SUPPORTING STATEMENT
Expanded Access to Investigational Drugs for Treatment Use – Final Rule

A. Justification

1. Circumstances Making the Collection of Information Necessary

Submission Requirements for All Expanded Access Uses --

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

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

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

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

Individual Patient Expanded Access --

Section 312.310(b) contains additional submission requirements that apply to use of an investigational drug for the treatment of an individual patient by a licensed physician. The expanded access submission must include information adequate to satisfy FDA that the criteria for all expanded access uses and those specific to individual patient expanded access have been met. The individual patient expanded access criteria are: (1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition and (2) FDA must determine that the patient cannot obtain the

drug under another type of IND.

Section 312.310(b)(1) states that if the drug is the subject of an existing IND, the expanded access submission may be made by a commercial sponsor or by a licensed physician.

Section 312.310(b)(2) states that a sponsor may satisfy the submission requirements by amending its existing IND to include an individual patient expanded access protocol.

Section 312.310(b)(3) states that a licensed physician may satisfy the submission requirements by obtaining a right of reference to pertinent information in the IND and providing any other required information not contained in the IND (usually only the information specific to the individual patient).

Intermediate Size Patient Populations --

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

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

Treatment IND or Protocol --

Section 312.320 describes the treatment IND or treatment protocol currently codified in §§ 312.34 and 312.35. Section 312.320(b) states that the expanded access submission must include information adequate to satisfy FDA that the criteria for all expanded access uses and those specific to the treatment IND or protocol have been met. The criteria specific to a treatment IND or treatment protocol are: (1) The drug is being investigated in a controlled clinical trial designed to support a marketing application for the expanded access use or all clinical trials of the drug have been completed; (2) the sponsor is pursuing marketing approval of the drug for the expanded access use with due diligence; and (3) there is sufficient clinical evidence of safety and effectiveness to support the treatment use. Such evidence will ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials. When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, could provide a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and will not expose patients to an unreasonable and significant risk of illness or injury. This evidence will ordinarily

consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

2. Purpose and Use of the Information Collection

The final rule is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and who may benefit from such therapies. The final rule is also intended to increase public knowledge and awareness of expanded access and, thus, to make investigational drugs more widely available. In addition, by establishing clear eligibility criteria and submission requirements, the final rule will ease administrative burdens on physicians seeking investigational drugs for their patients and on sponsors who are willing to make promising unapproved therapies available for treatment use.

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

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

The Analysis of Economic Impacts section 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 major purpose of the final rule is to expand access to investigational drugs for patients with serious and immediately life-threatening conditions who lack satisfactory therapeutic alternatives. Patients who lack effective therapeutic alternatives and would be unable to benefit from access to investigational drugs, physicians would be unable to obtain investigational drugs for their patients, and drug sponsors would be unable to make investigational drugs available to patients.

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 75147), FDA proposed to amend its regulations permitting access to investigational drugs to treat patients with serious or immediately life-threatening diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. 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 IND content and format submission requirements (§ 312.23), treatment use of investigational new drugs (§ 312.35(a) and (b)), and emergency use of an investigational new drug (§ 312.36). This analysis pertains only to the incremental increase in reporting burden as a result of the final rule, which, as explained below, results in an increase in the number of submissions for expanded access for individual patients and for intermediate size patient populations.

Individual Patient Expanded Access --

The final rule results in an incremental increase of 329 INDs for individual patient

expanded access. This is based on our analysis that, from 1997 to 2005, we received on average approximately 659 submissions for the treatment use of investigational drugs by individual patients per year. We expect the number of individual patient expanded access submissions to increase by 329 because the final rule will increase awareness of the option for individual patients to gain access to investigational drugs and decrease the perceived difficulty of obtaining such access.

We estimate that preparation and submission of an individual patient expanded access IND or protocol submission will require a total of approximately 8 hours.

Intermediate Size Patient Population Expanded Access --

The final rule results in an incremental increase of 13 INDs for intermediate size patient population expanded access. This is based on our analysis that, from 2000 through 2002, we received approximately 55 submissions per year that we consider expanded access for an intermediate size patient population under the final rule. We expect the number of intermediate size patient population expanded access submissions to increase by 13 because there will be greater awareness of this option. In addition, the anticipated increase in volume of submissions for expanded access for individual patients discussed previously is expected to increase the number of submissions for expanded access for intermediate size patient populations because the final rule encourages the consolidation of multiple individual patient INDs or protocols for a given expanded access use.

Information provided by our review divisions indicates that preparation and submission of an intermediate size patient population IND will require a total of approximately 120 hours.

Costs --

As described in the "Analysis of Economic Impacts" section of the final rule, the incremental burden imposed by the final rule will be in the form of additional annual or recurring costs associated with the increased number of expanded access submissions estimated previously in this document. The preparation and submission of an individual patient expanded access submission will require a total of approximately 8 hours. This time burden will be divided among physicians (approximately 15 percent or 1.2 hours) and nurses, nurse practitioners, or medical administrators (approximately 85 percent or 6.8 hours). According to the U.S. Department of Labor, Bureau of Labor Statistics, total employer costs per hour worked for employee compensation for registered nurses in the health care and social assistance sector was $44.21 as of March, 2008. Thus, the cost of the estimated 6.8 hours of nurse time required to prepare and submit an individual patient expanded access submission will be approximately $301 ($300.62 = $44.21 per hour x 6.8 hours). Historically, most of the treatment use requests submitted to the agency have been prepared by physicians in the hematology/oncology specialty category. Data available on the Internet indicate that the median expected total compensation for a physician in the hematology/oncology specialty category was $387,739 as of March 2008. This median total compensation figure corresponds to approximately $186 per hour ($186.41 = $387,739 / 2,080 hours). Thus, the cost for the 1.2 hours of physician time required to prepare and submit an individual patient expanded access submission is about $224 ($223.69 = $186.41 per hour x 1.2 hours). Therefore, the cost resulting from the incremental increase of 329 INDs for individual patient expanded access is $172,725 ($301 + $224 x 329).

Preparation and submission of an intermediate size patient population expanded access IND or protocol is expected to require a total of about 120 hours of staff time. This time burden will be divided between a Medical Director or Director of Clinical Research, typically a medical doctor (approximately 50 percent or 60 hours), a Regulatory Affairs Director (approximately 20 percent or 24 hours), and a Clinical Research Associate (approximately 30 percent or 36 hours). Information available on the Internet suggests that the median total compensation for a physician serving as a Medical Director is about $316,134 per year. This translates into an estimated hourly total compensation figure of about $152 ($151.98 = $316,134 / 2,080 hours). Thus, the cost associated with the 60 hours of Medical Director time required to prepare and submit an intermediate size patient population expanded access submission is approximately $9,120 ($9,120 = 60 hours x $152). Information available on the Internet also indicates that the median total compensation for a Regulatory Affairs Director is approximately $235,149 per year. This translates into an estimated hourly total compensation figure of about $113 ($113.05 = $235,149 / 2,080 hours). Thus, the cost associated with the 24 hours of Regulatory Affairs Director time required to prepare and submit an intermediate size patient population expanded access submission is approximately $2,712 ($2,712 = 24 hours x $113). Finally, information available on the Internet indicates that the median total compensation for a Clinical Research Associate is approximately $86,890 per year. This translates into an estimated hourly total compensation figure of about $42 ($41.77 = $86,890 / 2,080 hours). Thus, the cost associated with the 36 hours of Clinical Research Associate time required to prepare and submit an intermediate size patient population expanded access submission is approximately $1,512 ($1,512 = 36 hours x $42). Thus, the total cost to prepare and submit an intermediate size patient population expanded access submission will be approximately $13,350 ($13,344 = $9,120 + $2,712 + $1,512). Therefore, the cost resulting from the incremental increase of 13 INDs for intermediate size patient population expanded access is $173,472 ($9,120 + $2,712 + $1,512 x 13).

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

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

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
§ 312.310(b) Individual patient expanded access & § 312.305(b) submission requirements generally.	329	1	329	8	2,632
§ 312.315(c) Intermediate size patient population expanded access & § 312.305(b) submission requirements	13	1	13	120	1,560

Table 1 --Estimated Incremental Change in Annual Reporting Burden Due to this Rule					
generally.					
TOTAL					4,192

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

As described in the "Analysis of Impacts" section of the final rule, the total one-time costs of the final rule will be negligible. FDA expects that the annual costs of this final rule will range from a low of about $109,000 to $219,000 in the first year following publication of the final rule to a high of about $325,000 to $568,000 in the fourth and fifth years. These estimates suggest total annual costs for the final rule of between $1.2 and $2.2 million for the 5-year period following implementation of any final rule based on this proposal. The agency expects that the estimated incremental cost burdens associated with this final rule are likely to be widely dispersed among affected entities for several reasons. First, given the historical volume of various types of treatment use submissions, the agency believes that a particular drug sponsor--or a physician acting on behalf of a patient--will submit a request for expanded access to investigational drugs fairly infrequently. Second, the final rule encourages the consolidation of multiple expanded access INDs or protocols for individual patients for a particular expanded access use under an intermediate size patient population expanded access IND or protocol. Such consolidation should, to some extent, offset incremental administrative burdens caused by increased patient access. Making the transition from multiple individual patient expanded access INDs or protocols to a single IND or protocol for an intermediate size patient population should reduce for sponsors the administrative burdens associated with making a drug available for expanded access use. In addition, provisions of the final rule are designed to minimize the amount of information and paperwork required to support a particular expanded access request. Physicians and drug sponsors will need to review the rule to become familiar with its provisions and to gather the evidence and information necessary to support an expanded access submission. However, in instances where a current IND already exists, a sponsor need only submit an amendment describing the information relevant to the expanded access protocol. Also, another sponsor or individual physician acting on behalf of a patient may, with the written permission of the original sponsor, reference information in the current IND already on file. The agency believes that a majority of expanded access submissions will have such a right of reference, either because the sponsor is also the drug developer or the developer will generally be willing to grant the request. To the extent that these provisions minimize the informational burden on potential sponsors or physicians, the final rule will enhance both efficiency and cost effectiveness. Therefore, the agency does not expect a significant increase in current budgeted costs for FDA resulting from this final rule.

15. Explanation for Program Changes or Adjustments

As explained in section 12, including Table 1, the estimated incremental increase in annual reporting burden due to this rule is 4,192 hours. The estimated annual reporting 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 Reporting 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
Current § 312.23	659	1	659	8	5,272
Current § 312.23	55	1	55	120	6,600
Current § 312.35(a) & (b)	9	1.11	10	300	3,000
Current § 312.36	525	1.23	645	16	10,320
TOTAL					25,192

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 this rulemaking that are not already approved under 0910-0014.

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: Expanded Access to Investigational Drugs for Treatment Use – Final Rule

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

9. Keywords human drugs safety reporting

10. Abstract: The final rule clarifies existing regulations and adds new types of expanded access for treatment use. Under the final rule, expanded access to investigational drugs for treatment use is available to individual patients, including in emergencies; intermediate-size patient populations; and larger populations under a treatment protocol or treatment investigational new drug application (IND).

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
a. Number of respondents – 342 _____
b. Total annual responses – 342 _____
1. Percentage of these responses collected electronically – 25%
c. Total annual hours requested – 4,192 _____
d. Current OMB inventory – 11,872 hours in 0910-0014 ___
e. Difference – 7,680 _____
f. Explanation of difference
1. Program change – Final rule resulting in incremental increase in burden _____
2. Adjustment _____

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 _____

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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