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

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

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

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

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

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

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

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

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

§ 312.320 Treatment IND or treatment protocol.

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

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

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

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

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

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

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

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

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

Dated: December 6, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 06–9684 Filed 12–11–06; 10:01 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 312

[Docket No. 2006N–0061]

RIN 0910–AF13

Charging for Investigational Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its investigational new drug application (IND) regulation concerning charging patients for investigational new drugs. FDA is proposing to revise the current 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 proposed 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. The proposed rule is intended to permit charging for a broader range of investigational and expanded access uses than is explicitly permitted in current regulations.

DATES: Submit written or electronic comments by March 14, 2007. Submit written comments on the information collection requirements by January 16, 2007.

ADDRESSES: You may submit comments, identified by Docket No. 2006N–0061 and/or RIN number 0910–AF13, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

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

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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

Instructions: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or

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

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

FOR FURTHER INFORMATION CONTACT:

For the Center for Drug Evaluation and Research: Colleen L. Locicero, Center for Drug Evaluation and Research (HFD–101), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 4200, Silver Spring, MD 20993–0002, 301–796–2270.

For the Center for Biologics Evaluation and Research: Steve Ripley, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–6210.

SUPPLEMENTARY INFORMATION:

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I. The Current Regulation

FDA's current regulation on charging for an investigational drug is § 312.7(d) (21 CFR 312.7(d)). Section 312.7(d) was first proposed in the **Federal Register** of June 9, 1983 (48 FR 26720), and reproposed March 19, 1987 (52 FR 8850) (the 1987 proposal). The final rule published in the **Federal Register** of May 22, 1987 (52 FR 19466) (the 1987 final rule). Under § 312.7(d), FDA may 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.

Section 312.7(d)(1) provides that a sponsor who wishes to charge for an investigational drug in a clinical trial must provide a full written explanation of why charging is 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.

Section 312.7(d)(2) sets out the following four conditions that must be met to charge for an investigational drug used under a treatment protocol or treatment IND:

- There must be adequate enrollment in the ongoing clinical investigations under the authorized IND;
- Charging must not constitute commercial marketing of a new drug for which a marketing application has not been approved;
- The drug must not be commercially promoted or advertised; and
- The sponsor of the drug must be actively pursuing marketing approval with due diligence.

Section 312.7(d)(2) also provides that to charge for an investigational drug used in a treatment IND or treatment protocol, the sponsor must submit an information amendment under § 312.31 (21 CFR 312.31) of the IND regulations. Authorization for charging goes into effect automatically 30 days after FDA receives the information amendment, unless the agency notifies the sponsor to the contrary.

Section 312.7(d)(3) provides that a sponsor may 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.

Section 312.7(d)(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.

II. Why the Current Charging Rule Needs to be Revised

A. Overview

There are three principal reasons for revising the current charging regulation.

First, the provisions of the current charging regulation concerning charging for investigational drugs in a clinical trial need to be revised to take into account circumstances that were not anticipated when the 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 has received few such requests. Far more common are requests to charge for approved drugs in trials when the drugs must be obtained from another company. The approved drug may be used in a trial of the sponsor's drug as an active control or in combination with the sponsor's drug. Even more common are requests to charge for approved drugs used in studies by a third party (not a manufacturer) that are intended to study new uses of the approved drug or to compare two drugs. FDA believes 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 drug being tested in a clinical trial. Accordingly, the agency believes the current charging regulation needs to be revised to provide criteria for charging for approved drugs used in clinical trials.

Second, the provisions of the current charging regulation related to treatment use provide for charging patients for investigational drugs only when those drugs are provided under a treatment IND or treatment protocol. Elsewhere in this issue of the **Federal Register**, FDA is proposing to add to part 312 (21 CFR part 312) new subpart I concerning ''Expanded Access to Investigational Drugs for Treatment Use.'' That proposed rule would retain the treatment IND and treatment protocol provisions in the current regulation with minor modifications, and provide for two additional categories of expanded access for treatment use—expanded access for individual patients and expanded access for intermediate size patient populations. The current charging rule needs to be revised to provide authority to charge for investigational drugs for these two new categories of expanded access for treatment use.

Third, FDA believes the current charging regulation needs to be revised to specify the types of costs that can be

recovered. The language of the current charging rule is not very specific and does not provide sufficient guidance to sponsors on the costs that can be recovered. Moreover, because of the different justifications for charging in a clinical trial and charging for treatment use, the agency believes that the costs appropriate for recovery also differ.

The reasons why FDA believes the current charging regulation needs to be revised are described more fully in sections II.B, C, and D of this document.

B. Criteria for Charging in a Clinical Trial

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. If the investigational drug proves successful in clinical trials, the sponsor will recoup its development costs by marketing the drug for its approved indication. Because research subjects who participate in a clinical trial are permitting themselves to be exposed to a drug that has not been proven to be effective and that may also pose safety risks, subjects generally should not be expected to pay for the drug. In fact, in return for their willingness to be exposed to an unapproved drug, subjects in clinical trials are usually compensated, rather than charged for the drug.

The current regulation on charging requires a sponsor who wishes to charge for an investigational drug in a clinical trial to provide a full written explanation of why charging is necessary for the sponsor to undertake or continue the clinical trial (e.g., why distributing the study drug to test subjects should not be considered part of the normal cost of doing business). However, the regulation does not specify the criteria that FDA would use to evaluate the sponsor's explanation for why charging is necessary to undertake the trial or why the cost of a drug should not be considered part of the normal cost of doing business.

The preambles to the reproposed and final rules, however, were more specific about the circumstances in which FDA believed charging for an investigational drug in a clinical trial might be appropriate. In the preamble to the 1987 reproposal, the agency stated that ''extremely high costs could warrant the sale of drugs used in clinical trials'' (52 FR 8850 at 8854). The agency indicated that allowing charging for very expensive drugs could be particularly advantageous by ''permitting small and fledgling companies to test products that are extremely expensive to produce * * *'' (52 FR 8850 at 8854). In the preamble to the 1987 final rule, the agency also stated 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 19474).

Thus, the philosophy behind the current charging regulation was that authorizing charging in a clinical trial required an exceptional circumstance, including evidence that the drug might provide an advantage over available therapy and that the study for which charging is requested is necessary to further the development of the drug and could not be conducted without charging. FDA is now proposing to describe in regulation specific criteria for charging that are consistent with the policies articulated in the preambles to the reproposed and final rules. These criteria are described in greater detail in section III.B of this document.

As discussed in section II.A of this document, FDA now believes that charging for an investigational drug in a clinical trial may also be appropriate when the clinical trial includes approved drugs that must be obtained from another company. The approved drug may be used in a trial of the sponsor's drug as an active control or in combination with the sponsor's drug. In another situation, an approved drug may need to be obtained from the marketer of that drug for use in studies by a third party (not the manufacturer) that are intended to study a new use for the approved drug or to compare two drugs. Thus, FDA is now proposing to revise the charging rule to include criteria that apply to these two situations when an approved drug is used in a clinical trial. These criteria are described in section III.B of this document.

C. Charging for Expanded Access for Treatment Use

Charging for the cost of an investigational drug for expanded access for treatment use is a very different situation from charging for a drug in a clinical trial. Treatment use is not a necessary part of the drug development process and does not benefit the pharmaceutical companies by leading to systematic accumulation of data intended to support marketing authorization. Rather, treatment use is primarily intended to benefit very sick patients by permitting them to receive investigational drugs to treat their diseases and conditions, with collection of information about the drug being incident to the intent to treat. FDA wants to encourage sponsors to make investigational drugs available to seriously ill patients who lack satisfactory alternative treatment and might benefit from these drugs. However, making investigational drugs available for expanded access for treatment use is potentially costly, especially when many patients are involved. Therefore, the agency believes that sponsors should be permitted to charge patients for investigational drugs for expanded access for treatment use, provided that charging will not impede the progress of drug development.

The current charging regulation in § 312.7(d)(2) contains FDA's criteria for allowing a sponsor to charge for investigational drugs for treatment use under a treatment IND or treatment protocol in accordance with §§ 312.34 and 312.35. Elsewhere in this issue of the **Federal Register**, FDA is proposing to add to part 312 new subpart I (Expanded Access to Investigational Drugs for Treatment Use), which would retain the treatment IND and protocol provisions in the current regulation with minor modifications, and provide for two additional categories of expanded access for treatment use that have not previously been described in regulation, (1) expanded access for individual patients and (2) expanded access for intermediate size patient populations. FDA is proposing to revise the current charging regulation to incorporate criteria to permit charging for these newly described categories of expanded access for treatment use. The criteria that must be met to charge for these uses are described in more detail in section III.C of this document.

D. Recoverable Costs

FDA is also proposing to revise the regulation on charging to clearly describe the costs a sponsor can include in its cost recovery calculation for an investigational drug. Under the current charging regulation, a sponsor may not charge a price ''larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug'' (§ 312.7(d)(3)). In FDA's experience, this provision has been prone to varied interpretations, sometimes resulting in unrealistic cost calculations. For example, some sponsors have interpreted the provision as allowing cost recovery for all possible costs associated with the research, development, manufacture, and handling of the drug from the inception of drug development. Some sponsors have also interpreted § 312.7(d)(3) as permitting cost recovery for the entire

cost of facilities designed to produce the drug in quantities that would be adequate for the ultimate marketing of the drug. These interpretations typically result in a cost that cannot reasonably be recovered from the number of patients who will be receiving the investigational drug.

FDA believes the current cost recovery provision was intended to permit a sponsor to recover the costs associated with providing an expensive drug product to study subjects in a clinical trial or making a drug product available for treatment use. FDA does not believe the intent was to allow a sponsor to recover the costs of research and development of a drug before it is marketed. The proposed rule is intended to clearly describe what costs may be recovered by a sponsor by providing criteria that are less susceptible to varied interpretations. These criteria are described in section III.D of this document.

III. Description of the Proposed Rule

The proposed rule would remove paragraph (d) of current § 312.7 that discusses charging for and commercialization of investigational drugs. The proposed rule would create new § 312.8 describing general requirements for charging for investigational drugs, specific requirements pertaining to charging for investigational drugs in a clinical trial, charging for investigational drugs for treatment use under proposed subpart I (described elsewhere in this issue of the **Federal Register**), and requirements for determining what costs can be recovered when charging for an investigational drug.

A. General Requirements

Proposed § 312.8(a) describes the following general requirements and conditions for charging for investigational new drugs. 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 treatment use) (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)).

The requirement in the proposed rule to obtain prior written authorization from FDA to charge for any investigational drug would be a change from the provisions of the current charging regulation. At the present time, sponsors must obtain prior written approval from FDA to charge for an investigational drug in a clinical trial (§ 312.7(d)(1)). On the other hand, authorization to charge for an investigational drug in a treatment protocol or treatment IND goes into effect automatically 30 days after receipt by FDA of an information amendment concerning charging, unless FDA notifies the sponsor to the contrary (§ 312.7(d)(2)). The proposal to require sponsors to obtain prior written authorization to charge for all types of expanded access is consistent with the agency's current practice of reviewing requests to charge for investigational drugs in treatment protocols or treatment INDs. The agency wants to review requests to charge for any type of expanded access to ensure that the criteria for charging have been met and that the amount to be charged does not exceed the costs permissible under the proposed rule.

Proposed § 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.

B. Clinical Trials

Proposed § 312.8(b) describes specific requirements pertaining to charging for an investigational drug in a clinical trial. This provision addresses three situations in which FDA may authorize charging for an investigational drug in a clinical trial, including investigational use of an approved drug.

Proposed § 312.8(b)(1) describes criteria for charging for the sponsor's own drug in a clinical trial. 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. 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. Accordingly, the proposed rule provides that a sponsor wishing to charge for its investigational drug in a clinical trial must 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 (proposed § 312.8(b)(1)(i)).

Second, charging should be permitted only for a trial that is necessary for the development of the drug. Therefore, the sponsor must 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 (proposed § 312.8(b)(1)(ii)). For example, the trial could be designed to provide data that would support approval of a new indication or generate important comparative safety information. The type of products that are likely to meet these two criteria 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,'' including the priority review policies for the Centers for Drug Evaluation and Research and Biologics Evaluation and Research in appendix 3 (available on the Internet at *http://www.fda.gov/cder/guidance/index.htm*)).

Third, charging must be necessary to the conduct of the clinical trial. Under proposed § 312.8(b)(1)(iii), a sponsor would be 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 extraordinary circumstances.

Proposed § 312.8(b)(2) describes criteria for 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 effectiveness or safety of the sponsor's investigational drug. In these situations, the study subjects typically must receive some therapy for their disease or condition because using a placebo control would be unethical. In addition, the subjects often would be treated with the approved drug in the course of medical practice if they were not participating in the clinical trial. Therefore, FDA believes the threshold for charging in this situation should be lower than the threshold for charging by a sponsor for the sponsor's own investigational drug. To charge for an approved drug in this situation, a

sponsor must demonstrate that the trial is of adequate design to evaluate the safety or effectiveness of the sponsor's drug and that the drug is not being provided free of charge by its manufacturer (proposed § 312.8(b)(2)(i) and (b)(2)(ii)).

Proposed § 312.8(b)(3) describes criteria for 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). This provision is primarily intended to enable sponsors who are not commercial entities in the business of drug development to study new uses of approved drugs that might not be of commercial interest to the drug's manufacturer or to conduct studies that provide additional information about a drug that might not otherwise be obtained. Typically, these sponsors are sponsor-investigators conducting relatively small trials at a single site. Such sponsors lack the resources of commercial sponsors and are not conducting the research for commercial purposes, so 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. Therefore, FDA believes the threshold for charging by a sponsor in this situation should be lower than the threshold for charging for the sponsor's own investigational drug. To charge for an approved drug in this situation, a sponsor must demonstrate that the clinical trial of the approved drug is of adequate design to evaluate the safety or effectiveness of a new indication, or provide important safety information related to an approved indication, and that the drug is not being provided free of charge by its manufacturer (proposed § 312.8(b)(3)(i) and (b)(3)(ii)).

Proposed § 312.8(b)(4) 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, proposed § 312.8(b)(4) 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. Expanded Access for Treatment Use

Proposed § 312.8(c) sets forth the criteria for charging for the three types of expanded access to investigational drugs for treatment use described in proposed subpart I of part 312 described elsewhere in this issue of the **Federal Register**. Proposed 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 existing charging regulation. 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, proposed § 312.8(c)(1) would require a sponsor wishing to charge for an investigational drug for any of the three types of expanded access under proposed 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 (§ 312.305 of proposed subpart I) or intermediate size patient population expanded access (§ 312.310 of proposed subpart I) 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 protocol (§ 312.320 of proposed subpart I). Treatment INDs or 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, proposed § 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 protocol will not interfere with drug development. Sponsors would be 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 (proposed § 312.8(c)(2)(i)). Sponsors would also be required to provide evidence of adequate progress in the development of the drug for marketing approval (proposed § 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 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)).

Proposed § 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 would be limited to a single patient. Similarly, the authorization to charge under an intermediate size patient population expanded access submission would be limited to the number of patients permitted to receive the drug under that particular intermediate patient population expanded access IND or protocol.

Proposed § 312.8(c)(4) provides that FDA will ordinarily authorize charging for expanded access for treatment use under proposed subpart I to continue for 1 year from the time of FDA authorization. It also provides FDA the discretion to specify a shorter authorization. FDA proposes to limit 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 would exercise its discretion to specify a shorter duration when there is a particular concern that charging could interfere with drug development. Proposed § 312.8(c)(4) provides that a sponsor may request that FDA reauthorize charging for additional periods.

D. Recoverable Costs

Proposed § 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 proposed 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 a drug when the drug is extraordinarily expensive. Thus, proposed § 312.8(d)(1) would limit cost recovery to the direct costs of making the investigational drug available in these situations. Indirect costs could not be recovered.

Proposed § 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, are not appropriate for cost recovery for these investigational uses because these are costs that would be incurred even if the clinical trial or expanded access use for which charging is authorized did not occur. Proposed § 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 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, proposed § 312.8(d)(2) would permit a sponsor to recover the costs of administering treatment use programs for intermediate size patient populations and for treatment INDs and protocols, as well as the direct costs of the drug. The proposed rule would not authorize sponsors to recover administrative costs associated with expanded access for individual patients because these costs would be so minor.

Proposed § 312.8(d)(2) provides that, in addition to the direct costs of the drug described in proposed § 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 of proposed subpart I.

Sponsors who provide investigational drugs for expanded access for treatment use for intermediate size patient populations and for treatment INDs and 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, proposed § 312.8(d)(2) would permit a sponsor to recover the costs of administering treatment use programs for intermediate size patient populations and for treatment INDs and protocols, as well as the direct costs of the drug. The proposed rule would not authorize sponsors to recover administrative costs associated with expanded access for individual patients because these costs would be so minor.

Proposed § 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 proposed § 312.8(d). If such documentation relies on financial information or accounting methods beyond the expertise of FDA reviewers, FDA may request that a sponsor provide independent certification that its cost recovery calculation is consistent with the requirements of this section.

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 proposed rule. This proposed rule would clarify and slightly expand the charging scheme that is already in place. It is based on the agency's[1] 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 proposed rule would add to and clarify the existing IND regulations by revising the current charging regulation 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 proposed rule. One of that section's preconditions to providing an investigational drug for treatment use is that the sponsor submit a protocol consistent with regulations issued under section 505(i) of the act. (See section 561(b)(1)(4) and (c) of the act.) This rulemaking, proposed under section 505(i) of the act, 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 proposed 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 proposed rule is not an economically significant regulatory action as defined by the Executive order.

[1] 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.''

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

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is approximately $122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any one-year expenditure that would meet or exceed this amount.

A. Objectives of the Proposed Action

FDA is proposing this action to clarify and expand on an existing regulation (in place since 1987) that permits sponsors to charge patients for investigational drugs. Currently, FDA may authorize charging for an investigational drug used in a clinical trial or under a treatment IND or treatment protocol. This proposed rule would expand the agency's authority to permit charging for investigational drugs in a number of other situations. In clinical trial settings, the proposed rule would add provisions that permit charging for another entity's approved drug—either for use as an active control, as combination therapy with its own drug, or to study new indications. The proposed rule would also add provisions that permit charging for investigational drugs for all of the various types of expanded access for treatment use described under proposed subpart I of part 312. Finally, the proposed rule describes more specifically the types of costs that could be recovered when charging for an investigational drug.

B. The Need for the Proposed Rule

This proposed rule is needed for several reasons. The current charging regulation only provides for charging for a sponsor's own drug in a clinical trial. However, since the charging rule was adopted in 1987, FDA has received requests to charge in a clinical trial for approved drugs that must be obtained from another company. In one situation, an approved drug is being used in a clinical trial as an active control or in combination with the sponsor's drug. In another situation, a third party who is not a manufacturer requests permission to charge for an approved drug that is being studied in the hope of discovering new uses for that drug. The proposed rule would authorize charging for approved drugs in these situations and provide criteria governing such requests to charge.

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

Finally, the proposed rule is needed to clarify and better explain the types of costs sponsors are permitted to recover through charging. The current regulatory language 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 current regulatory language 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. An extraordinary 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 study subjects typically must receive some therapy for their disease or condition because using a placebo control would be unethical. In addition, the subjects often would be treated with the approved drug in the course of medical practice if they were not participating in the clinical trial. Therefore, FDA believes the threshold for charging in this situation should be lower than the threshold for charging for the sponsor's own investigational drug.

In other situations, an approved drug must be obtained by a third party (not the manufacturer) to study the drug in a clinical trial for a new indication 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. Therefore, FDA believes the threshold for charging by a sponsor in this situation should be lower than the threshold for charging for the sponsor's own investigational drug.

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 1.1 treatment IND or treatment protocol charging requests per year during this period. Thus, requests to charge under treatment INDs or treatment protocols were associated with about 0.06 percent (0.0006 = 1.1 / 2,046.6) of all INDs received by the agency each year. Finally, FDA received an average of 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 treatment protocols. Such situations would generally include requests to charge for expanded access in intermediate-size patient populations and under clinical trials. Because the intermediate-size patient population IND or protocol is not currently 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 each year from 1997 through 2005. This information is summarized in table 1 below.

TABLE 1. BASELINE DATA FOR NUMBER OF INDS AND CHARGING REQUESTS BY CATEGORY

Category	Total INDs	All Charging Requests	Treatment IND/ or Protocol Requests	Other Charging Requests
Number	2,046.6	22.6	1.1	15.6
Percent of all INDs	100.0%	1.1%	0.06%	0.76%

FDA also received an average of 659 individual patient and emergency INDs per year during the period 1997 through 2005. This number represents approximately 32.2 percent (0.322 = 659 / 2,046.6) of all INDs received by the agency each year. During this same period, FDA received an average of 7.1 charging requests for individual patient or emergency INDs or protocols per year. Thus, charging requests are associated with about 1.1 percent (0.0108 = 7.1 / 659) of all individual patient and emergency INDs or protocols received by the agency each year. This information is summarized in table 2 below.

TABLE 2: BASELINE DATA FOR NUMBER OF INDIVIDUAL PATIENT/EMERGENCY INDS

Category	Individual Patient or Emergency INDs	Charging Requests
Number	659.0	7.1
Percent	100.0%	1.1%

E. Nature of the Impact

The proposed rule would affect patients who lack effective therapeutic alternatives for serious and life-threatening conditions; sponsors who develop drugs to treat serious and life-threatening conditions; 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 proposed rule would improve patient access by providing a financial incentive for sponsors to make promising therapies more widely available. Thus, this proposed 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 situations in which charging for an investigational drug may be permitted, this proposed rule would likely increase the volume of charging requests somewhat. However, by clarifying the circumstances under which charging would be permitted and specifying the types of costs that sponsors could recover, this proposed 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 proposed rule will not be significant.

This proposed rule could also increase treatment expenses for some patients who obtain investigational drugs for which charging is permitted, or for third party payors if they choose to reimburse patients for some or all of the costs of such drugs. The agency believes that such costs 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 otherwise be made available without charging. The potential impact of specific provisions of the proposed rule is discussed in greater detail in the following paragraphs.

1. Charging in a Clinical Trial

a. *Charging for a sponsor's drug in a clinical trial.* The existing charging regulation has permitted charging for investigational drugs in clinical trials intended to support marketing approval since 1987. This proposed 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 proposed rule to have a significant effect on the number of requests to charge for sponsors'

investigational drugs in clinical trials to support initial marketing approval.

b. *Charging for an approved drug in a clinical trial.* As discussed in section II.A of this document, a major reason for revising the current charging regulation is to describe criteria for charging for approved drugs in clinical trials that are subject to part 312. These criteria are needed because the bulk of the requests to charge in the clinical trial setting have been requests to charge for approved drugs and the existing criteria do not readily apply to this situation.

By explicitly acknowledging that charging for an approved drug in a clinical trial subject to part 312 is possible under appropriate circumstances, this proposed rule should increase awareness of this option and thus stimulate requests to charge. The extent to which the volume of such requests might increase is uncertain. FDA's experience is that sponsors are most likely to request to charge when the drug is quite expensive and that expense represents a substantial burden relative to the sponsor's resources. Because prescription drugs are becoming increasingly expensive, it is reasonable to expect that approved products used in clinical trials will become increasingly expensive as well. However, because charging may affect a sponsor's ability to enroll subjects in clinical trials in a timely manner, FDA believes that sponsors will continue to be reluctant to charge unless the cost is truly burdensome. Therefore, FDA does not anticipate a substantial increase in the number of these requests to charge.

2. Charging for Expanded Access for Treatment Uses Described Under Proposed Subpart I

a. *Expanded access for individual patients.* FDA anticipates that there would be some increase in the number of requests to charge for investigational drugs for expanded access for individual patients. By establishing in regulation that it may be permissible to charge for an investigational drug for expanded access for individual patients, this proposed rule should increase awareness of the option to charge and thereby stimulate additional requests. In addition, as discussed in the preamble to the expanded access proposed rule, that rule is anticipated to initially increase the overall volume of expanded access for individual patients, which may also lead to some increase in the volume of requests to charge.

For the period 1997 through 2005, FDA received an average of 7.1 requests per year to charge for such use, or about 1.1 percent (0.011 = 7.1 charging requests/659 single patient INDs per year) of all individual patient treatment use. The extent to which the volume of requests to charge for expanded access for individual patients would increase under the proposed rule is uncertain. Historically, sponsors have been willing to provide an investigational drug to an individual patient free of charge in most cases, presumably because the cost is not great. However, this willingness may be tempered somewhat if there is an increase in the volume of requests for expanded access for individual patients received by a particular sponsor, especially if the cost of the drug is relatively high. There may also be some increase in the number of requests to charge for expanded access for individual patients because the prevalence of costly drugs is increasing. At this time, FDA has no reasoned basis to project a percentage increase in the number of charging requests for expanded access to investigational drugs for individual patients. However, because the cost of providing a drug to a single patient is usually not a substantial burden for a sponsor, FDA believes that the number of requests to charge for individual patient expanded access would continue to represent a relatively small percentage of such use.

b. *Expanded access for intermediate size patient populations.* By establishing in regulation that it is possible to charge for expanded access to an investigational drug for treatment use in an intermediate size patient population, the proposed rule should increase awareness that charging may be permitted for such uses, thereby stimulating requests to charge. Because access to expanded access for intermediate size patient populations has to date been authorized informally, FDA does not have records to indicate the number of times charging has been requested or permitted for this type of treatment use. If charging has been permitted in these situations, the authorizations would have been grouped with, and cannot be differentiated from, the authorizations to charge under clinical trials.

FDA does not anticipate a significant number of charging requests for expanded access for intermediate size patient populations. Historically, sponsors have been willing to provide drugs free of charge to a limited number of patients for treatment use. As in the case of expanded access for individual patients, we expect this behavior would continue.

c. *Treatment INDs and treatment protocols.* The agency's current regulations allowing charging for investigational drugs under a treatment IND or treatment protocol (in place since 1987) would be clarified, but not significantly altered, by the proposed rule. Therefore, the agency does not anticipate that the proposed rule would lead to a change in the number of requests to charge under treatment protocols or treatment INDs.

3. Costs Recoverable When Charging for an Investigational Drug

Finally, the proposed rule clarifies and better explains the types of costs sponsors are permitted to recover through charging. In particular, sponsors would be limited to recovery of the direct or marginal costs associated with making an investigational drug available for the approved treatment use. Direct costs that would be recoverable under the proposed rule include per unit manufacturing costs and shipping and handling costs. In addition, the proposed rule would permit 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 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 proposed rule does not significantly change the existing regulation. The agency does expect some incremental impact from the proposed provisions that would allow charging for approved drugs in clinical trial and for expanded access for single patients and intermediate size patient populations. The agency believes the impact of these provisions would be limited for the reasons described previously in this document, but we are unable to estimate the quantitative impact because of a lack of reliable data. Thus, the following discussion describes, in general terms, the nature of the associated benefits and costs.

F. Benefits of the Proposed Rule

Because FDA currently has no data that would allow us to predict the quantitative impact of the proposed rule, it is not possible to accurately quantify the magnitude of any expected incremental benefits at this time. We would expect the number of requests to charge for investigational drugs for expanded access use to increase somewhat. However, the number of additional patients that would gain

access to investigational drugs as a result and the extent to which these patients would 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 would ease the administrative burdens associated with obtaining authorization to charge and could improve patient access to investigational drugs for treatment use. Private benefits would accrue to individual patients receiving the drugs, whereas social benefits would accrue if society also values these individual patient benefits. Because the overall impact of the proposed rule is not expected to be significant, the potential for any new regulatory benefits is somewhat limited.

In formulating the proposed 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 and life-threatening conditions (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 would experience diminished social benefits due to the reduced or delayed availability of new therapies approved for marketing by FDA.

The proposed rule would address 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 proposed rule would effectively address the interests of those patient populations that would 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 proposed rule would limit sponsors to recovery of the direct or marginal costs associated with making the drug available. Direct costs that are recoverable under the proposed 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 would be specifically excluded under the cost recovery provisions of the proposed rule. The agency believes that these cost recovery provisions would 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 would also ensure that drug development costs that properly belong to sponsors are not shifted to patients.

G. Costs of the Proposed Rule

Although the proposed rule largely clarifies current agency practice, some additional paperwork costs would 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 proposed rule are not expected to impose a significant burden. Drug sponsors who wish to charge for investigational drugs would 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 would 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 proposed rule would be limited to the new charging provisions for the following: (1) Clinical trials using approved drugs and (2) the new mechanisms for expanded access for treatment use described under proposed subpart I of part 312. Second, the agency does not expect that these proposed charging provisions would 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 would increase substantially. Finally, requests to charge are relatively infrequent and the expense necessary to prepare a charging request would ordinarily be small compared to the overall cost of preparing the expanded access submission.

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

FDA believes that 80 percent, or about 38 hours, of this burden would 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 would 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) was approximately $102,000 per year in 2004 or about $49 per hour ($102,138/2,080 hours).[2] Thus the cost associated with certifying the amount to be charged is expected to be about $1,900 ($49 per hour x 38 hours) per charging request.

The remaining burden—20 percent or about 10 hours—for the preparation of a charging request would 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 would 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 would likely be performed by a mid-level regulatory affairs person. Information available on the Internet indicates that the total median compensation for a Regulatory Affairs Specialist II (intermediate level) was approximately $80,000 or about $39 per hour in 2004 ($80,288/2,080 hours).[3] Thus, the cost to demonstrate

[2]See *http://swz.salary.com/salarywizard/layoutscripts/swzl_newsearch.asp*, last viewed 7/6/05. (FDA has verified the Web site address, but we are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

[3]See *http://swz.salary.com/salarywizard/layoutscripts/swzl_newsearch.asp*, last viewed 7/6/05. (FDA has verified the Web site address, but we

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that a charging request meets appropriate criteria is about $400 (10 hours x $39 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 would thus be about $2,300 ($1,900 + $400). We also believe that the total costs associated with this proposed rule will be widely dispersed among affected entities because charging requests are rare, and thus, a particular sponsor would be expected to submit such a request very infrequently.

A significant concern with the proposed 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 would continue.

H. Minimizing the Impact on Small Entities

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

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 would not be submitted by small entities. Most single patient INDs are for treatment use and are submitted by individual physicians, and these entities would 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 would increase substantially. Because expanded access for intermediate size patient populations is not currently tracked by the agency, no data exist that would allow the agency to identify either the number of sponsors in this category or the number that would qualify as small entities. FDA believes that requests to charge for investigational drugs in clinical trials of a sponsor's drug, whether the drug charged for is the sponsor's own drug or is an approved drug used for combination therapy or as an active control, would generally be submitted by large commercial drug sponsors. Requests to charge for an approved drug that is being studied for a new use would likely come from researchers or research organizations that meet the SBA standards for small business. In sum, the agency believes that some entities submitting charging requests would meet SBA small businesses criteria. However, because this determination is uncertain, the agency specifically requests detailed public comment regarding the number and size distribution of entities that would be affected by the proposed rule, as well as the economic impact of the rule on those entities. As discussed in section V.E of this document, the agency expects that any incremental burden associated with the proposed rule would be small and widely dispersed among affected entities.

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

- Do not revise the current charging rule.

FDA considered and rejected this alternative because the current charging rule does not address all of the types of requests to charge for drugs in clinical trials received by the agency. Furthermore, the current charging rule does not address all of the types of expanded access to investigational drugs for treatment use specified under proposed subpart I of part 312.

- Do not permit charging for approved drugs in clinical trials.

FDA considered this alternative. However, requests to charge for investigational drugs in a clinical trial would then be limited to requests to charge for the sponsor's drug that was being tested in the trial. In fact, the agency has received few such requests. Far more common are requests to charge for approved drugs in trials when the drugs must be obtained from another company. The approved drug may be used in a trial of the sponsor's drug as an active control or in combination with the sponsor's drug. Even more common are requests to charge for approved drugs used in studies by a third party (e.g., not the manufacturer) that are intended to evaluate the approved drug, for example, to discover a new use. FDA believes that requests to charge for investigational drugs in these situations may be appropriate; thus the agency believes the current charging rule should be revised to specifically contemplate such requests and to provide criteria applicable to such requests.

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

FDA considered not revising the current regulation 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 proposing to amend 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 that proposal 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 propose to permit charging for investigational drugs in all expanded access settings to improve access to investigational drugs for patients with serious or life-threatening diseases or conditions who lack other therapeutic options and who may benefit from such therapies.

VII. Paperwork Reduction Act of 1995

This proposed rule contains collections of information that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). ''Collection of information'' includes any request or requirement that persons obtain, maintain, retain, or report information to the agency, or disclose information to a third party or to the public (44 U.S.C. 3502(3) and 5 CFR 1320.3(c)). The title, description, and respondent description of the information collection are shown in the following paragraphs, with an

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are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

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

Title: Charging for Investigational Drugs

Description: The proposed 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 proposed 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 proposed rule also describes the types of costs that can be recovered when charging for an investigational drug.

Section 312.8(a)(1) of the proposed rule 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 charging in a clinical trial or charging for expanded access.

Section 312.8(b) of the proposed rule describes the criteria for charging in a clinical trial in three situations.

Proposed § 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 cost of the drug is extraordinary. 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.

Proposed § 312.8(b)(2) describes criteria for 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 effectiveness or safety of the sponsor's investigational drug. To charge for an approved drug in this situation, a sponsor must demonstrate that the trial is of adequate design to evaluate the safety or effectiveness of the sponsor's drug and that the drug is not being provided free of charge by its manufacturer.

Proposed § 312.8(b)(3) describes criteria for 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). To charge for an approved drug in this situation, a sponsor must demonstrate that the clinical trial of the approved drug is of adequate design to evaluate the safety or effectiveness of a new indication or provide important safety information related to an approved indication and that the drug is not being provided free of charge by its manufacturer.

Proposed § 312.8(c) describes criteria for charging for an investigational drug for 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) of the proposed rule provides that a sponsor who wishes to charge for an investigational drug must justify the amount to be charged.

Section 312.8(d) of the proposed rule describes more specifically the costs that are potentially recoverable. Proposed § 312.8(d)(1) provides that a sponsor may recover only the direct costs of making the investigational drug available. Proposed § 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.

Proposed § 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, e.g., 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.

Proposed § 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 1 of this document presents the estimated annualized reporting burden for the total number of charging requests. The estimates in the table have been derived in the following manner. Between 1999 and 2003, FDA received approximately 25 requests to charge for investigational drugs annually. FDA estimates that there will be a 25 to 50 percent increase in requests to charge if

the proposed rule is finalized. These requests are expected to be requests to charge for expanded access for single patients and intermediate size patient populations and for approved drugs in clinical trials. Accordingly, table 1 of this document gives the total annual responses as 38 (25 x 1.50 = 37.5). FDA's experience has been that, in general, a single sponsor does not make multiple requests to charge for investigational drugs in the same year. However, the agency anticipates 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 35.

FDA believes the largest portion of the paperwork burden associated with the proposed rule would be 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 (proposed § 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 (proposed § 312.8(d)(2)). The sponsor would also need to support its suggested charge for these expenses.

The remaining portion of the paperwork burden associated with the proposed rule would be to show that the criteria applicable to the specific type of charging request (i.e., the type of clinical trial (proposed § 312.8(b)) or type of expanded access (proposed § 312.8(c))) have been met.

FDA estimates the average number of hours needed to prepare a request to charge for an investigational drug under the proposed rule as 48. This estimate is based on FDA's experience in reviewing charging requests in the past and on a projection of the increased paperwork burden associated with the proposed rule.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours Per Response	Total Hours
312.8	35	1.08	38	48	1,824

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

VIII. Federalism

FDA has analyzed this proposed 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.

IX. Request for Comments

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

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, it is proposed that 21 CFR part 312 be amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR part 312 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.

§ 312.7 [Amended]

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.

(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 treatment use under subpart I of this part.

(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. 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.

(2) *Charging for an approved drug obtained from another entity for use as an active control or in combination with another drug.* A sponsor who wishes to charge for an approved drug that it must obtain from another entity for use as an active control or in combination with its investigational drug in a clinical trial of the sponsor's investigational drug must:

(i) Demonstrate that the clinical trial is adequately designed to evaluate the safety or effectiveness of the sponsor's drug; and

(ii) Demonstrate that the holder of the approved application is not providing the drug to the sponsor free of charge.

(3) *Charging for an approved drug obtained from another entity in a clinical trial of that drug.* A sponsor who wishes to charge for an approved drug that it must obtain from another source for use in a clinical trial intended to evaluate the acquired drug must:

(i) 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

(ii) Demonstrate that the holder of the approved application is not providing the drug to the sponsor free of charge.

(4) *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, 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 one 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 the 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 and 312.320, 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.

(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.

Dated: December 6, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 06–9685 Filed 12–11–06; 10:01 am]

BILLING CODE 4160–01–S

PENSION BENEFIT GUARANTY CORPORATION

29 CFR Parts 4050 and 4281

RIN 1212–AB08

Mortality Assumptions

AGENCY: Pension Benefit Guaranty Corporation.

ACTION: Proposed rule.

SUMMARY: This proposed rule is a companion to PBGC's direct final rule (published today in the ''Rules and Regulations'' section of the **Federal Register**) making changes to the mortality assumptions under parts 4050 (Missing Participants) and 4281 (Duties of Plan Sponsor Following Mass Withdrawal) of its regulations. PBGC is making these changes as a direct final rule without prior proposal because we view them as non-controversial revisions and anticipate no significant adverse comment. We have explained our reasons in the preamble to the direct final rule. If we receive no significant adverse comment, no further action on this proposed rule will be taken. However, if we receive significant adverse comment, we will withdraw the direct final rule and it will not take effect. In that case, we will address all public comments in a subsequent final rule based on this proposed rule. We will not institute a second comment period on this rule. Any parties interested in commenting must do so at this time.

DATES: Comments must be received on or before January 16, 2007.

ADDRESSES: Comments, identified by RIN number 1212–AB08, may be submitted by any of the following methods:

- Federal eRulemaking Portal: *http://www.regulations.gov.* Follow the Web site instructions for submitting comments.
- E-mail: *reg.comments@pbgc.gov.*
- Fax: 202–326–4224.
- Mail or Hand Delivery: Legislative and Regulatory Department, Pension Benefit Guaranty Corporation, 1200 K Street, NW., Washington, DC 20005–4026.

All submissions must include the Regulatory Information Number for this rulemaking (RIN number 1212–AB08). Comments received, including personal information provided, will be posted to *http://www.pbgc.gov.* Copies of comments may also be obtained by writing to Disclosure Division, Office of the General Counsel, Pension Benefit Guaranty Corp., 1200 K Street, NW, Washington, DC 20005–4026 or calling