SUPPORTING STATEMENT
Charging for Investigational Drugs under an IND – Final Rule

A. Justification

1. Circumstances Making the Collection of Information Necessary

The final rule replaces the previous charging regulation at § 312.7(d). The final rule clarifies the circumstances in which charging for an investigational drug in a clinical trial is appropriate, sets forth criteria for charging for an investigational drug for the different types of expanded access for treatment use, and clarifies what costs can be recovered for an investigational drug. The final rule permits charging for a broader range of investigational and expanded access uses than was explicitly permitted previously.

The final rule identifies three principal reasons for replacing the previous charging regulation. First, the provisions of the former charging regulation concerning charging for investigational drugs in a clinical trial needed to be revised to take into account circumstances that were not anticipated when the original rule was adopted in 1987. Far more common were requests to charge for approved drugs in trials when the drugs needed to be obtained from another entity. These approved drugs may have been used in a trial of the sponsor's drug as an active control or in combination with the sponsor's drug. Even more common were requests to charge for approved drugs used in trials by a third party (not the holder of the approved application) that were intended to study new uses of the approved drug or to compare two drugs. FDA 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 own drug being tested in a clinical trial. Accordingly, the final rule revises the former charging regulation to provide criteria for charging for approved drugs used in clinical trials.

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

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

2. Purpose and Use of the Information Collection

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

Section 312.8(a)(1) provides that a sponsor who wishes to charge for an investigational drug must meet the criteria applicable to the specific sections of the rule relating to charging in a clinical trial or charging for expanded access.

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

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

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

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

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

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

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

3. Use of Improved Information Technology and Burden Reduction

FDA's guidance document "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" provides information on submitting electronically the information under 21 CFR 312 and other regulatory submissions. This guidance document is available at FDA's guidance document web site http://www.fda.gov/cder/guidance/index.htm.

4. Efforts to Identify Duplication and Use of Similar Information

This rulemaking would not result in duplicate reporting.

5. Impact on Small Businesses or Other Small Entities

Section VI (Analysis of Economic Impacts) of the final rule discussed the impact of the rulemaking on small entities. The analysis concluded:

"The Regulatory Flexibility Act requires agencies to analyze regulatory options that will minimize any significant impact of a rule on small entities. Our economic analysis for the proposed rule did not indicate any significant new regulatory burden, and we did not receive any comments that would cause us to reconsider this determination. Therefore, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities."

6. Consequences of Collecting the Information Less Frequently

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.

7. Special Circumstances Relating to the Guidelines in 5 CFR 1320.5

None of the collection requirements are inconsistent with 5 CFR 1320.5(d)(2).

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In the Federal Register of December 14, 2006 (71 FR 75168), FDA proposed to amend its investigational new drug application regulations concerning charging patients for investigational new drugs (former § 312.7(d) (21 CFR 312.7(d))) and add new § 312.8 (charging for investigational drugs). Many comments were submitted from industry and the public. The final rule summarizes and responds to these comments.

9. Explanation of Any Payment or Gift to Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under this provision.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of the information submitted is safeguarded by 21 CFR 312.130 and 21 CFR part 20.

11. Justification for Sensitive Questions

This information collection does not contain questions pertaining to sex, behavior, attitude, religious beliefs, or any other matters that are commonly considered private or sensitive in nature.

12. Estimates of Annualized Hour Burden and Costs

Annualized Hour Burden –

FDA currently has approval (under OMB Control Number 0910-0014) for all information collection under 21 CFR 312, which includes the submissions required under "charging for and commercialization of investigational drugs" (§ 312.7(d)). This analysis pertains only to the incremental changes in burden as a result of the charging final rule. As explained below, there is an increase in the total number of burden hours incurred by sponsors to

submit requests to charge for an investigational drug under the final rule.

The final rule results in an incremental increase of 576 hours to submit requests to charge for investigational drugs. This is the difference between the projected estimate of 1,632 total hours to comply with new § 312.8 in the final rule, and the current estimate of 1,056 total hours to comply with current § 312.7(d) (see OMB Control Number 0910-0014).

The largest portion of the burden hours associated with the final rule is to justify the request to charge by showing that the amount proposed to be charged is limited to the direct costs of making the drug available (§ 312.8(d)(1)). When the sponsor requests to charge for making the drug available for expanded access by an intermediate-size patient population or through a treatment IND or treatment protocol, the sponsor may also recover the costs of monitoring the treatment use protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access (§ 312.8(d)(2)). The sponsor also needs to support its suggested charge for these expenses. The remaining portion of the burden is to show that the criteria applicable to the specific type of charging request (i.e., the type of clinical trial (§ 312.8(b)) or type of expanded access (§ 312.8(c))) have been met. Thus, we estimate that the average number of hours needed to prepare a request to charge for an investigational drug under the final rule is 48. This estimate is based on our previous estimates for preparing charging requests and, as explained above, on a projection of the increased burden hours associated with the final rule. Previously, the average number of hours needed to prepare a request to charge for an investigational drug has been estimated to be 24 (see OMB Control Number 0910-0014).

Costs –

As stated above, we estimate that, on average, 48 hours will be needed to prepare a request to charge under the final rule. As explained in Section VI of the final rule, "Analysis of Economic Impacts," FDA's experience implies that 80 percent, or about 38 hours, of this burden will be associated with establishing that the amount proposed to be charged is limited to the direct costs of making the drug available. The agency believes that the cost justification portion of the charging request will need to be performed by a cost accountant qualified to assess the direct costs of charging. Information available on the Internet indicates that median total compensation for a Cost Accountant IV (senior level) is approximately $117,000 per year in 2008 or about $56 per hour ($116,857 / 2,080 hours). Thus the cost associated with certifying the amount to be charged is expected to be about $2,130 ($56 per hour x 38 hours) per charging request. The remaining burden -- 20 percent or about 10 hours -- for the preparation of a charging request will consist of a brief demonstration that the criteria for charging that are not related to the amount to be charged have been met. When the request is to charge for a drug used in a clinical trial, this information will ordinarily be available as part of the normal drug development process. When the request is to charge for a drug for expanded access, the primary criterion is to show that charging will not interfere with development of the drug for marketing. FDA believes that preparation of this portion of the charging request will likely be performed by a mid-level regulatory affairs person. Information available on the Internet indicates that the total median compensation for a Regulatory Affairs Specialist II (intermediate level) is approximately $100,000 or about $48 per hour in 2008 ($99,930/2,080 hours). Thus, the cost to

demonstrate that a charging request meets appropriate criteria is about $480 (10 hours x $48 per hour) per charging request.

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

The following table presents the estimated incremental change in annual burden hours due to this rule, as explained above.

Table 1 -- Estimated Incremental Change in Annual Burden Hours Due to this Rule

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
§ 312.8	2	(0.45)	(10)	24	576

13. Estimates of Other Total Annual Cost Burden to Respondents and Recordkeepers

There are no other costs, including capital costs and operating and maintenance costs, associated with this collection.

14. Annualized Cost to the Federal Government

Because requests to charge are already submitted to FDA reviewers under 21 CFR 312, the agency does not expect a notable increase in current budgeted costs resulting from this final rule.

15. Explanation for Program Changes or Adjustments

As explained in section 12, including Table 1, the estimated incremental change in annual burden hours due to this rule is 576 hours. The estimated annual burden resulting from this final rule that is already included in OMB Control Number 0910-0014 is described in Table 2.

Table 2 - Estimated Annual Burden Already Included in OMB Control Number 0910-0014

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
312.7(d)	28	1.58	44	24	1,056

16. Plans for Tabulation and Publication and Project Time Schedule

No comprehensive tabulation of the data is planned or anticipated.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

There are no forms in § 312.8.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification statement identified in Item 19, A Certification for Paperwork Reduction Act Submission, of OMB Form 83-I.

PAPERWORK REDUCTION ACT SUBMISSION

Please read the instructions before completing this form. For additional forms or assistance in completing this form, contact your agency's Paperwork Clearance Officer. Send two copies of this form, the collection instrument to be reviewed, the supporting statement, and any additional documentation to: Office of Information and Regulatory Affairs, Office of Management and Budget, Docket Library, Room 10102, 725 17th Street NW, Washington, DC 20503.

1. Agency/Subagency originating request

FDA

2. OMB control number b. [ ] None

a. 0910 -

3. Type of information collection (*check one*)

a. [x] New Collection

b. [X] Revision of a currently approved collection

c. [ ] Extension of a currently approved collection

d. [ ] Reinstatement, without change, of a previously approved collection for which approval has expired

e. [ ] Reinstatement, with change, of a previously approved collection for which approval has expired

f. [ ] Existing collection in use without an OMB control number

For b-f, note Item A2 of Supporting Statement instructions

4. Type of review requested (*check one*)
a. [x] Regular submission
b. [ ] Emergency - Approval requested by at close of comment period
c. [ ] Delegated

5. Small entities
Will this information collection have a significant economic impact on a substantial number of small entities? [ ] Yes [x] No

6. Requested expiration date
a. [X] Three years from approval date b. [ ] Other Specify:____/___

7. Title: Charging for Investigational Drugs under an IND – Final Rule

8. Agency form number(s) (*if applicable*)

9. Keywords human drugs safety reporting

10. Abstract: The final rule replaces the previous charging regulation at § 312.7(d). The final rule clarifies the circumstances in which charging for an investigational drug in a clinical trial is appropriate, sets forth criteria for charging for an investigational drug for the different types of expanded access for treatment use, and clarifies what costs can be recovered for an investigational drug. The final rule permits charging for a broader range of investigational and expanded access uses than was explicitly permitted previously.

11. Affected public (*Mark primary with "P" and all others that apply with "x")*
a. ___ Individuals or households d. ___ Farms
b. _x_ Business or other for-profit e. ___ Federal Government
c. ___ Not-for-profit institutions f. ___ State, Local or Tribal Government

12. Obligation to respond (*check one*)
a. [ ] Voluntary- (guidance document)
b. [x] Required to obtain or retain benefits
c. [Mandatory

13. Annual recordkeeping and reporting burden; INCREMENTAL ONLY
a. Number of respondents – 2 _____
b. Total annual responses – (10) _____
1. Percentage of these responses collected electronically – 25%
c. Total annual hours requested – 576 _____
d. Current OMB inventory – 1,056___
e. Difference (480) _____
f. Explanation of difference
1. Program change – Charging rule resulting in increase in burden hours
_____

14. Annual reporting and recordkeeping cost burden *(in thousands of dollars)*
a. Total annualized capital/startup costs _0_____
b. Total annual costs (O&M) _0_____
c. Total annualized cost requested _0_____
d. Current OMB inventory _0_____
e. Difference _____
f. Explanation of difference This is a proposed rule___
1. Program change _____
2. Adjustment _____

2. Adjustment _____	
15. Purpose of information collection (*Mark primary with "P" and all others that apply with "X"*) a. _ Application for benefits e._ Program planning or management b. _ Program evaluation f._ Research c. _ General purpose statistics g. x Regulatory or compliance d. _ Audit	16. Frequency of recordkeeping or reporting *(check all that apply)* a. [ ] Recordkeeping b. [ ] Third party disclosure c. [x] Reporting 1. [x] On occasion 2. [ ] Weekly 3. [ ] Monthly 4. [ ] Quarterly 5. [ ] Semi-annually 6. [] Annually 7. [ ] Biennially 8. [x] Other (describe) one-time
17. Statistical methods Does this information collection employ statistical methods [ ] Yes [x] No	18. Agency Contact (person who can best answer questions regarding the content of this submission) Name: Elizabeth Berbakos Phone: _____

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