SUPPORTING STATEMENT
Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans
Final Rule

JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

The final rule amends FDA regulations governing safety reporting requirements for human drug and biological products subject to an investigational new drug application (IND). The final rule codifies the agency's expectations for timely review, evaluation, and submission of relevant and useful safety information and implements internationally harmonized definitions and reporting standards. The revisions will improve the utility of IND safety reports, reduce the number of reports that do not contribute in a meaningful way to the developing safety profile of the drug, expedite FDA's review of critical safety information, better protect human subjects enrolled in clinical trials, subject bioavailability and bioequivalence studies to safety reporting requirements, promote a consistent approach to safety reporting internationally, and enable the agency to protect and promote public health.

This final rule amends parts 312 and 320 of FDA regulations by revising the requirements for IND safety reporting and for bioavailability and bioequivalence studies. The final rule clarifies what safety information must be reviewed under § 312.32(b) and clarifies FDA's expectations for analysis of previous, similar reports (§ 312.32(c)(1)). The final rule clarifies how and when to submit IND safety reports to FDA and participating investigators, including the requirement in § 312.32(c)(1)(v) that certain reports be submitted in a narrative format (proposed § 312.32(c)(1)(iii)). It provides examples of the kinds of evidence that suggest a causal relationship between the drug and the adverse event when determining whether a serious and unexpected adverse event qualifies for expedited reporting (§ 312.32(c)(1)(i)). The final rule requires that sponsors submit expedited reports of findings from clinical studies, epidemiological studies, or pooled analyses of multiple studies that suggest a significant risk in

humans (§ 312.32(c)(1)(ii)); animal or in vitro testing that suggests a significant risk in humans (§ 312.32(c)(1)(iii)); and expedited reports of an increased rate of occurrence of serious, expected suspected adverse reactions (§ 312.32(c)(1))(iv)). The final rule also provides for alternative reporting arrangements (§ 312.32(c)(3)) and provides that study endpoints not be reported except in unusual cases (§ 312.32(c)(5)). The final rule clarifies in § 312.32(c)(1)(v) that the period of time for submitting additional data requested by the agency is 15 calendar days (i.e., the same period of time that is allowed for submitting followup information under § 312.32(d)(3)). The final rule allows for alternative reporting arrangements, as provided in former § 312.32(c)(3). The final rule revises the statement, "FDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph" by replacing the word "request" with "require" to reflect the existing process. In addition, the final rule clarifies the reporting requirements for clinical investigations of drug products that are marketed in the United States (§ 312.32(c)(4)). The final rule makes minor editorial changes to § 312.32(d)(2) to clarify the followup reporting requirements. In addition, the final rule eliminates the redundant submission requirements for information amendments and annual reports under § 312.32(d)(4) because they are already contained in §§ 312.31 and 312.33. The final rule clarifies the requirements for investigators to submit reports of serious adverse events to the sponsor and clarifies the requirement for reporting study endpoints that are serious adverse events (§ 312.64(b)). Finally, the final rule requires that applicants submit to FDA reports of serious adverse events from bioavailability and bioequivalence studies. Proposed § 320.31(d) would have required that these studies be subject to the proposed IND safety reporting requirements, making broadly applicable all reports under proposed § 312.32 (e.g., reports of serious and unexpected SADRs, reports of information sufficient to consider product administration changes). On its own initiative, FDA tailored the rule to require only those reports that FDA believes would be most informative (i.e., reports of all serious adverse events). FDA also revised this provision to make it consistent with the final revisions for submission of IND safety

reports and reports of any fatal or life-threatening adverse event.

2. Purpose and Use of the Information Collection

Revising and clarifying the IND safety reporting requirements is a critical component of FDA's stated efforts to: (1) Improve the overall quality of safety reporting, thereby strengthening the agency's ability to review critical safety information, (2) monitor the safety of human drug and biological products, and (3) harmonize safety reporting internationally.

First, the revisions to the IND safety reporting requirements will improve the overall quality of safety reporting and the agency's ability to review critical safety information by ensuring that the information that FDA receives in an IND safety report is relevant and useful. Under former regulations, there may have been over-reporting of serious adverse events for which there is little reason to believe that the drug caused the event, complicating or delaying FDA's ability to detect a safety signal. In this final rule, FDA clarifies definitions, provides examples of the types of evidence that suggest a causal relationship for purposes of reporting a suspected adverse reaction to the IND and participating investigators, and revises the requirements for expedited reporting of serious and unexpected suspected adverse reactions to the IND. The final rule also provides for sponsors to arrange alternative formats and/or frequencies for reporting and provides that study endpoints must not be submitted as an IND safety report except in unusual cases. These revisions not only have an impact on which reports are sent to FDA and participating investigators, but also which reports are sent by investigators to Institutional Review Boards (IRBs) for review and monitoring of clinical trials. These revisions and clarifications will minimize reports that do not contribute to FDA's understanding of the developing safety profile of the drug and decrease the number of uninterpretable reports (so-called "noise") in the system. In addition, the revisions and clarifications will help to make clear under what circumstances a study blind needs to be broken and will help to minimize unnecessary unblinding. Ultimately, these revisions and

clarifications should contribute toward more useful adverse reaction information for inclusion in product labeling.

Second, by requiring expedited reports of certain safety information that was not reported expeditiously under former IND safety reporting requirements or bioavailability or bioequivalence requirements, the final rule will help FDA to monitor the safety of human drug and biological products and better protect human subjects enrolled in clinical trials. Under the final rule, FDA will receive expedited reports of:

- Findings from clinical studies, epidemiological studies or pooled analyses of multiple studies that suggest a risk in humans exposed to the drug,
- Serious expected suspected adverse reactions that occur at an increased rate than listed in the protocol or investigator brochure, and
- Serious adverse events from bioavailability and bioequivalence studies.

By receiving these reports expeditiously, FDA will be better able to review and monitor the drug's safety.

Finally, FDA had proposed certain revisions to its IND safety reporting requirements to harmonize with recommendations by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and by the World Health Organization's Council for International Organizations of Medical Sciences (CIOMS), and which have been adopted by the European Union. After reviewing the comments on the proposal and after discussions with our ICH partners, FDA has revised the definitions and reporting standards to be as consistent as possible with international definitions and standards, recognizing that there may be inconsistencies within ICH documents and among the other member ICH nations' interpretations of these definitions and standards.

3. Use of Improved Information Technology and Burden Reduction

The final rule revises several provisions to allow for electronic submission of reports. First, in § 312.32(c)(1)(v) "Submission of IND safety reports," FDA renamed and revised proposed § 312.32(c)(1)(iii) "Submission of written reports." Second, FDA revised proposed § 312.32(c)(2) "Telephone and facsimile transmission safety reports" to permit other means of rapid communication (e.g., e-mail) for reports that are unexpected and fatal or life-threatening and renamed the provision "Unexpected fatal or life-threatening safety reports." Last, in § 320.31(d)(3), FDA revised the proposed requirement for submission of IND safety reports and unexpected fatal or life-threatening reports from bioavailability and bioequivalence studies to mirror these revisions.

In addition, FDA has issued several guidances for industry to improve the use of information technology in the submission of marketing applications for human drugs and related reports. These guidance documents are available at FDA's web site http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

4. Efforts to Identify Duplication and Use of Similar Information

There are no duplicate submissions resulting from the final rule. In fact, the rule, for example, eliminates the redundant submission requirements for information amendments and annual reports under § 312.32(d)(4) because they are already contained in §§ 312.31 and 312.33.

Generally, the IND regulations, and the information collection required by them, do not conflict with or duplicate other regulations. An IND authorizes only one respondent to conduct a unique set of tests for a unique drug. Consequently, without the authorization, no information can be produced, maintained, or reported. FDA is the only agency that collects this IND information.

5. Impact on Small Businesses or Other Small Entities

The impact of the rule on small entities is analyzed in section VI of the final rule, Analysis of Impacts: As shown in the table below (reproduced from the Analysis of Impacts), the unit costs of a safety report total less than 0.2 percent of the average value of shipments for the smallest entities. According to this analysis, we do not believe that the rule will have a significant economic impact on a substantial number of small entities, but the impact is uncertain. Although some final requirements extend to investigators, we anticipate no additional burden on investigators that would meet SBA determination of small entity.

Unit Costs of Safety Reports as a Percentage of the Average Value of Shipments for Very Small Establishments

	Pharmaceutical Preparation Manufacturing (NAICS 325412) [1]		Biological Product Manufacturing (NAICS 325414) [2]	
Number of employees	<5	<10	<5	<10
Total value of shipments ($1,000)	187,933	561,636	32,011	115,307
Number of establishments	228	339	67	109
Average value of shipments ($)	824,268	1,656,743	477,776	1,057,862
Unit costs of an IND safety report as a percentage of the average value of shipments [3]	0.0% to 0.1%	0.0% to 0.0%	0.1% to 0.2%	0.0% to 0.1%
Unit costs of a bioavailability or bioequivalence report as a percentage of the average value of shipments [4]	0.1%	0.1%	0.2%	0.1%

Numbers are rounded.
[1] Source: U.S. Department of Commerce, Bureau of the Census, 2002 Economic Census, Manufacturing Industry Series, Pharmaceutical Preparation Manufacturing, Table 4, EC02-311-325412 (RV).
[2] Source: U.S. Department of Commerce, Bureau of the Census, 2002 Economic Census, Manufacturing Industry Series, Biological Product Manufacturing, Table 4, EC02-311-325414 (RV).
[3] Based on a unit cost ranging from $250 to $750.
[4] Based on a unit cost = $950.

6. Consequences of Collecting the Information Less Frequently

The revisions to the IND safety reporting requirements, as submitted in the provided frequency, will improve the agency's ability to review critical safety information by ensuring that the information that FDA receives in an IND safety report is relevant and useful. In the final rule, FDA clarifies

definitions, provides examples of the types of evidence that suggest a causal relationship for purposes of reporting a suspected adverse reaction to the IND and participating investigators, and revises the requirements for expedited reporting of serious and unexpected suspected adverse reactions to the IND. The final rule also provides for sponsors to arrange alternative formats and/or frequencies for reporting and provides that study endpoints must not be submitted as an IND safety report except in unusual cases. These revisions not only have an impact on which reports are sent to FDA and participating investigators, but also which reports are sent by investigators to Institutional Review Boards (IRBs) for review and monitoring of clinical trials. Ultimately, these revisions and clarifications should contribute toward more useful adverse reaction information for inclusion in product labeling.

In addition, by requiring expedited reports of certain safety information that was not reported expeditiously under former IND safety reporting requirements or bioavailability or bioequivalence requirements, the final rule will help FDA to monitor the safety of human drug and biological products and better protect human subjects enrolled in clinical trials.

Generally, the prescribed frequencies for submitting information to FDA are based on the agency's view of its statutory responsibility. Thus, in order to determine the risks posed by particular studies for human subjects, FDA must have information about the studies before they begin. Similarly, in monitoring the progress of ongoing studies, FDA believes it must have timely information on serious adverse effects and on significant new information derived from animal studies, from foreign marketing experience, and so forth. Less frequent submissions would increase the chance that human subjects would be unnecessarily exposed to unsafe drugs.

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

In general, the IND regulations comply with 5 CFR 1320.5 except as follows: First, FDA requires submission of safety information (i.e., information on adverse drug reactions as well as other

information on new studies or modifications of existing studies) more often than quarterly (21 CFR 312.32). This increase in reporting frequency is crucial to FDA's safety monitoring responsibilities. Second, these regulations prescribe a specific format for the IND application and follow-up amendments that may not be the same format as that employed by sponsors for their own purposes. These formatting requirements are intended to expedite FDA review and to save agency resources that can be invested in assisting sponsors in developing approvable marketing applications.

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

All comments received on the pre-marketing sections of the March 14, 2003, proposed rule are summarized and responded to in this final rule. Most comments pertained to specific types of reports and how the reports are to be submitted to FDA. Some comments specifically pertained to the estimates in the proposal's Analysis of Impacts and Paperwork Reduction Act sections:

As discussed under "(Comment 43)" in the preamble to the final rule, comments from industry stated that FDA underestimated the number of IND safety reports and that the proposed SADR definition could increase the volume of IND safety reports from 2-fold to 10-fold. Furthermore, comments claimed that any additional reports would be uninformative. An increase in the number of uninformative safety reports would create an additional burden on investigators and IRBs without a corresponding benefit. Comments noted that FDA's analysis failed to account for the potential impact of these additional reports on IRBs and investigators. Moreover, in some cases, additional uninformative reports could force sponsors to unnecessarily break the blind of a clinical trial, potentially reducing the power of double-blind clinical trials to detect safety issues and imposing additional burdens to industry.

As discussed in response to comment 1 of the preamble to the final rule, the agency has decided not to adopt the proposed SADR definition, and instead adopted definitions for the terms "adverse

event" and "suspected adverse reaction." In addition, FDA clarified under what circumstances to submit IND safety reports. With these changes, the comments stating that FDA underestimated the number of IND safety reports are no longer applicable.

As discussed under "(Comment 44)" in the preamble to the final rule, some industry comments stated that FDA underestimated the number of hours required to prepare a narrative report based on information sufficient to consider changes in product administration or risk profile. These comments stated that preparing a narrative report requires more than 8 hours.

None of these comments provide alternative estimates. Without other information, FDA is unable to respond directly to these comments. Nevertheless, we recognize that there may be some situations and types of findings that would require sponsors to spend more time preparing a narrative report. Therefore, to capture the uncertainty of this estimate, FDA has decided to use a range of hours (from 4 to 12 hours) to estimate the incremental burden of this requirement instead of the 4-hour estimate used in our initial analysis of impacts (section VI of the document) or the total 8-hour estimate used in the initial paperwork burden analysis (section VII of the document).

9. Explanation of Any Payment or Gift to Respondents

No remuneration has been provided.

10. Assurance of Confidentiality Provided to Respondents

The release of information submitted to FDA under an IND is governed by the provisions of 21 CFR 312.5 and 314.430. In general, these provisions do not permit public disclosure of information in IND files unless that information has previously been publicly disclosed. The unauthorized use or disclosure of trade secrets required in applications is specifically prohibited under Section 310(j) of the act.

11. Justification for Sensitive Questions

There are no questions of a sensitive nature.

12. Estimates of Annualized Hour Burden and Costs

Annualized Hour Burden -

The rule finalizes revisions to the IND safety reporting requirements found in part 312 and the safety reporting requirements for bioavailability and bioequivalence studies found in part 320. For the initial PRA analysis for the proposed rule, FDA estimated for the annual reporting burdens for collections of information for the entire proposal (i.e., pre- and postmarketing safety reporting requirements). For this PRA analysis, FDA has estimated only for the annual reporting burdens for collections of information included in this final rule (i.e., requirements found in §§ 312.32, 312.64, and 320.31). In addition, in the initial PRA analysis for the proposed rule, FDA estimated for the total reporting burden associated with the proposed reporting requirements in §§ 312.32, 312.64, and 320.31 (as opposed to only the increased burdens associated with the proposed rule). Because OMB has approved paperwork burdens for many of the reporting requirements found in §§ 312.32 and 312.64, for purposes of this final rule and this PRA analysis, FDA is providing estimates for only the additional burdens not already approved by OMB for §§ 312.32, 312.64, and 320.31 (OMB control number 0910-0014). The following provisions of the final rule contain collections of information and the following burden estimates are based on those discussed in the Analysis of Impacts (section VI.B) of this document.

Section 312.32(c)(1)(i) specifies the requirements for reporting to FDA in an IND safety report potential serious risks from clinical trials within 15 calendar days for reports of serious and unexpected suspected adverse reactions and provides examples of what evidence supports a suggestion that there is a causal relationship between the drug and the adverse event. For purposes of this final rule, there is no

new information collection because the reporting burden is unchanged from former § 312.32 and the information collection is already approved by OMB (OMB Control Number 0910-0014).

Section 312.32(c)(1)(ii) requires reporting to FDA in an IND safety report potential serious risks from clinical trials within 15 calendar days for findings from epidemiological studies, pooled analyses of multiple studies, or other clinical studies that suggest a significant risk in humans exposed to the drug. This reporting requirement was not included in former § 312.32. Section 312.32(c)(1)(iii) specifies the requirements for reporting to FDA in an IND safety report potential serious risks from clinical trials within 15 calendar days for findings from animal or in vitro testing that suggest a significant risk to humans. While reports from in vitro testing that suggest a significant risk to humans were not required to be reported under former § 312.32, reports from any finding from tests in laboratory animals were required to be reported (former § 312.32(c)(1)(i)(B)). For purposes of this final rule, for the provisions that are unchanged from former § 312.32, the information collection is already approved by OMB (OMB Control Number 0910-0014). For the additional reporting requirements (i.e., the proposed narrative reports excluding animal testing) in the initial PRA analysis, FDA estimated that sponsors would spend a total of 8 hours per report to prepare and submit these narrative reports. In response to comments, FDA has revised the estimate from an incremental 4 hours to a range from 4 hours to 12 hours per report. Given this range, the upper estimate of additional paperwork burden associated with this requirement for each applicant could be an additional 12 hours to prepare each narrative report. Therefore, for an additional 600 reports, FDA estimates the total annual reporting burden of this final rule could be as high as 7,200 hours.

Section 312.32(c)(1)(iv) requires reporting to FDA in an IND safety report within 15 calendar days any clinically important increase in the rate of occurrence of serious, expected suspected adverse reactions (§ 312.32(c)(1)(iv)). These reports were not required to be submitted within 15 days under former § 312.32. FDA estimates that the minimal incremental burden for this requirement to be

approximately 10 reports per year. Using the same upper estimate for the burden as discussed above (i.e., 12 hours to prepare each report), FDA estimates the additional burden associated with this requirement could be as high as 120 hours. We request industry to comment on whether the requirement will impose an increased burden and if so, provide an estimate of the reporting burden.

Section 312.32(c)(2) requires reporting within 7 days any unexpected fatal or life-threatening suspected adverse reaction. For purposes of this final rule, there is no new information collection because the reporting burden is unchanged from former § 312.32 and the information collection is already approved by OMB (OMB control number 0910-0014).

Section 312.32(c)(4) requires a sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND to submit safety reports for suspected adverse reactions that are observed in the clinical study. For purposes of this final rule, there is no new information collection because the reporting burden is unchanged from former § 312.32 and the information collection is already approved by OMB (OMB Control Number 0910-0014).

Section 312.32(c)(5) clarifies the circumstances under which study endpoints should be submitted to FDA. FDA believes that these clarifications to former § 312.32 are likely to result in a reduction in the number of expedited reports that currently are accounted for by OMB. However, FDA has insufficient information to provide an estimate and was unable to ascertain from industry an estimate for such a reduction. Therefore, FDA requests that industry comment on the impact of this provision on reporting burdens. Any reduction in reports will be reflected the next time the information collection for § 312.32 (OMB Control Number 0910-0014) is extended.

Section 312.32(d)(1)-(3) requires followup reporting requirements. For purposes of this final rule, there is no new information collection because the reporting burden is unchanged from former § 312.32 and the information collection is already approved by OMB (OMB Control Number 0910-0014).

Section 312.64(b) requires investigators to report immediately to the sponsor any serious adverse event and include an assessment of whether there is a reasonable possibility that the drug caused the event. FDA revised former § 312.64(b) for clarity and to reflect current practices for investigator reporting to sponsors. For purposes of this final rule, there is no new information collection because we believe that the reporting burden is unchanged from former § 312.64 and the information collection is already approved by OMB (OMB Control Number 0910-0014).

Finally, § 320.31(d)(3) subjects bioavailability and bioequivalence studies to safety reporting requirements. This reporting requirement was not included in former § 320.31. Therefore, all of these reports would be new. For purposes of the initial PRA analysis and this PRA analysis, FDA estimated up to 200 new safety reports required under § 320.31(d) from bioavailability and bioequivalence studies. For these 200 reports, FDA estimates that it could take applicants an additional 14 hours to prepare and submit each report. The burden for bioavailability and bioequivalence safety reporting requirements would total 2,800 hours per year as a result of this final rule.

Description of Respondents: Business or other for-profit organizations.

The table below presents the estimated annualized reporting burden of the final rule, providing estimates for those safety reports not already approved under OMB Control Number 0910-0014.

Estimated Annual Reporting Burden of the Final Rule[1]

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
320.31(d) Bioavailability and Bioequivalence Safety Reports	10	20	200	14	2,800
312.32(c)(1)(ii) and (c)(1)(iii) IND Safety Reports[2]	100	6	600	12	7,200
312.32(c)(1)(iv) IND Safety Reports[3]	10	1	10	12	120
TOTAL					10,120

[1]There are no capital costs or operating and maintenance costs associated with this collection. The estimates are for the additional burdens beyond those already approved for then-current §§ 312.32 and 312.64.

[2] Includes reports based on findings suggesting a significant risk in humans from epidemiological studies, pooled analysis of multiple studies, other clinical studies, or in vitro testing. Reports from animal testing are not included.

[3] Includes reports of clinically important increases in the rate of occurrence of serious, expected suspected adverse reactions.

Costs –

The costs of this rulemaking are analyzed in section VI, Analysis of Impacts, as follows:

As shown in the table below (reproduced from the Analysis of Impacts), we estimate that it takes an average of 14 hours to prepare a safety report for a bioavailability and bioequivalence study. Based on 2007 hourly median wages for the pharmaceutical manufacturing industry, each of these reports will cost sponsors about $950.

As discussed under "(comment 44)" of the preamble to the final rule, the additional time needed to prepare a report of findings suggesting a significant risk in humans may vary. We estimate that sponsors could spend from 4 to 12 hours additional time to prepare a narrative IND safety report. The average incremental cost of a narrative IND safety report ranges from $250 to $750.

Estimated Incremental Burden and Unit Costs for IND Safety Reports

Type of Report	Burden (hours) and Type of Expertise Required			Total Burden (hours)	Total Cost ($) [4]
	Clerical [1]	Epidemiology and Clinical Medicine [2]	Regulatory Affairs [3]		
Bioavailability and Bioequivalence Safety Reports	2	1	11	14	950
IND Safety Reports - lower estimate [5]	1	1	2	4	250
IND Safety Reports - upper estimate [5]	3	3	6	12	750

Numbers are rounded.
Source: U.S. Department of Labor, Bureau of Labor Statistics, May 2007 National Industry-Specific Occupational Employment and Wage Estimates. NAICS 325400 - Pharmaceutical and Medicine Manufacturing, extracted September 3, 2008, http://www.bls.gov/oes/current/naics4_325400.htm

[1] Based on median hourly wages for Office and Administrative Support Occupations (43-0000) and 40 percent benefits ($24.43 = $17.44 x 1.4).

[2] Based on median hourly wages for Medical and Health Services Managers (11-9111) and 40 percent benefits ($75.03 = $53.59 x 1.4).

[3] Based on median hourly wages for Management Occupations (11-0000) and 40 percent benefits ($74.96 = $53.54 x 1.4).

[4] Unit costs are rounded.

[5] Includes reports based on findings suggesting a significant risk in humans from epidemiological studies, pooled analysis of multiple studies, other clinical studies, or in vitro testing. Reports from animal testing are not included.

The table below (reproduced from the Analysis of Impacts) summarizes the estimated total costs of the final rule. Annually, sponsors will submit up to 200 safety reports for bioavailability and bioequivalence studies and up to 610 IND safety reports. We estimate that the total costs of the final rule will equal less than $0.7 million annually.

Estimated Total Costs of the Final Rule

Type of Report	Unit Costs ($)	Annual Number of Reports	Total Annual Costs ($)
Bioavailability and Bioequivalence Safety Reports[1]	950	200	190,000

IND Safety Reports[2]	250 to 750	610	150,000 to 460,000
Total Costs			340,000 to 650,000

Numbers are rounded.

[1] We received no comments that provided sufficient information to revise our initial estimate. Because these events occur sporadically and the number of reports will vary from year to year, these numbers represent reasonable estimates of the annual average number of reports.

[2] The annual number of IND safety reports includes the proposed 600 reports of information suggesting a significant human risk (from epidemiological studies, pooled analysis of multiple studies, other clinical studies, or in vitro testing, but not from animal testing and an additional 10 reports of increases in the occurrence rates of serious, expected suspected adverse reactions.

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

Other than those costs calculated under section 12 above, there are no other costs resulting from this rulemaking.

14. Annualized Cost to the Federal Government

FDA estimates that the currently calculated Federal burden for all submissions under 21 CFR 312 would also cover all revised submissions under this final rule. There are approximately 1114 FTEs devoted to new drug evaluation. Approximately 35% of new drug evaluation review is devoted to IND review. In addition, for biological products, approximately 189 FTEs are devoted to IND review. If each FTE equals approximately $145,000.00, the total cost burden to the Federal Government for all of 21 CFR 312 would be approximately $83,955,000 (1114 x 35% + 189 x $145,000).

15. Explanation for Program Changes or Adjustments

This is a new collection and does not revise or extend an existing OMB Control Number.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no publications or other schedules.

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

The expiration date will be displayed on those forms that are part of this information collection.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification statement identified in Item 19, "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. [ ] 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 Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans -- Final Rule

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

9. Keywords application, applicants, drugs

10. Abstract: Information collection from sponsors who apply for approval of an investigational new drug application in order to develop a drug for marketing.

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. [ ] Required to obtain or retain benefits

c. [x] Mandatory

13. Annual recordkeeping and reporting burden

a. Number of respondents -- __120_____

b. Total annual responses/records -- 810

1. Percentage of these responses collected electronically -- approx. 25%

c. Total annual hours requested – 10,120 _____

d. Current OMB inventory – none___

e. Difference – none _____

f. Explanation of difference

1. Program change __

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 ____0_____

f. Explanation of difference

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. [x] Annually

7. [ ] Biennially 8. [ ] Other (describe) _____

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: 796-3792 _____