not be required to pay any costs associated with an investigational drug and that health insurance plans should be required to cover all costs associated with such drugs. Another comment stated that the rule should specify that patients who are uninsured, or those whose insurance excludes payment for investigational drugs, cannot be charged for an investigational drug. One comment recommended that permission to charge by commercial sponsors be tied to a requirement that a percentage of drugs will be provided at no cost to the uninsured and those whose insurers do not cover the costs. Two comments recommended that the rule specify that a certain percentage of an investigational drug for which charging is permitted be made available free of charge.

(Response) The agency cannot require third-party payers to cover the costs of investigational drugs made available under expanded access programs. We also cannot require sponsors to provide a drug free of charge to those who lack insurance or whose insurance does not cover investigational drugs. The agency encourages sponsors to include provisions in their expanded access programs to assist patients who are unable to pay for investigational drugs. The details of such plans (e.g., the percentage of patients eligible to obtain a drug free of charge or the percentage of drug supply that will be made available free of charge) should be determined based on the circumstances of the particular expanded access program.

3. Ethical Considerations

(Comment 40) Two comments stated that there are ethical concerns with charging patients for expanded access use of investigational drugs that may have no benefit and pose safety concerns.

(Response) In determining whether to permit an expanded access use of an investigational drug, FDA assesses whether the potential risks are reasonable in light of the potential benefits, sometimes on the basis of quite limited clinical evidence. Therefore, FDA agrees that there is a risk that the investigational drug will have no benefit and, therefore, that a patient will pay for an investigational drug that provides no benefit. However, if a drug has a potential benefit that is reasonable in light of the risks associated with the drug, and the sponsor must charge to make the drug available, FDA believes the public health is best served by making the drug available to patients for a fee, even if the potential benefit is not realized in a given patient. FDA believes that the ethical concerns expressed in these comments can be addressed by an informed consent that accurately reflects the costs, potential risks, and potential benefits.

4. Non-Interference With Drug Development

(Comment 41) One comment asked that FDA define what it means to interfere with the development of a drug for marketing approval.

(Response) FDA will use several criteria to determine whether charging for an investigational drug in a treatment IND will interfere with drug development. These criteria were described in the proposed rule. Proposed § 312.8(c)(2) described specific criteria needed to provide FDA reasonable assurance that charging for an investigational drug under a treatment IND or treatment protocol (new § 312.320) is not interfering with drug development. Proposed § 312.8(c)(2)(i) required sponsors to provide evidence of sufficient enrollment in any ongoing clinical trials needed for marketing approval. Proposed § 312.8(c)(2)(ii)) required sponsors to provide evidence of adequate progress in the development of the drug for marketing approval. Such evidence could include successful meetings with FDA before submission of an NDA (e.g., a pre-NDA meeting), submission of an NDA, or completion of other significant drug development milestones. Sponsors would also be required to submit information under their general investigational plans (§ 312.23(a)(3)(iv)) specifying the drug development milestones they plan to meet in the coming year (proposed § 312.8(c)(2)(iii)). FDA could then evaluate actual progress made versus planned progress to assess the impact, if any, of charging for an investigational drug under a treatment IND. Negative effects on these criteria would be considered indications of interference with drug development.

The proposed rule did not provide specific criteria for individual (new § 312.310) and intermediate-size patient population access INDs (new § 312.315). The kinds of situations that present with these types of INDs can vary greatly, from situations in which there is no drug development to assess, to anywhere along the spectrum from very early in drug development to the last stages of drug development. The scope can range from a single isolated incidence of an individual patient treatment use for a use not being developed to a late stage intermediate-size population IND for over 100 patients. The agency believes the factors that are relevant to such a determination will be as varied as the timeframes and scopes for these types of INDs. Therefore, FDA does not believe it is necessary or helpful to try to describe in regulation specific criteria that a potential sponsor of an individual patient or intermediate-size population IND must meet to provide reasonable assurance of non-interference with drug development. However, because the populations are smaller than for a treatment IND, the risk of interference with drug development is less than with a treatment IND, so FDA does not believe it will be difficult to demonstrate non-interference with drug development for most individual patient and intermediate-size population INDs.

5. Treatment INDs or Treatment Protocols

For treatment INDs or treatment protocols (new § 312.320), the proposed rule included additional criteria for charging. Section 312.8(c)(2) of the proposed rule provided that for a

treatment IND or protocol, the sponsor must provide:

- Evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval to reasonably assure FDA that the trial(s) will be successfully completed as planned,
- Evidence of adequate progress in the development of the drug for marketing approval, and
- Information submitted under the general investigational plan (§ 312.23(a)(3)(iv)) specifying the drug development milestones the sponsor plans to meet in the next year.

(Comment 42) One comment stated that ''evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval'' (§ 312.8(c)(2)(i)) and ''evidence of adequate progress in the development of the drug for marketing approval'' (§ 312.8(2)(ii)) are too vague and do not provide adequate safeguards to ensure that charging for an investigational drug under a treatment IND will not interfere with a drug's development for marketing. The comment asked that FDA also require a sponsor to submit a copy of, or cross-reference to, its general investigational plan, including a development timeline and clinical trial accrual estimates. The comment stated that when requesting reauthorization, a sponsor should be required to show that its actual enrollment is no more than 5 percent less than its original estimates or, if lower, provide a satisfactory explanation for the deviation from planned accrual (e.g., smaller than anticipated population with the disease of interest from which to draw subjects). One comment stated that determining whether charging is interfering with the development of a drug for marketing approval would require FDA to analyze patterns of enrollment in clinical studies and the causes of insufficiencies in enrollment, and assess what delays are unacceptable.

(Response) FDA acknowledges that applying the criteria concerning drug development progress involves judgment, but does not agree that these criteria are too vague. Modern drug development involves the progressive development of a body of evidence to support a marketing application and generally follows a relatively predictable course. For given diseases, it is possible to predict timeframes for development generally and specific components of development (e.g., individual clinical trials) with some precision. It is also true that initial time expectations can be overly optimistic and require adjustment. However, FDA believes a marked deviation from expectations that coincides with the beginning of an expanded access program can be easily recognized and interpreted as related to the availability of the drug under a treatment IND. For this reason, FDA believes that the identified criteria provide a reasonable basis upon which to judge drug development progress, both before and after the initiation of a treatment IND, to determine if progress is adversely affected.

FDA does not believe a 5-percent decrease in clinical trial accrual from a planned clinical trial accrual rate would be a useful benchmark for determining whether a treatment IND is interfering with drug development. Typically, planned accrual rates are crude estimates and lack the precision needed to make a 5-percent deviation meaningful. In addition, the precision with which accrual rates can be predicted likely varies for different diseases based on their prevalence and other factors. For these reasons, FDA does not believe that specifying a percentage deviation from expected clinical trial accrual would be useful for evaluating potential interference with drug development by a treatment IND. FDA also does not agree that determining whether charging for a treatment IND is affecting drug development will require comprehensive analyses of clinical trial accrual patterns. FDA anticipates that a finding that reauthorization is not appropriate because charging is interfering with enrollment in clinical trials will ordinarily be based on very strong evidence of a significant effect contemporaneous with onset of an access program, and not on subtle deviations from historical accrual patterns for clinical trials in the disease of interest.

6. 1-Year Authorization

Section 312.8(c)(4) of the proposed rule provided that charging for any type of expanded access to an investigational drug for treatment use may continue for 1 year from the time of FDA authorization unless FDA specifies a shorter period. It also provided that a sponsor may ask FDA to reauthorize charging for additional periods. The preamble to the proposed rule stated that FDA will ordinarily authorize charging for the drug for a period of 1 year, unless ''there is a particular concern that charging would interfere with drug development'' (71 FR 75168 at 75172).

(Comment 43) One comment stated that the 1-year authorization period was unnecessary because FDA can always withdraw authorization if the criteria are no longer being met. The comment added that the provision could delay getting drugs to patients if there were a delay in reauthorizing charging.

(Response) The agency does not believe it is reasonable to place the burden on FDA to investigate whether the criteria for charging continue to be met because FDA does not have independent access to the information needed to make that determination. FDA would need to request that the sponsor provide the necessary information. Therefore, FDA believes it would be more efficient if that sponsor simply provided to FDA the information on an annual basis. We do not agree that requiring that charging be reauthorized annually will delay patient access to investigational drugs provided sponsors make a timely and complete submission seeking reauthorization to charge. In most cases, FDA believes the determination will be straightforward and the review will be completed expeditiously.

(Comment 44) Another comment recommended reducing the time that a sponsor may charge before seeking reauthorization to charge from 1 year to 6 months because charging for investigational drugs always presents a risk of compromising enrollment in clinical trials.

(Response) FDA believes the 1-year anniversary is a reasonable point in time to re-evaluate the charging request for most authorizations to charge. If FDA has concerns about charging for a particular treatment IND, for example, where there is a concurrent clinical trial still enrolling subjects, the rule provides FDA the option to specify a shorter period in which to re-evaluate whether the criteria for charging continue to be met.

F. Costs Recoverable When Charging for an Investigational Drug

Proposed § 312.8(d) described the types of costs that a sponsor can recover when charging for an investigational drug in a clinical trial and for treatment use under an expanded access IND. Proposed § 312.8(d)(1) provided that a sponsor may only recover the direct costs of making an investigational drug available.

Proposed § 312.8(d)(1)(i) described direct costs as those incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery. Direct costs include costs per unit to manufacture the drug (e.g., raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging

is authorized) or costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug.

Proposed § 312.8(d)(1)(ii) described indirect costs (those costs that can not be recovered when charging for an investigational drug) as costs incurred primarily to produce the drug for commercial sale (e.g., costs for facilities and equipment used to manufacture the supply of investigational drug, but that are primarily intended to produce large quantities of the drug for eventual commercial sale) and research and development, administrative, labor, or other costs that would be incurred even if the clinical trial or treatment use for which charging is authorized did not occur.

1. Direct and Indirect Costs

(Comment 45) One comment stated that FDA lacked the expertise to decide whether the price proposed by the sponsor would only cover direct costs. The comment stated that FDA accountants would need to scrutinize each sponsor's asserted direct costs to ensure fairness and consistency in its handling of the policy and that distinguishing between direct and indirect costs is likely to be complicated.

(Response) The agency believes that, when charging for investigational drugs, a sponsor of a clinical trial or expanded access program should not be permitted to commercialize (e.g., profit from the sale of) the drug. Thus, the proposed rule set forth criteria that permit a sponsor to recover only costs specifically attributable to making the investigational drug available in the trial or expanded access program for which cost recovery is authorized (i.e., only those costs that would not have been incurred but for the provision of the drug). We believe the direct cost provision as proposed, by differentiating between direct costs and indirect costs, and not providing for apportionment of indirect costs (e.g., overhead and general research and development costs) simplifies the cost recovery calculation to the extent possible and makes clear FDA's objectives concerning what costs can be recovered. Therefore, FDA does not anticipate major controversies concerning cost recovery calculations under this rule, or the need to rely heavily on financial experts to adjudicate such calculations. In the event of a significant controversy, FDA expects that it will be able to require the sponsor to produce supporting documentation prepared by an independent financial expert attesting that the calculation is consistent with the cost recovery provisions in this rule.

(Comment 46) Several comments argued that sponsors should be permitted to charge for other types of costs in addition to those provided for in the proposed rule. One comment stated that cost recovery should include the costs of clinical trials, all related research and development costs, and administrative, labor, and other costs. Two comments stated that FDA should permit some cost recovery for research and development costs in clinical trials. One of the comments requested that FDA reconsider its decision to exclude research and development costs from the cost recovery calculation. The comment argued that FDA could provide criteria to better define recoverable research and development costs, thus avoiding the subjectivity and arbitrariness concerning recovery of research and development costs in the 1987 charging rule. One comment asked that cost recovery be permitted for production fixed costs such as capital investment and fixed manufacturing expenses. Two comments agreed that sponsors should only be permitted to charge for direct costs. One of the comments agreed with the statement in the proposed rule that provision of unapproved drugs should ordinarily be considered part of the cost of doing business and that charging for indirect costs and overall development costs should not be permitted. One comment stated that the proposed rule's description of recoverable costs is subject to varying interpretations by accounting professionals and would thus result in inconsistent application of the cost recovery provisions.

(Response) FDA does not agree that the cost recovery provision should provide for recovery of research and development costs incurred to develop the drug for marketing approval. For a drug that has not yet been approved for any purpose, the intent of permitting charging for that drug in a clinical trial is to provide the opportunity to recoup the cost of making the drug available when the cost of that drug is extraordinary in relation to drug costs generally, or in relation to the resources of the sponsor, and therefore, highly burdensome for a sponsor. The intent is not to subsidize the overall development of the drug. In general, the costs associated with drug development are very large, so it is not reasonable to expect the relatively small number of patients participating in a clinical trial (compared to those who will obtain a drug once it is on the market) to be able to meaningfully subsidize those costs.

The intent of allowing cost recovery for expanded access uses is to remove any financial disincentive for a sponsor to make a drug available by permitting the sponsor to recover direct costs of making the drug available plus monitoring and administrative costs directly associated with the expanded access use. The intent is not to allow a sponsor to begin recouping its general drug development investment in advance of marketing approval. FDA believes that allowing recovery of those generalized costs prior to marketing approval would be effectively permitting commercialization of an unapproved drug.

The agency also does not agree that the cost recovery provision should provide for recovery of capital investment and fixed manufacturing costs, which are incurred by the sponsor primarily for the purpose of manufacturing sufficient quantities of the drug for commercial sale. These costs also should be recouped during commercial marketing of the drug.

(Comment 47) One comment asked that FDA revise the proposed rule to permit cost recovery for the cost of drug delivery, which includes formulation, packaging, instrumentation, monitoring, disposables, setup, nursing, and similar costs.

(Response) It is not necessary to make the suggested revisions because such costs can be recovered without authorization from FDA. Section 312.8(d)(1) is intended to permit a sponsor to recover its direct costs incurred in making a drug available from the onset of manufacturing to the point it arrives at the destination to which it was shipped, or acquisition, shipping, and handling costs for a drug acquired from another source (e.g., where manufacturing is outsourced). Subsequent costs incurred at a clinical trial site (e.g., a hospital or clinic), including pharmacy costs (e.g., the cost to reformulate a drug for infusion), nursing costs (e.g., costs associated with administering a drug and monitoring study subjects), equipment costs (e.g., intravenous (IV) administration sets), and costs for study-related procedures (e.g., chemistry labs, radiographic procedures), are outside the scope of this rule. That is, the costs of these items and services can be recovered without prior authorization from FDA (also see response to comment 64, which includes a link to the Center for Medicare and Medicaid Services (CMS) policy concerning reimbursement for clinical trial related items and services).

(Comments 48) One comment stated that there might be substantial differences in the amount charged per

patient for the same drug if the cost were allocated across a small population clinical trial compared to a large population trial.

(Response) We agree that this result is possible. For example, if a sponsor is permitted to charge for a drug in a small clinical trial, and the sponsor then submits a separate request to charge for the drug in a larger subsequent trial of the same drug, the drug cost may be lower in the larger trial due to economies of scale. FDA believes the higher cost for the smaller population is probably unavoidable and is a reasonable outcome for cost recovery purposes.

(Comment 49) One comment stated that limiting the amount of cost recovery for an approved drug to acquisition and handling costs, instead of permitting investigators and pharmacies to seek normal reimbursement amounts, would create serious administrative problems because it would require investigators to establish separate billing and inventory accounting systems for trial drugs. The comment added that, to the extent that community pharmacies are furnishing drugs in clinical trials, the proposal to limit what they can charge does not seem feasible, because they would not even be aware of the customer's status as a clinical trial subject.

(Response) As discussed in comment 27 and 31, FDA has revised the proposed rule so that sponsors that must obtain the study drug or an active control from another entity (i.e., a sponsor who is not the applicant who holds the approved application for a drug and commercially markets the drug) are not required to obtain authorization to charge for the drug. FDA believes such sponsors should be able to cause the approved drug to be distributed to trial subjects through ordinary distribution channels for approved drugs (e.g., an inpatient or outpatient pharmacy) pursuant to a physician's order or prescription and to cause subjects to be charged the same amount that would be charged to a patient who received the drug in the course of clinical practice. As discussed in comment 26, sponsors that conduct trials of their own approved drug (e.g., a drug that the sponsor commercially markets) must obtain prior authorization to charge for the trial drug pursuant to the criteria set forth in § 312.8(b)(1) of this final rule. Such sponsors are permitted to recover only their direct costs for making the trial drug available to subjects as described in § 312.8(d) of this final rule.

(Comment 50) One comment was concerned that limiting the amount a sponsor would be able to charge for an approved drug in a clinical trial to cost only would have implications for the rebates and discounts that must be made to eligible entities (private entities receiving grants under the Public Health Service Act, and certain hospitals) under the Medicaid Rebate and the 340B Program (section 340B of the Public Health Service Act (42 U.S.C. 256b)). The comment stated that rebates and discounts for a drug under these programs are based in part on the ''best price'' to any purchaser during each calendar quarter and was concerned that if the amount charged under this rule were included in the ''best price'' determination, the sponsor could incur a large liability for rebates and discounts to eligible entities. The comment stated that such pricing could also be construed to establish most favored customer pricing that could be used to set prices under the Federal Supply Schedule contracts with the Federal Government.

(Response) FDA believes that recovery of drug costs associated with making an approved drug available to subjects in a clinical trial is distinct from the commercial sale of drugs. The former does not involve a commercial sale of the drug and is not intended to make a drug available for use in a clinical practice setting. FDA believes that the primary objective of programs for Medicaid and the 340B program (by which certain federally funded grantees and safety net providers may purchase prescription drugs at significantly reduced prices) and of those agencies that administer Federal Supply Schedules for pharmaceuticals (e.g., the Veterans Administration) is to obtain fair pricing relative to the prices paid by other entities in the commercial marketplace for drugs used in clinical practice settings (e.g., in a hospital, for outpatient use), and not relative to the amount a sponsor charges in the unusual circumstance in which it seeks to recover its drug cost in a clinical trial. However, sponsors who intend to charge for an approved drug in a clinical trial should consult with CMS concerning the implications of cost recovery on the best price determination. Sponsors should also consult with the agencies that administer Federal Supply Schedule contracts for pharmaceuticals concerning the implications for prices under those contracts.

(Comment 51) One comment asked that FDA permit cost recovery for direct manufacturing costs for equipment and reusable supplies used to manufacture the investigational drug and marginal costs to produce additional investigational drugs.

(Response) The intent of the cost recovery provision is to permit cost recovery for whatever direct costs are attributable to providing the amount of drug needed for the clinical trial or expanded access use. The rule purposefully excludes many other costs (e.g., overhead, depreciation, reusable supplies, equipment, manufacturing facility) that would be incurred even if the amount of drug needed was not produced, but a small fraction of which could be apportioned to the drug supply produced under general accounting principles. FDA believes these costs would ordinarily be a very small percentage of the total cost when apportioned to the amount of drug produced for a clinical trial or expanded access program, so permitting recovery for these types of costs would create needless complexity and administrative burdens. For example, FDA would need to retain personnel with financial expertise to assess a relatively small number of very complex cost recovery calculations. FDA also believes permitting cost recovery for a broader array of costs might invite expansive and unwarranted interpretations of allowable costs, which would create additional administrative burdens.

(Comment 52) Three comments stated that FDA should allow charging for the market value of an approved drug being studied for a new indication. One comment stated that when charging for approved drugs, normal charges incurred at the site at which the drug is dispensed (e.g., outpatient or inpatient pharmacy) should be permitted.

(Response) As discussed in comment 31, FDA has revised the proposed rule to eliminate the requirement for prior approval to charge for an approved drug being studied for a new indication when the sponsor must obtain the drug from another entity. In this situation, the sponsor can cause the drug to be distributed to subjects through ordinary distribution channels for marketed drugs (e.g., inpatient or outpatient pharmacies).

However, a sponsor must obtain prior approval to charge, and may recover only the sponsor's direct costs for making a drug available, in the sponsor's trial of a new indication or use of its own approved drug. FDA believes that entities that are marketing an approved drug should generally not charge for the drug in such trials. As discussed in comment 26, sponsors that also market the approved trial drug should not be able to commercialize an unapproved use by charging subjects

market value for the drug in a trial of the unapproved use.

2. Recoverable Costs for Expanded Access Uses

Proposed § 312.8(d)(2) provided that when charging for an expanded access use under proposed § 312.315 (intermediate-size patient population IND or intermediate-size patient population protocol) and § 312.320 (treatment IND or treatment protocol), a sponsor may recover, in addition to the direct costs of the investigational drug as described in proposed § 312.8(d)(1)(i), 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 use.

(Comment 53) Two comments recommended that sponsors be allowed to charge a reasonable administrative fee, rather than basing charging on an FDA-reviewed calculation of direct costs. The comments suggested that the fee could be set by the sponsor after consultation with patient groups or based on a comparison of the cost of treatment with other drugs in the class or other therapies. The comments further stated that this proposal would simplify the administrative burden and encourage sponsor participation in expanded access programs.

(Response) FDA believes its proposed approach to determining what costs can be recovered for making investigational drugs available for expanded access uses—permitting a sponsor to recover its direct drug costs plus costs of monitoring the expanded access IND or protocol, regulatory compliance associated with the IND or protocol, and other direct administrative costs—is preferable because it simply permits a sponsor to recover all costs it incurs to provide the drug under the expanded access IND or protocol. An administrative fee approach involving consultation with affected patient groups and comparisons of treatment costs for similar or related treatment options seems to add needless complexity and invite arbitrary cost recovery determinations. In addition, this approach would provide FDA no tangible criteria by which to assess whether the amount charged represents commercialization of an unapproved drug.

(Comment 54) Two comments asked FDA to clarify the evidence required to support the amount to be charged under an expanded access program, especially for orphan indications. One of the comments asked that FDA develop guidance with examples of acceptable cost recovery determinations.

(Response) The recoverable costs for orphan indications under an expanded access program will be the same as for other indications: The direct costs of the drug plus its monitoring, regulatory compliance, and other administrative costs. FDA believes the rule clearly reflects this intent and no additional criteria or guidance are needed concerning what costs can be recovered for investigational drugs for orphan indications. As discussed in the response to comment 48, it is likely that the unit cost of a drug will increase as the size of the population to be treated decreases, but this correlation is unavoidable and does not require any special considerations in the cost recovery calculation. Although FDA believes the cost recovery provisions are sufficiently clear, FDA will evaluate how the rule is implemented and, if there is confusion concerning recoverable costs for expanded access purposes, FDA will consider developing guidance to assist implementation.

(Comment 55) One comment stated that sponsors will continue to be reluctant to charge for a product made available for an expanded access use where the safety and efficacy is unproven, for which there is no reimbursement to help patients pay such costs, and where the allowable charges are limited to the ''direct costs'' of manufacturing and distributing the proposed product.

(Response) FDA is not advocating that sponsors charge for investigational drugs in expanded access programs. The purpose of permitting cost recovery for expanded access use is to remove any financial disincentive to making a drug available for such use. FDA hopes that sponsors that have the resources to make investigational drugs available for expanded access use will continue to make such drugs available free of charge.

(Comment 56) One comment stated that monitoring or reporting costs for expanded access appear to be excluded by the rule.

(Response) The comment misinterpreted the proposed rule. Proposed § 312.8(d)(2) specifically provided that, for expanded access to an investigational drug for treatment use under proposed §§ 312.315 (intermediate-size patient population) and 312.320 (treatment IND or treatment protocol), in addition to the direct costs described in proposed paragraph (d)(1)(i) of § 312.8, 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 these two types of expanded access.

3. Supporting Documentation

Proposed § 312.8(d)(3) provided that a sponsor must provide supporting documentation to show that its cost recovery calculation is consistent with the recoverable costs requirements in paragraphs (d)(1) and, if applicable, (d)(2).

(Comment 57) One comment asked FDA to clarify that if the sponsor challenges FDA's calculation or authorization of recoverable costs, any affected person, including patients, may be a party to that review.

(Response) If FDA determines that the amount sought to be charged must be lowered by a specified amount and the sponsor formally disputes that determination, third parties would not be allowed to be party to the dispute resolution without the sponsor's consent because the discussion would invariably involve commercial confidential information. A sponsor's formal dispute of an FDA denial of a charging request would present the same problem for third parties seeking to be a party to the dispute resolution. Therefore, FDA believes it cannot provide for third-party participation in formal disputes concerning charging determinations without the consent of the sponsor disputing the FDA determination. Moreover, FDA anticipates that most disputed issues with a charging request will be resolved informally in discussions between FDA and the sponsor seeking charging, so a formal dispute will be rare.

(Comment 58) One comment stated that the rule should provide that documentation of recoverable costs follow accepted accounting practices. Another comment stated that it would be difficult for FDA to verify the costs requested, pointing out that the proposed rule stated that if requester's supporting documentation relies on financial information or accounting methods beyond the expertise of FDA reviewers, FDA may request that a sponsor provide independent certification.

(Response) FDA agrees that the documentation provided to support a calculation of recoverable costs for charging purposes should be prepared by a professional who is competent to make the required determinations. FDA also agrees that it may lack expertise to verify the costs requested. Accordingly, the proposed rule has been revised to state that the documentation must be accompanied by a statement that a

certified public accountant has reviewed and approved the calculations.

(Comment 59) One comment noted that the proposed rule needs to address the tax implications for sponsors of investigational drug charges.

(Response) It is not within FDA's expertise to interpret the tax implications of these charging regulations. Sponsors and individuals who take advantage of the cost recovery option afforded by these regulations are responsible for determining the tax consequences of that cost recovery.

4. Authority to Set Pricing

(Comment 60) Two comments stated that FDA has no statutory authority to regulate the price for which medicine is sold, whether it is approved or unapproved, and such regulation is outside FDA's statutory mission to ensure the safety and effectiveness of marketed drug products.

(Response) The comment misunderstands FDA's statutory basis and goals for regulating charging. FDA is not setting a price for a medication for commercial sale. This final rule intends only to permit recovery of certain costs associated with making an investigational drug available in a clinical trial or for an expanded access use, not to permit FDA to set the price for commercial sale of drugs. In the preamble to the proposed rule, FDA discussed its legal authority (71 FR 75168 at 75173, citing 52 FR 19466 at 19472 (May 22, 1987)). FDA concluded that permitting a sponsor to charge an amount greater than necessary to recover its costs (i.e., to permit a sponsor to profit) would be considered commercialization. For that reason, FDA stated that sponsors could only recover their costs associated with making an investigational drug available. This final rule merely refines what would be considered allowable costs to address some confusion and varied interpretations with the 1987 charging rule.

(Comment 61) One comment asked for clarification about what would be an acceptable independent certification for cost recovery calculations.

(Response) Independent certification from an outside accountant is likely to be adequate documentation concerning the recoverable costs that can be incorporated into the unit cost of the investigational drug. The final rule states that the documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculations.

5. Confidentiality

(Comment 62) Three comments expressed concern about the confidentiality of the documentation used to support cost calculations. Two comments stated that financial information should be considered proprietary and should not be available to the public either before or after approval.

(Response) FDA will maintain the confidentiality of documentation submitted to support charging requests in a manner consistent with the requirements of 21 CFR part 20. The sponsor is responsible for ensuring that the party providing the certification keeps confidential the information relied on in making that certification.

6. Effect on Payment Systems (CMS and Insurance)

(Comment 63) Several comments expressed concern about the relationship between the proposed rule and payment systems, specifically systems of CMS and health insurance companies. One comment suggested that there should be regulatory changes to require Medicare Part D and other third-party payers to pay for investigational drugs used in clinical trials for which FDA has permitted charging. The comment suggested that the proposed rule could also be revised to provide that FDA authorization to charge for an investigational drug in an expanded access program constitutes approval of the drug so that third-party payers such as insurance companies and Medicare Part D would reimburse patients. Two comments stated that if Medicare covers a drug used in a clinical trial under its coverage with evidence development policy (see CMS ''Coverage with Evidence Development,'' *http://www.cms.hhs.gov/CoverageGenInfo/03_CED.asp* (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**.)), FDA should permit charging for the drug. Another comment recommended that FDA advise CMS to develop a reimbursement model for drugs being used under expanded access programs because private health insurers will then follow suit and there will be more equitable access to investigational drugs. One comment suggested that FDA should require insurers to agree that investigational drugs will be listed on a reimbursable formulary for the indications tested in trials or used in expanded access programs.

(Response) FDA authority to provide for an exception to the general prohibition on charging for investigational drugs, and its policies concerning charging, are distinct from CMS authority to identify the medical interventions for which it will reimburse. FDA has no authority to require that CMS reimburse for investigational drugs for which FDA has permitted charging. Similarly, FDA has no authority to dictate reimbursement policy to private health insurers. FDA notes that there is a trend toward providing reimbursement for medical care related to participation in a clinical trial, and reimbursing for investigational uses of products when there is a certain level of evidence to support the use. FDA believes these are encouraging developments and hopes that third-party payers will continue to develop policies to provide reimbursement for investigational therapies in appropriate circumstances.

7. Collaboration With CMS and the National Cancer Institute

(Comment 64) One comment stated that it would be useful if FDA, CMS, and the National Cancer Institute were to collaborate on the reimbursement implications of this new rule to ensure there are no obstacles to Medicare payment for these investigational drugs.

(Response) FDA discussed the implications of the proposed charging regulation with CMS prior to publishing the proposed rule so CMS could assess the implications of the rule on its reimbursement programs. FDA has also discussed this final rule with CMS. Under current part B policy, CMS does not cover the costs of an investigational drug used in a clinical trial unless the drug is otherwise covered outside the clinical trial. However, certain routine costs associated with medical care obtained due to clinical trial participation may be covered (see Medicare Clinical Trial Policies, *http://www.cms.hhs.gov/ClinicalTrialPolicies/* (follow link to Current Policy, NCD for Routine Costs in Clinical Trials (310.1))). In Part D, the statute clearly defines the drugs that may be covered under the program (and their accepted indications).

(Comment 65) One comment asserted that States will create mandated insurance coverage to mirror the proposed rule expansion. The comment stated that if health insurers are required to cover the cost of these drugs, they will need to increase premiums and that increasing premiums will cause more people to become uninsured.

(Response) Currently, States generally do not mandate reimbursement for

investigational medical interventions. That States may, at some point in the future, begin to institute policies mandating coverage of investigational drugs for which FDA has authorized charging is speculative, and thus not a basis for modifying current FDA policies. In addition, the likelihood that this final rule will further reduce access to health insurance because of increased costs associated with reimbursement for investigational therapies seems remote even if reimbursement were required, as investigational drugs provided under this regulation would constitute only a tiny fraction of overall drug use.

G. Miscellaneous Comments

1. Promotion

(Comment 66) One comment pointed out that FDA regulations at § 312.7 prohibit promotion of an investigational drug and asked that FDA clarify that this final rule permits an approved drug to be promoted outside of a clinical trial for its approved uses, even if the drug is used in a clinical trial.

(Response) FDA agrees with the comment. Nothing in this final rule should be construed as a constraint on a manufacturer's ability to promote an approved drug for its approved indications.

2. Liability

(Comment 67) One comment notes that there are potential liability concerns that need to be addressed that may result from subjects experiencing serious adverse events when charged for an investigational drug not approved by FDA.

(Response) When the amount charged for the investigational drug is merely the sponsor's cost, and subjects have given their informed consent to participate in a trial in which there is charging for study drug, FDA does not believe there would be a meaningful difference in a sponsor's product liability exposure when it charges for the drug compared to when it does not.

3. Product Labeling

(Comment 68) One comment pointed out that § 312.6(a) requires that the immediate package of an investigational new drug bear a label advising that the drug is limited by law to investigational use. The comment expressed concern that the proposed rule could be interpreted as requiring approved drugs to bear that statement.

(Response) FDA does not interpret this final rule as requiring use of the statement required by § 312.6(a) on the label of an approved drug product. The labeling approved for marketing of the product is acceptable. However, nothing in this final rule prevents a sponsor from designating a clinical supply of approved drug for use only in a clinical investigation and labeling the product in the manner provided by § 312.6(a).

4. Analysis of Impact

(Comment 69) One comment disputed FDA's conclusion that Executive Order 12866 does not apply because the proposed rule is not an economically significant regulatory action. The comment maintained that expanding the scope of treatment uses for which charging is permitted to include charging for drugs made available under intermediate-size patient populations and for individual patients could result in a significant financial impact. The comment also noted that one of the reasons for allowing charging in clinical trials is that the development of the investigational drug may be extraordinarily expensive. The comment stated that since FDA is predicting that requests for charging in clinical trials, and hence charging for extraordinarily expensive drugs will increase, there would likely be a significant financial impact. The comment asked that FDA perform an economic impact analysis or provide a better reason the Executive order does not apply.

(Response) Based on our analysis (incorporating changes made to the proposed rule), we conclude that the final rule is not economically significant as defined under Executive Order 12866. The comment does not provide any data or alternative analyses that would lead the agency to change this conclusion. Historical data indicate that only a very small percentage of all INDs submitted to FDA for clinical trials or treatment use include requests to charge for the drug. FDA expects only a slight increase in the already limited number of requests to charge as a result of the final rule. Our analysis of impacts predicts only a slight increase in charging for individual patient INDs, and a modest increase in charging for intermediate-size patient population INDs (see section VI.E.2 of this document) (upper bound of less than 800 total patients affected). Because provisions for allowing charging in a clinical trial have been in the regulation since 1987, and this rule merely clarifies the criteria for allowing such charging, FDA does not anticipate a meaningful increase in charging requests in that setting. Thus, we do not believe that the final rule will have a significant economic or financial impact.

(Comment 70) One comment disputed FDA's assertion in the proposed rule that the ''costs [associated with making investigational drugs available for treatment use] would not be excessive and would be justified by the primary benefit of this proposed rule, making investigational drugs available for treatment use that could not be otherwise made available without charging'' (71 FR 75168 at 75175). The comment stated that there is little evidence for these claims, arguing that the costs are likely to be very high in some cases and relatively low in other cases.

(Response) FDA agrees that there will be a range of costs for investigational drugs made available for treatment use and subject to charging, and that costs could be quite high in some cases. However, the differing costs of drugs across different expanded access programs does not undermine FDA's conclusion that costs of this final rule are justified in light of the potential benefits associated with broader access to investigational drugs for treatment use. That conclusion is not intended to imply that costs and benefits are offset in each individual case in which there is charging for drugs made available for treatment use, so variation in cost across different expanded access programs does not undermine the overall conclusion.

(Comment 71) One comment reviewed claims data on the treatment of diseases likely to fall under the FDA's proposed rule changes. The comment assumed that physicians would request access to investigational drugs only when available therapies have failed or when conventional therapies do not exist. The comment also assumed that, depending on the circumstances, investigational drugs will be used as first-line therapy, second-line therapy, monotherapy and combined therapy with FDA-approved medications. Based on these assumptions, the comment estimated the additive cost of the proposed rule as it would apply to enrollees in commercial/private health plans to be $273,700,000. The comment expressed the belief 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 the final rule will be small. In response to the comment, we have included estimates of the number of individual patients charged for investigational drugs under current rules, and the number of additional patients we expect may be charged for investigational drugs under this final rule. FDA's estimates indicate that, on average, as many as 12,566 patients per year may be charged for

investigational drugs under current rules. In addition, we estimate that as many as 770 additional patients per year may be charged for 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 of the comments received.

The estimate of 67,500 patients affected per year in the comment draws no distinction between patients who may be charged for investigational drugs under current rules and those additional patients who may be charged under this final rule. In assessing the impact of the final rule, it is the incremental effect, or additional patients that may be charged for investigational drugs, that must be considered. Patients who may be charged for investigational drugs under current rules are not relevant to an analysis of impacts for this final rule. The comment appears to assume that all patients who may be eligible to obtain an investigational drug under an expanded access IND would seek access, and that an appropriate drug would be available in all cases. In addition, the comment appears to assume that all patients with access to investigational drugs will also be charged for those drugs. Our analysis of historical data indicates that, on average, only about 1.1 percent of all IND submissions per year are associated with charging requests.

The only direct costs that are relevant to this final rule are the costs to drug sponsors to prepare and submit charging requests to FDA. The comment did not provide an estimate of these costs.

IV. Legal Authority

FDA has the authority under the Federal Food, Drug, and Cosmetic Act (the act) to permit charging for an investigational new drug under the conditions set forth in this final rule. This final rule clarifies and slightly expands the charging scheme that is already in place. It is based on the agency's[2] authority to issue regulations pertaining to the investigational use of drugs, section 505(i) of the act (21 U.S.C. 355(i)), its authority pertaining to expanded access to unapproved drugs for treatment use, section 561 of the act (21 U.S.C. 360bbb), and its general grant of rulemaking authority for the efficient enforcement of the act, section 701(a) of the act (21 U.S.C. 371(a)).

Section 505(i) of the act directs the agency 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. It is this authority that underlies FDA's IND regulations in part 312. The final rule adds to and clarifies the previous IND regulations by revising the 1987 charging rule to explain the circumstances under which charging for an investigational drug is appropriate in a clinical trial and to clarify what costs can be recovered.

Section 561 of the act, added by the Food and Drug Administration Modernization Act of 1997 (Public Law 105–115), provides additional authority for this final rule. One of that section's preconditions to providing an investigational drug for treatment use is that the sponsors submit a protocol consistent with regulations issued under section 505(i) of the act (see section 561(b)(1), (b)(4), and (c) of the act). This rulemaking sets out the circumstances under which charging for an investigational drug is appropriate for treatment use in an expanded access program as well as in a clinical trial and clarifies what costs can be recovered.

Section 701(a) of the act gives FDA the authority to issue regulations for the efficient enforcement of the act. Further discussion of FDA's legal authority regarding charging can be found at 52 FR 19466 at 19472 (May 22, 1987).

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 will 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.

Preparing additional charging requests accounts for the anticipated costs of this final rule. The agency estimates that, the cost for a sponsor to prepare and submit a charging request is approximately $2,500, and that these costs will be widely dispersed among affected entities. Because such requests are rare, the incremental number of requests generated by this final rule, as well as the total costs of the rule, will probably be quite small. Permitting charging for a broader range of treatment uses for investigational drugs will increase sponsors' incentives to undertake such activities, thereby promoting development of new products, as well as the development of new uses for already approved products. 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 Rule

The objectives of the final rule are to clarify and expand on 1987 charging rule that permits sponsors to charge patients for investigational drugs. Under this 1987 charging rule, FDA could authorize charging for an investigational drug used in a clinical trial or under a treatment IND or protocol. The final rule describes more specifically the types of

[2] In light of section 903(d) of the act (21 U.S.C. 393(d)), and the Secretary of Health and Human Service'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.''

costs that can be recovered when charging for an investigational drug. The final rule also adds provisions that permit charging for investigational drugs for all of the various types of expanded access use described under final subpart I of part 312.

B. The Need for the Final Rule

The final rule is needed to establish charging provisions for additional types of expanded access use other than the treatment IND or protocol. Elsewhere in this issue of the **Federal Register**, FDA is amending part 312 of its regulations by adding subpart I concerning expanded access to investigational drugs. In addition to the treatment IND or protocol previously described in FDA regulations, the expanded access final rule specifically authorizes expanded access use for individual patients, including in emergencies, and expanded access use for intermediate-size patient populations. The expanded access final rule is intended to improve access to investigational drugs for patients with serious diseases who have exhausted other therapeutic options and may benefit from such therapies. This final rule is necessary to establish provisions that permit charging for investigational drugs for all of the categories of expanded access use described under final subpart I.

The final rule is also needed to clarify and better explain the types of costs sponsors are permitted to recover through charging. The 1987 charging rule describing the costs a sponsor can recover when charging for an investigational drug has proven difficult to interpret and apply. Some sponsors have interpreted the language broadly to permit recovery of costs much greater than those directly attributable to providing the investigational drug for the approved treatment use. In addition, ambiguities in the 1987 charging rule may have caused inefficiencies leading some drug sponsors to devote more resources than necessary to the preparation and submission of charging requests.

C. Why Allow Charging?

The expense of conducting a clinical trial is considered a normal cost of drug development that should be recovered through sales after marketing approval. However, in some clinical trial settings, a sponsor may incur extraordinary costs compared to typical drug development expenses. Such a cost burden may arise because of unusually high manufacturing costs, the quantity of the drug required, the number of patients involved, the expected duration of treatment, or some combination of these factors. The agency believes that allowing cost recovery through charging may be appropriate in these instances, but only as a last resort source of funding to facilitate development of a promising new therapy that could not otherwise be developed.

In some clinical trials, it may be necessary for a sponsor to obtain an approved drug from another entity. The approved drug may be used as an active control or in combination with the sponsor's drug in a clinical trial designed to evaluate the effectiveness or safety of the sponsor's investigational drug. In these situations, the trial subjects typically must receive some therapy for their disease because using a placebo control will be unethical. In addition, the subjects often will be treated with the approved drug in the course of medical practice if they were not participating in the clinical trial. FDA had proposed criteria for charging in these situations that presented a much lower threshold than for charging for the sponsor's own investigational drug. Based on comments received, FDA has elected not to require sponsors who must obtain an approved drug from another entity for use as an active control, or in combination with the sponsor's own drug, to obtain authorization to charge for the drug and otherwise fulfill the requirements in § 312.8. Under this final rule, such sponsors can charge at their own discretion in this circumstance.

In other situations, an approved drug must be obtained by a third party (not the holder of the approved application) to study the drug in a clinical trial for a new use or to obtain important safety information about an approved indication. Researchers conducting such clinical trials are primarily noncommercial entities who are not in the business of drug development. Typically, these sponsor-investigators conduct relatively small trials at a single site. Since such sponsors lack the resources of commercial sponsors and do not conduct the research for commercial purposes, they will not be able to recover the cost of obtaining the approved drug by marketing the drug, for example, for a new indication. The agency believes these kinds of trials should be encouraged because they may yield important data about less commercially viable uses of a drug or additional drug safety information. FDA had proposed criteria for charging in these situations that presented a much lower threshold than for charging for the sponsor's own investigational drug. Based on comments received, FDA has elected not to require sponsors who must obtain an approved drug from another entity for a study of the approved drug (e.g., a study of a new use) to obtain authorization to charge for the drug and otherwise comply with the requirements of § 312.8. Under this final rule, such sponsors can charge at their own discretion in this circumstance.

In contrast to clinical trials, granting expanded access to investigational drugs for treatment use primarily benefits individual patients and is not intended typically to generate data needed to support marketing approval. Thus, the costs to sponsors associated with making a drug available for expanded access are not considered typical drug development expenditures. For this reason, the agency believes that it is generally more appropriate to permit sponsors to charge for expanded access to investigational drugs for treatment use. Allowing charging in expanded access settings may also provide financial incentives for sponsors to make investigational drugs more widely available in these situations.

D. Baseline for the Analysis

During the period 1997 through 2005, FDA received an average of 2,046.6 INDs per year. During this same period, the agency received an annual average of 22.6 requests to charge patients for investigational drugs. Thus, only about 1.1 percent (0.011 = 22.6 / 2,046.6) of all INDs received by the agency on an annual basis were associated with charging requests. Similarly, FDA received an average of 4.6 treatment IND or protocol submissions and 1.1 treatment IND or protocol charging requests per year during this period. Thus, requests to charge under treatment INDs or protocols were associated with about 0.05 percent (0.0005 = 1.1 / 2,046.6) of all INDs received by the agency, and approximately 23.9 percent (0.239 = 1.1 / 4.6) of all treatment IND or protocol submissions per year.

FDA also received an average of 55 other IND submissions and 15.6 other charging requests per year during this period. These requests were to charge patients for expanded access to investigational drugs in situations other than individual patient or emergency INDs, and treatment INDs or protocols. Such situations generally included requests to charge for expanded access in intermediate-size patient populations and under clinical trials. Because the intermediate-size patient population IND or protocol was not previously established in regulation, a more precise distribution of other charging requests cannot be determined. Nevertheless, other charging requests were associated

with about 0.76 percent (0.0076 = 15.6 / 2,046.6) of all INDs received by the agency, and approximately 28.4 percent (0.284 = 15.6 / 55) of all other IND submissions each year from 1997 through 2005.

Finally, FDA received an average of 659 individual patient or emergency IND submissions and 5.9 charging requests for individual patient or emergency INDs per year. Thus, single patient or emergency IND charging requests are associated with about 0.29 percent (0.0029 = 5.9 / 2046.6) of all INDs, and approximately 0.9 percent (0.009 = 5.9 / 659) of all single patient or emergency INDs received by the agency each year. This information is summarized in table 1 of this document.

TABLE 1.—BASELINE DATA FOR AVERAGE ANNUAL NUMBER OF IND SUBMISSIONS AND CHARGING REQUESTS BY CATEGORY

Category	All Charging Requests	Treatment IND/ Protocol Requests	Other Charging Requests	Individual Patient/ Emergency Requests
Number of charging requests	22.6	1.1	15.6	5.9
Percent of all INDs	1.1%	0.05%	0.76%	0.29%
Average number of submissions		4.6	55	659
Percent of submissions		23.9%	28.4%	0.9%

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 of patients receiving investigational drugs and subject to charging requests under current rules, in place since 1987.

Based on the information presented in table 1 of this document, FDA currently receives an average of 5.9 charging requests for individual patient or emergency INDs per year. Thus, approximately 5.9 individuals per year may currently be charged for investigational drugs under single patient or emergency INDs. FDA believes that it is reasonable to assume that a typical intermediate-size patient population will include between 10 and 100 individuals. Given that FDA currently receives an average of 15.6 charging requests for such submissions per year, we estimate that between 156 and 1,560 individuals may currently be charged for investigational drugs under intermediate-size patient populations. A treatment IND or protocol can vary significantly in size and may include between 100 and 10,000 patients. Thus, an average of 1.1 treatment IND or protocol charging requests per year could affect between 110 and 11,000 individuals. Based on this information, FDA estimates that between 272 and 12,566 individuals may currently be charged for investigational drugs each year under rules in place since 1987. The wide range of these estimates reflects significant variation in the number of patients enrolled in intermediate-size patient populations, and treatment INDs or protocols. These estimates are summarized in table 2 of this document.

TABLE 2.—APPROXIMATE NUMBER OF INDIVIDUALS AFFECTED ANNUALLY BY CHARGING RULES FOR INVESTIGATIONAL DRUGS IN PLACE SINCE 1987

Category	Average Number of Requests	Number of Patients	Minimum Number of Individuals	Maximum Number of Individuals
Individual patient or emergency IND	5.9	1	5.9	5.9
Small patient population/other	15.6	10—100	156	1,560
Treatment IND or protocol	1.1	100—10,000	110	11,000
Total			272	12,566

E. Nature of the Impact

The final rule will affect patients who lack effective therapeutic alternatives for serious diseases; sponsors that develop drugs to treat such diseases; and FDA in determining whether to authorize charging for investigational drugs. By clarifying requirements and establishing the full range of situations in which it may be appropriate to charge for an investigational drug, the final rule will improve patient access by providing a financial incentive for sponsors to make promising therapies more widely available. Thus, this final rule should help to facilitate patient access to drugs that could not be provided without charging and permit sponsors to study drugs that might otherwise be too costly to develop.

By describing in regulation the full range of treatment use situations in which charging for an investigational drug may be permitted, this final rule will likely increase the volume of charging requests for treatment use somewhat. However, by clarifying the circumstances under which charging will be permitted and specifying the types of costs that sponsors can recover, this final rule should also make the process of obtaining authorization to charge more transparent and more efficient. Given the small percentage of all INDs that include charging requests, FDA believes that the impact of the final rule will be small.

This final rule could also increase treatment expenses for some patients who obtain investigational drugs for which charging is permitted or for third-party payers if they choose to reimburse patients for some or all of the costs of such drugs. The agency believes that such costs will not be excessive and will

be justified by the primary benefit of this final rule, making investigational drugs available for treatment use that could not otherwise be made available without charging. The potential impact of specific provisions of the final rule is discussed in greater detail in the following paragraphs.

1. Charging in a Clinical Trial

Since 1987, FDA regulations have permitted charging for investigational drugs in clinical trials intended to support marketing approval. This final rule is intended only to clarify the situations in which charging for a sponsor's investigational drug in such a clinical trial is appropriate. Therefore, FDA does not expect this final rule to have a substantial effect on the number of requests to charge for sponsors' investigational drugs in clinical trials to support initial marketing approval.

Based on comments received, FDA has elected not to require sponsors who must obtain an approved drug from another entity for use as an active control or in combination with the sponsor's drug to obtain authorization to charge for the drug. In addition, FDA has elected not to require sponsors who must obtain an approved drug from another entity for a study of the approved drug (e.g., a study of a new use) to obtain authorization to charge for the drug. Under this final rule, such sponsors can charge for investigational drugs under these circumstances at their own discretion. Therefore, our original conclusion in the proposed rule that there would not be a substantial impact on the number of charging requests in clinical trial situations is unchanged in the final rule.

2. Charging for Expanded Access Uses Described Under Final Subpart I

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 patients that may be charged for investigational drugs under this final rule. Information presented in tables in the analysis of impacts section of the expanded access final rule, published elsewhere in this issue of the **Federal Register**, will be used to generate these estimates.

FDA estimates that the expanded access final rule will generate between 132 and 395 additional single patient or emergency IND submissions per year. Information presented in table 1 of this document indicates that approximately 0.9 percent of all single patient or emergency INDs are associated with charging requests. Thus, the agency estimates that this final rule will generate between 1.2 (1.2 = 132 x 0.009) and 3.5 (3.5 = 395 x 0.009) additional charging requests for single patient or emergency INDs. These figures imply that approximately 1.2 to 3.5 additional patients may be charged each year for investigational drugs as a result of this final rule.

Similarly, the agency estimates that the expanded access final rule will generate between 3 and 27 additional intermediate-size patient population IND submissions per year. Information presented in table 1 of this document indicates that approximately 28.4 percent of all such IND submissions are associated with charging requests. Therefore, the agency estimates that this final rule will generate between 0.85 (0.85 = 3 x 0.284) and 7.67 (7.67 = 27 x 0.284) additional charging requests for intermediate-size patient population submissions per year. The agency believes it is reasonable to assume that an intermediate-size patient population will generally include between 10 and 100 individual patients. These figures imply that approximately 8.5 (8.5 = 0.85 x 10) to 767 (767 = 7.67 x 100) additional patients may be charged for investigational drugs under intermediate-size patient populations each year as a result of this final rule.

Because current regulations allowing charging for investigational drugs under a treatment IND or protocol are not significantly altered by this final rule, the agency does not anticipate that the final rule will lead to a change in the number of requests to charge. Therefore, FDA expects that between 10 (9.7 = 1.2 + 8.5) and 770 (770.5 = 3.5 + 767) additional patients may be charged for investigational drugs per year as a result of this final rule. The results of these calculations are summarized in table 3 of this document.

TABLE 3.—APPROXIMATE NUMBER OF ADDITIONAL INDIVIDUALS THAT MAY BE CHARGED FOR INVESTIGATIONAL DRUGS UNDER THIS FINAL RULE

Category	Number of Additional Submissions	Number of Additional Charging Requests	Number of Individuals per Request	Total Number of Individuals
Individual patient or emergency IND	132—395	1.2—3.5	1	1.2—3.5
Small patient population/other	3—27	0.85—7.67	10—100	8.5—767
Treatment IND or protocol	0	0	100—10,000	0
Total				10—770

3. Costs Recoverable When Charging for an Investigational Drug

Finally, § 312.8(d) of the final rule clarifies and better explains the types of costs sponsors are permitted to recover through charging. In particular, sponsors are limited to recovery of the direct or marginal costs associated with making an investigational drug available for the approved treatment use. Direct costs that are recoverable under the final rule include per unit manufacturing costs and shipping and handling costs. In addition, the final rule permits sponsors to recover the costs of monitoring an expanded access protocol, complying with IND reporting requirements, and other administrative costs directly associated with expanded access for an intermediate-size patient population and for a treatment IND or treatment protocol.

4. Summary

The agency does not expect the number of requests to charge for a sponsor's drug in a clinical trial, or to charge for an investigational drug under a treatment IND or treatment protocol, to be affected because the final rule does not significantly change the 1987 charging rule. We estimate that final provisions allowing charging for single patient or emergency INDs and intermediate-size patient populations will affect between 10 and 770 individuals.

F. Benefits of the Final Rule

Because FDA currently has no data that will allow us to predict the extent

to which the final amendments to existing regulations will generate direct benefits for consumers, it is not possible to accurately quantify the magnitude of any expected incremental benefits at this time. We expect the number of requests to charge for investigational drugs for expanded access use to increase somewhat. However, the number of additional patients who will gain access to investigational drugs as a result and the extent to which these patients will benefit from such access are highly uncertain. Establishing in regulation all of the situations in which charging is permissible and clearly specifying the types of costs that are eligible for recovery will ease the administrative burdens associated with obtaining authorization to charge and will improve patient access to investigational drugs for treatment use. Private benefits will accrue to individual patients receiving the drugs, whereas additional social benefits will accrue if others in society also value these individual patient benefits. Because the overall impact of the final rule is expected to be small, the potential for any new regulatory benefits is somewhat limited.

In formulating the final rule, FDA considered the interests of patients, drug sponsors, and the general public. Concerning charging for investigational drugs in expanded access settings, the agency concluded that seriously ill patients could often benefit from increased access to investigational drugs that have not yet been approved for marketing. On the other hand, greater patient access to investigational drugs outside of the clinical trial setting could have the potential to delay approvals of drugs to treat serious diseases (e.g., by reducing incentives for potential subjects to enroll in clinical trials). If allowing charging were to adversely affect the drug 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 this tension by allowing sponsors to charge for investigational drugs in expanded access settings as long as the sponsor provides reasonable assurance that charging will not interfere with development of the drug for marketing approval. In this way, the final rule will address the interests of those patient populations that will benefit from having greater access to investigational drugs and the broader interests of society in having safe and effective therapies approved for marketing and widely available.

The final rule limits sponsors to recovery of the direct or marginal costs associated with making the drug available. Direct costs that are recoverable under the final rule include per unit manufacturing costs and shipping and handling costs. Indirect or fixed costs incurred for joint or common objectives and physical plant and equipment expenditures for producing marketable quantities of the drug are specifically excluded under the cost recovery provisions of the final rule. The agency believes that these cost recovery provisions will prevent sponsors from inappropriately shifting the normal financial risks associated with new drug development onto patients when they charge for drugs in clinical trial settings. For expanded access use, the limitation to direct cost recovery will also ensure that drug development costs that properly belong to sponsors are not shifted to patients.

G. Costs of the Final Rule

Although the final rule largely clarifies current agency practice, some additional paperwork costs will be incurred to the extent that the rule increases the total number of sponsor requests to charge patients for investigational drugs. The information requirements associated with the final rule are not expected to impose a significant burden. Drug sponsors who wish to charge for investigational drugs will need to review the rule to become familiar with its provisions and to gather the evidence and information necessary to support charging requests. Because of the lack of data described previously in this document, we are unable to generate quantitative estimates of compliance costs at this time. The agency expects that any incremental cost burdens will likely be small and widely dispersed among affected entities for a number of reasons.

First, regulations covering charging for investigational drugs in clinical trials and under treatment INDs or treatment protocols have been in place since 1987. As a result, the primary incremental impact of the final rule will be limited to the new charging provisions for the new types of expanded access for treatment use described under final subpart I of part 312. Second, the agency does not expect that these final charging provisions will lead to a large increase in the total number of charging requests. Because it is not usually extraordinarily expensive to make an investigational drug available to a single patient or a limited number of patients, the agency does not anticipate that the number of charging requests for expanded access to investigational drugs for single patients or intermediate-size patient populations will increase substantially. Finally, requests to charge are relatively infrequent and the expense necessary to prepare a charging request will ordinarily be small compared to the overall cost of preparing the expanded access submission.

The agency estimates that, on average, 48 hours will be needed to prepare a request to charge under the final rule. This estimate is based on FDA's experience in reviewing charging requests under the 1987 charging rule and on a projection of the increased paperwork burden associated with the final rule.

FDA's experience implies that 80 percent, or about 38 hours, of this burden will be associated with establishing that the amount proposed to be charged is limited to the direct costs of making the drug available. The agency believes that the cost justification portion of the charging request will need to be performed by a cost accountant qualified to assess the direct costs of charging. Information available on the Internet indicates that median total compensation for a Cost Accountant IV (senior level) is approximately $117,000 per year in 2008 or about $56 per hour ($116,857 / 2,080 hours).[3] Thus the cost associated with certifying the amount to be charged is expected to be about $2,130 ($56 per hour x 38 hours) per charging request.

The remaining burden (20 percent or about 10 hours) for the preparation of a charging request will consist of a brief demonstration that the criteria for charging that are not related to the amount to be charged have been met. When the request is to charge for a drug used in a clinical trial, this information will ordinarily be available as part of the normal drug development process. When the request is to charge for a drug for expanded access, the primary criterion is to show that charging will not interfere with development of the drug for marketing. FDA believes that preparation of this portion of the charging request will likely be performed by a mid-level regulatory affairs specialist. Information available on the Internet indicates that the total median compensation for a Regulatory Affairs Specialist II (intermediate level) is approximately $100,000 or about $48 per hour in 2008 ($99,930/2,080

[3] See *http://swz.salary.com/salarywizard/layoutscripts/swzl_newsearch.asp*, last viewed 7/10/08. (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**.)

hours).[4] Thus, the cost to demonstrate that a charging request meets appropriate criteria is about $480 (10 hours x $48 per hour) per charging request.

Based on the figures presented previously in this document, FDA estimates the cost to prepare and submit a charging request will thus be about $2,610 ($2,130 + $480). The total costs associated with this final rule will probably be widely dispersed among affected entities because charging requests are rare, and thus, a particular sponsor will be expected to submit such a request very infrequently.

A significant concern with the final rule relates to the potential effect on access to investigational therapies for economically disadvantaged individuals and the uninsured. Allowing sponsors to charge could impose a significant financial burden on many seriously ill individuals who lack therapeutic alternatives and could preclude access by some needy patients. However, in the past, many companies that have provided investigational drugs for treatment use have often included assistance programs to cover the costs for those who could not otherwise afford them. FDA expects this practice will continue.

H. Minimizing the Impact on Small Entities

The agency does not believe that 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.

According to agency records, the majority of treatment INDs and treatment protocols (approximately 92 percent) are submitted by commercial sponsors and government agencies that are not likely to meet Small Business Administration (SBA) criteria defining a small entity in the relevant industry sector. Thus, the agency believes that the vast majority of requests to charge under expanded access submissions will not be submitted by small entities. Most single patient INDs are for treatment use and are submitted by individual physicians, and these entities will be classified as small entities. However, for reasons discussed previously, we do not anticipate that the volume of requests to charge for individual patient expanded access will increase substantially. Because expanded access for intermediate-size patient populations is not currently tracked by the agency, no data exist that will allow the agency to identify either the number of sponsors in this category or the number that will qualify as small entities. FDA believes that requests to charge for investigational drugs in clinical trials of a sponsor's drug will generally be submitted by large commercial drug sponsors. In sum, the agency believes that some entities submitting charging requests will meet SBA small businesses criteria. As discussed in section VI.E of this document, the agency expects that any incremental burden associated with the final rule will be small and widely dispersed among affected entities.

I. Alternatives

FDA considered several alternatives to the final rule. Each is discussed in the following paragraphs:

- Do not revise the 1987 charging rule.

FDA considered and rejected this alternative because the 1987 charging rule does not address all of the types of expanded access to investigational drugs for treatment use specified under final subpart I of part 312. Furthermore, the cost recovery provisions in the 1987 charging rule were vague and ambiguous and thus in need of clarification.

- Retain the proposed requirements that would have required sponsors who must obtain an approved drug from another entity for use in the study evaluation to obtain authorization from FDA to charge.

FDA considered this alternative. However, FDA believes the comments made a persuasive case for not requiring authorization to charge in these settings. The most common requests to charge are for approved drugs in trials when the drugs must be obtained from another company. For reasons discussed in section VI.C of this document, FDA believes that charging for investigational drugs in these situations is appropriate without prior authorization from FDA.

- Do not permit charging for expanded access for individual patients or for intermediate-size patient populations.

FDA considered not revising the 1987 charging rule concerning charging for treatment use and thus permitting charging only for treatment INDs and treatment protocols. However, elsewhere in this issue of the **Federal Register**, the agency is finalizing its regulations concerning the treatment use of investigational drugs to specifically authorize expanded access for individual patients and for intermediate-size patient populations. The purpose of those regulations is to expand access to investigational drugs. In some situations, permitting sponsors to charge for investigational drugs to be used by individual patients or by intermediate-size patient populations may be the only way that such patients can receive access to these therapies because sponsors may not be willing to provide the drugs free of charge. Thus, consistent with the philosophy of the expanded access rule, the agency decided to permit charging for investigational drugs in all expanded access settings to improve access to investigational drugs for patients with serious diseases who lack other therapeutic options and who may benefit from such therapies.

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 in the following paragraphs 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: Charging for Investigational Drugs Under an IND

Description: The final rule describes the types of investigational uses for which a sponsor may be able to charge, including uses for which charging was not previously expressly permitted, and the criteria for allowing charging for the identified investigational uses. The rule authorizes sponsors to request to charge for investigational drugs used in clinical trials and for investigational drugs for expanded access for treatment use. The rule also describes the types of costs that can be recovered when charging for an investigational drug.

Section 312.8(a)(1) provides that a sponsor who wishes to charge for an investigational drug must meet the criteria applicable to the specific sections of the proposal relating to

[4] See *http://swz.salary.com/salarywizard/layoutscripts/swzl_newsearch.asp*, last viewed 7/10/08. (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**.)

charging in a clinical trial or charging for expanded access.

Section 312.8(b) describes the requirements for charging in a clinical trial.

Section 312.8(b)(1) describes criteria for charging for the sponsor's own drug in a clinical trial. To charge in this situation, the sponsor must show the following three things. The sponsor must:

- Provide evidence that the drug has a potential clinical benefit that, if demonstrated in the clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition;
- Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of a drug, or would support a significant change in the labeling of an approved drug (e.g., new indication, inclusion of comparative safety information); and
- Demonstrate that the clinical trial could not be conducted without charging because the cose of the drug is extraordinary to the sponsor.

Section 312.8(c) describes criteria for charging for an investigational drug in an expanded access setting. The general criterion to charge for expanded access for treatment use is that the sponsor provide reasonable assurance that charging will not interfere with developing the drug for marketing approval.

For treatment use under a treatment IND or treatment protocol, the sponsor must also provide the following:

- Evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval to reasonably assure FDA that the trial(s) will be successfully completed as planned,
- Evidence of adequate progress in the development of the drug for marketing approval, and
- Information submitted under its general investigational plan (§ 312.23(a)(3)(iv)) specifying the drug development milestones the sponsor plans to meet in the next year.

Section 312.8(a)(2) provides that a sponsor who wishes to charge for an investigational drug must justify the amount to be charged.

Section 312.8(d) describes more specifically the costs that are potentially recoverable. Section 312.8(d)(1) provides that a sponsor may recover only the direct costs of making the investigational drug available. Section 312.8(d)(1)(i) defines direct costs as costs incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery. Direct costs include costs per unit to manufacture the drug (e.g., raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging is authorized) or costs to acquire the drug from another manufacturing source and direct costs to ship and handle (e.g., store) the drug.

Section 312.8(d)(1)(ii) states that indirect costs include costs that are incurred primarily to produce the drug for commercial sale. Such costs include, for example, costs for facilities and equipment that are used to manufacture the supply of investigational drug but that are primarily intended to produce large quantities of drug for eventual commercial sale and research and development, administrative, labor, or other costs that would be incurred even if the clinical trial or expanded access for which charging is authorized did not occur.

Section 312.8(d)(2) provides that when the sponsor is charging for making the drug available for expanded access for an intermediate-size patient population or for a treatment IND or protocol under subpart I, the sponsor may also recover the costs of monitoring the protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access in addition to the sponsor's direct costs.

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

Estimates of Reporting Burden: Table 4 of this document presents the estimated annualized reporting burden for the total number of charging requests we expect to receive under the final rule. The estimates in table 4 have been derived in the following manner. Based on baseline data presented in section VI of this document, ''Analysis of Economic Impacts,'' we estimate that we will receive a total of approximately 34 charging requests annually under the final rule. This estimate is the sum of the average number of charging requests we currently receive annually (i.e., 22.6), plus the additional charging requests, as described in the analysis of economic impacts, that we expect to receive annually as a result of the amendments in the final rule (i.e., 3.5 + 7.67). Concerning the number of respondents, our experience has been that, in general, a single sponsor does not make multiple requests to charge for investigational drugs in the same year. However, we anticipate that multiple requests may increase somewhat if, as we expect, the number of individual patient treatment uses increases. Thus, we have assumed that the number of annual respondents will be approximately 30.

The largest portion of the paperwork burden associated with the final rule is to justify the request to charge by showing that the amount proposed to be charged is limited to the direct costs of making the drug available (§ 312.8(d)(1)). When the sponsor requests to charge for making the drug available for expanded access by an intermediate-size patient population or through a treatment IND or treatment protocol, the sponsor may also recover the costs of monitoring the treatment use protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access (§ 312.8(d)(2)). The sponsor also needs to support its suggested charge for these expenses. The remaining portion of the paperwork burden associated with the final rule is to show that the criteria applicable to the specific type of charging request (i.e., the type of clinical trial (§ 312.8(b)) or type of expanded access (§ 312.8(c))) have been met. Thus, we estimate that the average number of hours needed to prepare a request to charge for an investigational drug under the final rule is 48. This estimate is based on our experience in reviewing charging requests in the past and, as explained previously, on a projection of the increased paperwork burden associated with the final rule.

TABLE 4.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
312.8	30	1.13	34	48	1,632

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

The information collection provisions of 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 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 concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

List of Subjects in 21 CFR Part 312

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

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

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

■ 1. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 371, 381, 382, 383, 393; 42 U.S.C. 262.

■ 2. Section 312.7 is amended by removing paragraph (d) and by revising the section heading to read as follows:

§ 312.7 Promotion of investigational drugs.

* * * * *

■ 3. Section 312.8 is added to subpart A to read as follows:

§ 312.8 Charging for investigational drugs under an IND.

(a) *General criteria for charging.* (1) A sponsor must meet the applicable requirements in paragraph (b) of this section for charging in a clinical trial or paragraph (c) of this section for charging for expanded access to an investigational drug for treatment use under subpart I of this part, except that sponsors need not fulfill the requirements in this section to charge for an approved drug obtained from another entity not affiliated with the sponsor for use as part of the clinical trial evaluation (e.g., in a clinical trial of a new use of the approved drug, for use of the approved drug as an active control).

(2) A sponsor must justify the amount to be charged in accordance with paragraph (d) of this section.

(3) A sponsor must obtain prior written authorization from FDA to charge for an investigational drug.

(4) FDA will withdraw authorization to charge if it determines that charging is interfering with the development of a drug for marketing approval or that the criteria for the authorization are no longer being met.

(b) *Charging in a clinical trial*—(1) *Charging for a sponsor's drug.* A sponsor who wishes to charge for its investigational drug, including investigational use of its approved drug, must:

(i) Provide evidence that the drug has a potential clinical benefit that, if demonstrated in the clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition;

(ii) Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of a drug, or would support a significant change in the labeling of an approved drug (e.g., new indication, inclusion of comparative safety information); and

(iii) Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor. The cost may be extraordinary due to manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed (e.g., due to the size or duration of the trial), or some combination of these or other extraordinary circumstances (e.g., resources available to a sponsor).

(2) *Duration of charging in a clinical trial.* Unless FDA specifies a shorter period, charging may continue for the length of the clinical trial.

(c) *Charging for expanded access to investigational drug for treatment use.* (1) A sponsor who wishes to charge for expanded access to an investigational drug for treatment use under subpart I of this part must provide reasonable assurance that charging will not interfere with developing the drug for marketing approval.

(2) For expanded access under § 312.320 (treatment IND or treatment protocol), such assurance must include:

(i) Evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval to reasonably assure FDA that the trial(s) will be successfully completed as planned;

(ii) Evidence of adequate progress in the development of the drug for marketing approval; and

(iii) Information submitted under the general investigational plan (§ 312.23(a)(3)(iv)) specifying the drug development milestones the sponsor plans to meet in the next year.

(3) The authorization to charge is limited to the number of patients authorized to receive the drug under the treatment use, if there is a limitation.

(4) Unless FDA specifies a shorter period, charging for expanded access to an investigational drug for treatment use under subpart I of this part may continue for 1 year from the time of FDA authorization. A sponsor may request that FDA reauthorize charging for additional periods.

(d) *Costs recoverable when charging for an investigational drug.* (1) A sponsor may recover only the direct costs of making its investigational drug available.

(i) Direct costs are costs incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery. Direct costs include costs per unit to manufacture the drug (e.g., raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging is authorized) or costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug.

(ii) Indirect costs include costs incurred primarily to produce the drug for commercial sale (e.g., costs for facilities and equipment used to manufacture the supply of investigational drug, but that are primarily intended to produce large quantities of drug for eventual commercial sale) and research and development, administrative, labor, or other costs that would be incurred even if the clinical trial or treatment use for which charging is authorized did not occur.

(2) For expanded access to an investigational drug for treatment use under §§ 312.315 (intermediate-size patient populations) and 312.320 (treatment IND or treatment protocol), in

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.

[FR Doc. E9–19004 Filed 8–12–09; 8:45 am]

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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.

FOR FURTHER INFORMATION CONTACT:

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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