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

OMB Control Number 0910-0672

SUPPORTING STATEMENT

Terms of Clearance: None.

A. Justification

1. Circumstances Making the Collection of Information Necessary

In the Federal Register of September 29, 2010 (75 FR 59960), FDA published a final rule entitled "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans." The rule clarified the agency's expectations for timely review, evaluation, and submission of relevant and useful safety information and implemented internationally harmonized definitions and reporting standards for Investigational New Drug (IND) safety reports. The rule also required safety reporting for bioavailability and bioequivalence studies. The rule was intended to improve the utility of IND safety reports, expedite FDA's review of critical safety information, better protect human subjects enrolled in clinical trials, and harmonize safety reporting requirements internationally.

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. The revisions to the IND safety reporting requirements are intended to 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. 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 rule helps FDA to monitor the safety of human drug and biological

products and better protect human subjects enrolled in clinical trials. Under the rule, FDA receives 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 is better able to review and monitor the drug's safety.

The rulemaking included the following information collection under the PRA that was not already included in 21 CFR part 312.32 and approved under OMB Control Number 0910-0014:

21 CFR 312.32(c)(1)(ii) and (c)(1)(iii) – Section 312.32(c)(1)(ii) requires reporting to FDA, in an IND safety report, of 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. 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 in vitro testing that suggest a significant risk to humans.

Section 312.32(c)(1)(iv) requires reporting to FDA in an IND safety report within 15 calendar days of any clinically important increase in the rate of occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure.

The rulemaking also included new information collection under the PRA by requiring safety reporting for bioavailability and bioequivalence studies (§ 320.31(d)).

2. Purpose and Use of the Information Collection

The information collection is intended to improve the utility of IND safety reports, expedite

FDA's review of critical safety information, better protect human subjects enrolled in clinical trials, and harmonize safety reporting requirements internationally.

3. Use of Improved Information Technology and Burden Reduction

The rule revised 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 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 was 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, the rule does not have a significant economic impact on a substantial number of small entities, but the impact is uncertain. Although some final requirements extend to investigators, there are no additional burdens 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 clarified definitions, provided 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 revised the

requirements for expedited reporting of serious and unexpected suspected adverse reactions to the IND. The final rule also provided for sponsors to arrange alternative formats and/or frequencies for reporting and provided 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 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 helps 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

In accordance with 5 CFR 1320.8(d), FDA published a 60 day notice for public comment in the FEDERAL REGISTER of 06/12/13 (78 FR 35283). No comments were received.

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

12a. Annualized Hour Burden Estimate

The rule includes the following information collection under the PRA that was not already included in 21 CFR 312.32 and approved under OMB Control Number 0910-0014.

21 CFR 312.32(c)(1)(ii) and (c)(1)(iii) – Section 312.32(c)(1)(ii) requires reporting to FDA, in an IND safety report, of 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. 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 in vitro testing that suggest a significant risk to humans. FDA estimates that approximately 100 sponsors spend a total of approximately 12 hours per report to prepare and submit approximately 600 reports annually.

Section 312.32(c)(1)(iv) requires reporting to FDA in an IND safety report within 15 calendar days of any clinically important increase in the rate of occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure. FDA estimates that approximately 10 sponsors spend a total of approximately 12 hours per report to prepare and submit approximately 10 reports annually.

The rulemaking also included new information collection under the PRA by requiring safety reporting for bioavailability and bioequivalence studies (§ 320.31(d)). FDA estimates that approximately 10 sponsors spend a total of approximately 14 hours per report to prepare and submit approximately 200 reports annually.

Table 1.--Estimated Annual Reporting Burden[1]

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Average Burden 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 of information. The estimates are for the additional burdens beyond those already approved for 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.

12b. Annualized Cost Burden Estimate

The costs of the rule were analyzed in the final rule 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/or Recordkeepers/Capital Costs

There are no capital, start-up, operating or maintenance costs associated with this information collection.

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 the 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

The burden analysis for this extension is the same as we calculated for the final rule 3 years ago. Control number 0910-0672 will be discontinued and merged into 0910-0014 during the extension for 0910-0014 in 2015.

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.