OMB INFORMATION COLLECTION
INVESTIGATIONAL NEW DRUG (IND) REGULATIONS
21 CFR PART 312

0910-0014
SUPPORTING STATEMENT

A. Justification

1. Circumstances Making the Collection of Information Necessary

FDA is requesting OMB approval for the reporting and recordkeeping requirements contained in the FDA regulations "Investigational New Drug Application" in part 312 (21 CFR part 312). Part 312 implements provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) (the act) to issue regulations under which the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products can be conducted.

FDA is charged with implementing statutory requirements that drug products marketed in the United States be shown to be safe and effective, properly manufactured, and properly labeled for their intended uses. Section 505(a) of the act provides that a new drug may not be introduced or delivered for introduction into interstate commerce in the United States unless FDA has previously approved a new drug application (NDA). FDA approves an NDA only if the sponsor of the application first demonstrates that the drug is safe and effective for the conditions prescribed, recommended, or suggested in the product's labeling. Proof must consist, in part, of adequate and well-controlled studies, including studies in humans, that are conducted by qualified experts. The IND regulations establish reporting requirements that include an initial application as well as amendments to that application, reports on significant revisions of clinical

investigation plans, and information on a drug's safety or effectiveness. In addition, the sponsor is required to give FDA an annual summary of the previous year's clinical experience. Submissions are reviewed by medical officers and other agency scientific reviewers assigned responsibility for overseeing the specific study. The IND regulations also contain recordkeeping requirements that pertain to the responsibilities of sponsors and investigators. The detail and complexity of these requirements are dictated by the scientific procedures and human subject safeguards that must be followed in the clinical tests of investigational new drugs.

The IND information collection requirements provide the means by which FDA can do the following: (1) Monitor the safety of ongoing clinical investigations; (2) determine whether the clinical testing of a drug should be authorized; (3) ensure production of reliable data on the metabolism and pharmacological action of the drug in humans; (4) obtain timely information on adverse reactions to the drug; (5) obtain information on side effects associated with increasing doses; (6) obtain information on the drug's effectiveness; (7) ensure the design of well-controlled, scientifically valid studies; (8) obtain other information pertinent to determining whether clinical testing should be continued and information related to the protection of human subjects. Without the information provided by industry in response to the IND regulations, FDA cannot authorize or monitor the clinical investigations which must be conducted prior to authorizing the sale and general use of new drugs. These reports enable FDA to monitor a study's progress, to assure subject safety, to assure that a study will be conducted ethically, and to increase the likelihood that the sponsor will conduct studies that will be useful in determining whether the drug should be marketed and available for use in medical practice.

There are two forms that are required under part 312:

Form FDA-1571 - "Investigational New Drug Application." A person who intends to conduct a clinical investigation submits this form to FDA. It includes the following information: (1) A cover sheet containing background information on the sponsor and investigator, (2) a table of contents, (3) an introductory statement and general investigational plan, (4) an investigator's brochure describing the drug substance, (5) a protocol for each planned study, (6) chemistry, manufacturing, and control information for each investigation, (7) pharmacology and toxicology information for each investigation, and (8) previous human experience with the investigational drug.

Form FDA-1572 - "Investigator Statement." Before permitting an investigator to begin participation in an investigation, the sponsor must obtain and record this form. It includes background information on the investigator and the investigation, and a general outline of the planned investigation and the study protocol.

FDA is requesting OMB approval for the following reporting and recordkeeping requirements in part 312:

REPORTING REQUIREMENTS

21 CFR 312.7(d) -- Applications for permission to sell an investigational new drug.

21 CFR 312.8 -- Charging for investigational drugs under an IND.

21 CFR 312.10 -- Applications for waiver of requirements under part 312. As indicated in § 312.10(a), estimates for this requirement are included under §§ 312.23 and 312.31. In addition, separate requests under § 312.10 are estimated in Table 1.

21 CFR 312.20(c) -- Applications for investigations involving an exception from informed consent under § 50.24 (21 CFR 50.24). Estimates for this requirement are included under § 312.23.

21 CFR 312.23 -- INDs (content and format).
.23(a)(1) -- Cover sheet FDA-1571.

.23(a)(2) --Table of Contents.
.23(a)(3) -- Investigational plan for each planned study.
.23(a)(5) -- Investigator's brochure.
.23(a)(6) -- Protocols - Phase 1, 2, and 3.
.23(a)(7) -- Chemistry, manufacturing, and control information.
.23(a)(7)(iv)(*a*),(*b*),(*c*) -- A description of the drug substance, a list of all components, and any placebo used.
.23(a)(7)(iv)(*d*) -- Labeling: Copies of labels and labeling to be provided each investigator.
.23(a)(7)(iv)(*e*) -- Environmental impact analysis regarding drug manufacturing and use.
.23(a)(8) -- Pharmacological and toxicology information.
.23(a)(9) -- Previous human experience with the investigational drug.
.23(a)(10) -- Additional information.
.23(a)(11) -- Relevant information.
.23(f) -- Identification of exception from informed consent.

21 CFR 312.30 -- Protocol amendments.
.30(a) -- New protocol
.30(b) -- Change in protocol
.30(c) -- New investigator.
.30(d) -- Content and format.
.30(e) -- Frequency.

21 CFR 312.31 -- Information amendments.
.31(b) -- Content and format.
-- Chemistry, toxicology, or technical information.

21 CFR 312.32 -- Safety reports.
.32(c)(1) -- Written reports to FDA and to investigators.
.32(c)(2) -- Telephone reports to FDA for fatal or life-threatening experience.
.32(c)(3) -- Format or frequency.
.32(d) -- Follow up submissions.

21 CFR 312.33 -- Annual reports.
.33(a) -- Individual study information.
.33(b) -- Summary information.
(b)(1) -- Adverse experiences.
(b)(2) -- Safety report summary.
(b)(3) -- List of fatalities and causes of death.
(b)(4) -- List of discontinuing subjects.
(b)(5) -- Drug action.
(b)(6) -- Preclinical studies and findings.
(b)(7) -- Significant changes.
.33(c) -- Next year general investigational plan.
.33(d) -- Brochure revision.

.33(e) -- Phase I protocol modifications.
.33(f) -- Foreign marketing developments.

21 CFR 312.35 -- Treatment use of investigational new drugs.
.35(a) -- Treatment protocol submitted by IND sponsor.
.35(b) -- Treatment IND submitted by licensed practitioner.

21 CFR 312.36 -- Requests for emergency use of an investigational new drug.

21 CFR 312.38(b) and (c) -- Notification of withdrawal of an IND.

21 CFR 312.42(e) -- Sponsor requests that a clinical hold be removed and submits a complete response to the issues identified in the clinical hold order.

21 CFR 312.44(c) and (d) -- Opportunity for sponsor response to FDA when IND is terminated.

21 CFR 312.45(a) and (b) -- Sponsor request for, or response to, inactive status determination of an IND.

21 CFR 312.47(b) -- "End-of-Phase 2" meetings and "Pre-NDA" meetings.

21 CFR 312.53(c) -- Investigator information.
Investigator report (Form FDA-1572) and narrative; Investigator's background information; Phase 1 outline of planned investigation and Phase 2 outline of study protocol.

21 CFR 312.54(a) and (b) -- Sponsor submissions concerning investigations involving an exception from informed consent under § 50.24.

21 CFR 312.55(b) -- Sponsor reports to investigators on new observations, especially adverse reactions and safe use. Only "new observations" are estimated under this section; investigator brochures are included under § 312.23.

21 CFR 312.56(b),(c), and (d) -- Sponsor monitoring of all clinical investigations, investigators, and drug safety; notification to FDA.

21 CFR 312.58(a) -- Sponsor's submission of records to FDA on request.

21 CFR 312.64 -- Investigator reports to the sponsor.
.64(a) -- Progress reports.
.64(b) -- Safety reports
.64(c) -- Final reports.

21 CFR 312.66 -- Investigator reports to Institutional Review Board. Estimates for this requirement are included under § 312.53.

21 CFR 312.70(a) -- Investigator disqualification; opportunity to respond to FDA.

21 CFR 312.83 -- Sponsor submission of treatment protocol. Estimates for this requirement are included under §§ 312.34 and 312.35.

21 CFR 312.85 -- Sponsors conducting phase 4 studies. Estimates for this requirement are included under § 312.23 in 0910-0014, and §§ 314.50, 314.70, and 314.81 in 0910-0001.

21 CFR 312.110(b) -- Request to export an investigational drug.

21 CFR 312.120 -- Submissions related to foreign clinical studies not conducted under an IND.

21 CFR 312.130(d) -- Request for disclosable information for investigations involving an exception from informed consent under § 50.24.

RECORDKEEPING REQUIREMENTS

21 CFR 312.52(a) -- Transfer of obligations to a contract research organization.

21 CFR 312.57 -- Sponsor recordkeeping.

21 CFR 312.59 -- Sponsor recordkeeping of disposition of unused supply of drugs. Estimates for this requirement are included under § 312.57.

21 CFR 312.62(a) -- Investigator recordkeeping of disposition of drugs.

21 CFR 312.62(b) -- Investigator recordkeeping of case histories of individuals.

21 CFR 312.120(d) -- Recordkeeping requirements for submissions related to foreign clinical studies not conducted under an IND. Estimates for this requirement are included under § 312.57.

21 CFR 312.160(a)(3) -- Records maintenance: shipment of drugs for investigational use in laboratory research animals or in vitro tests.

21 CFR 312.160(c) -- Shipper records of alternative disposition of unused drugs.

2. Purpose and Use of the Information Collection

The IND information collection requirements provide the means by which FDA can: (a) monitor the safety of ongoing clinical investigations; (b) determine whether the clinical testing of a drug should be authorized; (c) ensure production of reliable data on the metabolism and pharmacological action of the drug in humans; (d) obtain timely information on adverse reactions to the drug; (e) obtain information on side effects associated with increasing doses; (f) obtain information on the drug's effectiveness; (g) ensure the design of well-controlled, scientifically valid studies; (h) obtain other information pertinent to determining whether clinical testing should be continued and information related to the protection of human subjects. Without the information provided by industry in response to the IND regulations, FDA cannot authorize or monitor the clinical investigations that must be conducted prior to authorizing the

sale and general use of new drugs. These reports enable FDA to monitor a study's progress, to assure subject safety, to assure that a study will be conducted ethically, and to increase the likelihood that the sponsor will conduct studies that will be useful in determining whether the drug should be marketed and available for use in medical practice.

3. Use of Improved Information Technology and Burden Reduction

In the Federal Register of December 11, 2003, FDA issued a final rule amending FDA regulations governing the format in which certain labeling is required to be submitted for review with NDAs, certain BLAs, ANDAs, supplements, and annual reports. The final rule requires the electronic submission of the content of labeling (i.e., the content of the package insert or professional labeling, including all text, tables, and figures) in NDAs, certain BLAs, ANDAs, supplements, and annual reports electronically in a form that FDA can process, review, and archive.

The following guidances for industry are among those that have been developed to improve the use of information technology in the submission of marketing applications for human drugs and related reports:

- "Providing Regulatory Submissions in Electronic Format--NDAs". This guidance provides information on how to submit a complete archival copy of an NDA in electronic format and applies to the submission of original NDAs as well as to the submission of supplements and amendments to NDAs.
- "Providing Regulatory Submissions in Electronic Format--General Considerations" . This guidance includes a description of the types of electronic file formats that the agency is able to accept to process, review, and archive electronic documents. The guidance also states that documents submitted in electronic format should enable the user to: (1) Easily view a clear and legible copy of the information; (2) print each document page by page while maintaining fonts, special orientations, table formats, and page numbers; and (3) copy text and images electronically into common word processing documents.
- “Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format”. This guidance provides information to assist applicants in

submitting documents in electronic format for review and archive purposes as part of a BLA, product license application (PLA), or establishment license application (ELA).

• "Providing Regulatory Submissions in Electronic Format-—Prescription Drug Advertising and Promotional Labeling". This draft guidance discusses issues related to the electronic submission of advertising and promotional labeling materials for prescription drug and biological products.

• "Providing Regulatory Submissions in Electronic Format-—ANDAs". This guidance discusses issues related to the electronic submission of ANDAs and supplements and amendments to those applications.

• "Providing Regulatory Submissions in Electronic Format-—Annual reports for NDAs and ANDAs". This guidance discusses issues related to the electronic submission of annual reports for NDAs and ANDAs.

• "Providing Regulatory Submissions in Electronic Format-—Postmarketing Periodic Adverse Drug Experience Reports". This guidance discusses general issues related the electronic submission of postmarketing periodic adverse drug experience reports for NDAs, ANDAs, and BLAs.

• "Providing Regulatory Submissions in Electronic Format-—Human Pharmaceutical Product Applications and Related Submissions". This draft guidance discusses issues related to the electronic submission of ANDAs, BLAs, INDs, NDAs, master files, advertising material, and promotional material.

• "Providing Regulatory Submissions in Electronic Format-—General Considerations". This draft guidance discusses general issues common to all types of electronic regulatory submissions.

• "Providing Regulatory Submissions in Electronic Format-—Content of Labeling". This draft guidance discusses issues related to the submission of the content of labeling in electronic format for marketing applications for human drug and biological products.

These guidance documents and others are available at FDA's web site http://www.fda.gov/cder/guidance/index.htm.

4. Efforts to Identify Duplication and Use of Similar Information

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

FDA's authority and responsibility to ensure the safe use of investigational drugs applies to small as well as to large businesses involved in sponsoring drug studies. FDA believes that its responsibility requires the equal application of the regulations to all businesses. While FDA does not believe it can apply different standards with respect to statutory requirements, FDA does provide special help to small businesses. A small business coordinator has been assigned to the Commissioner's staff to ensure that small businesses have an adequate opportunity to express their concerns and to keep FDA management apprised of how regulatory decisions might impact the small business community. To provide additional assistance to small businesses, FDA has established an office whose exclusive concern is to provide small business with help in dealing with FDA regulatory requirements.

6. Consequences of Collecting the Information Less Frequently

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, etc. 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

These regulations comply with 5 CFR 1320.6 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), in the Federal Register of February 11, 2009 (74 FR 6889), a 60-day notice was published for public comment on this information collection. No comments were received that pertained to the information collection burden estimates.

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 --

In the tables below, the estimates for “number of respondents,” “number of responses per respondent,” and “total annual responses” were obtained from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) reports and data management systems for submissions received in 2007-2008 and from other sources

familiar with the number of submissions received under 21 CFR part 312. The estimates for "hours per response" were made by CDER and CBER individuals familiar with the burden associated with these reports and from estimates received from the pharmaceutical industry.

Costs –

FDA estimates an average industry wage rate of $74.00 per hour (including overhead and benefits) for preparing and submitting the information collection requirements under 21 CFR Parts 312 and 601. Using the averaged wage rate of $74.00 per hour, and multiplied times the total hour burden estimated below, the total cost burden to respondents is $10,470,419,988 ($141,492,162 x $74).

FDA estimates the burden of this collection of information as follows:

Table 1 -- Estimated Annual Reporting Burden for Human Drugs and Biologics (CDER)

21 CFR Section	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours Per Response	Total Hours
312.7(d)	28	1.57	44	24	1,056
312.10	4	1	4	10	40
312.23(a) through (f)	2,496	1.26	3,156	1600	5,049,600
312.30(a) through (e)	2,030	8.91	18,079	284	5,134,436
312.31 (b)	153	2.97	454	100	45,400
312.32(c) and (d)	985	23.06	22,713	32	726,816
312.33(a) through (f)	2,564	2.34	5,994	360	2,157,840
312.35(a) and (b)	9	1.11	10	300	3,000
312.36	525	1.23	645	16	10,320
312.38(b) and (c)	654	1.34	874	28	24,472
312.42(e)	149	1.10	164	284	46,576
312.44(c) and (d)	159	1.13	179	16	2,864
312.45(a) and (b)	254	1.43	362	12	4,344
312.47(b)	281	1.8	529	160	84,640
312.53(c)	900	26.51	23,855	80	1,908,400
312.54(a) and (b)	1	1	1	48	48
312.55(b)	985	2,306	2,271,300	48	109,022,400
312.56(b),(c), and (d)	18	1	18	80	1,440

312.58(a)	91	4.10	373	8	2,984
312.64	141,393	1	141,393	24	3,393,432
312.70(a)	4	1	6	40	240
312.110(b)	23	18.26	420	75	31,500
312.120	115	5	575	32	18,400
312.130(d)	3	1	3	8	24

[1] There are no capital and start-up, or operation, maintenance and purchase costs associated with the collection of information requirements.

Table 2 -- Estimated Annual Recordkeeping Burden for Human Drugs and Biologics (CDER)

21 CFR Section	Number of Recordkeepers	Number of Records Per Recordkeeper	Total Annual Records	Hours Per Record	Total Hours
312.52(a)	683	1	683	2	1,366
312.57	75	485.28	36,396	100	3,639,600
312.62(a)	14,732	1	14,732	40	589,280
312.62(b)	147,320	1	147,320	40	5,892,800
312.160(a)(3)	547	1.4	782	.5	391
312.160(c)	547	1.4	782	.5	391

[1] There are no capital and start-up, or operation, maintenance and purchase costs associated with the collection of information requirements.
Section 312.120 includes the burden estimates for both CDER and CBER.

Table 3. – Estimated Annual Reporting Burden for Biologics (CBER)

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Responses	Total Hours
312.7(d)	12	1.1	13	24	312
312.23(a) through (f)[2]	168	1.5	256	1,600	409,600
312.30(a) through (e)	372	6.4	2,369	284	672,796
312.31(b)[2]	703	7.7	5,417	100	541,700
312.32(c) and (d)	175	14.6	2,563	32	82,016
312.33(a) through (f)	512	2.3	1,168	360	420,480
312.35(a) and (b)	1	1	1	300	300
312.36	10	4	40	16	640
312.38(b) and (c)	81	1.5	120	28	3,360
312.42(e)	74	1.5	108	284	30,672
312.44(c) and (d)	34	1.1	39	16	624
312.45(a) and (b)	41	1.4	59	12	708
312.47(b)	31	1.2	37	160	5,920
312.53(c)	243	4.95	1,203	80	96,240
312.54(a) and (b)	1	1	1	48	48

312.55(b)	42	1	43	48	2,064
312.56(b), (c), and (d)	10	1.6	16	80	1,280
312.58(a)	7	1	7	8	56
312.64	2,728	3.82	10,411	24	249,864
312.70(a)	5	1	5	40	200
312.110(b)	18	1	18	75	1,350
312.130(d)	1	1	1	8	8

[1] There are no capital and start-up, or operation, maintenance and purchase costs associated with the collection of information requirements.
The reporting requirement for § 312.10 is included in the estimates for §§ 312.23 and 312.31.

Table 4. – Estimated Annual Recordkeeping Burden for Biologics (CBER)[1]

21 CFR Section	Number of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
312.52(a)	52	1.4	73	2	146
312.57	168	3.05	512	100	51,200
312.62(a)	2,560	1	2,560	40	102,400
312.62(b)	2,560	10	25,600	40	1,024,000
312.160(a)(3)	55	1.4	77	0.5	38.5
312.160(c)	55	1.4	77	0.5	38.5

[1] There are no capital and start-up, or operation, maintenance and purchase costs associated with the collection of information requirements.

Reporting Recordkeeping TOTAL					130,190,510 11,301,652 141,492,162

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

Except as described in section 12 above, there are no other costs, including capital and start-up, or operation, maintenance, and purchase costs.

14. Annualized Cost to the Federal Government

There are approximately 1114 FTEs devoted to new drug evaluation. Approximately 35% of new drug evaluation review is devoted to INDs. In addition, for biological products, approximately 189 FTEs are devoted to IND review. If each FTE equals approximately $110,000.00, the total cost burden to the Federal Government would be approximately $63,679,000 (1114 x 35% + 189 x $110,000).

15. Explanation for Program Changes or Adjustments

The previously approved burden for this information collection was 71,369,525 hours in 2006. This extension estimates a total burden of 141,492,162 hours. This change in burden hours is the result of an increase in the number of reports we have received under certain sections of 21 CFR 312, when multiplied by the hours per response. FDA data on the following sections showed especially large increases in submissions and, consequently, burden hours between 2006 and 2009:

21 CFR Section **Reporting**	Total Annual Responses	Hours Per Response	Total Hours	
312.23(a) through (f) - *IND Content & Format*	3,156 1,597	1600 1600	*2009* *2006*	5,049,600 2,555,200
312.30(a) through (e) - *Protocol Amendments*	18,079 16,687	284 284	*2009* *2006*	5,134,436 4,739,108
312.33(a) through (f) - *Annual Reports*	5,994 4,516	360 360	*2009* *2006*	2,157,840 1,625,760
312.55(b) - *Sponsor Reports to Clinical Investigators*	2,271,300 807,400	48 48	*2009* *2006*	109,022,400 38,755,200
312.64 - *Clinical Investigator Reports to Sponsors*	141,393 31,791	24 24	*2009* *2006*	3,393,432 762,984

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.