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 312.2(e) -- Requests for FDA advice on the applicability of part 312 to a planned clinical investigation.

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 312.38(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 § 312.320.

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.

21 CFR 312.310(b); 312.305(b) -- Submissions related to expanded access and treatment of an individual patient.

21 CFR 312.310(d) -- Submissions related to emergency use of an investigational new drug.

21 CFR 312.315(c); 312.305(b) -- Submissions related to expanded access and treatment of an intermediate size patient population.

21 CFR 312.320 -- Submissions related to treatment IND or treatment protocol.

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

FDA has developed 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 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 January 27, 2011 (76 FR 4914), 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 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.

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

Table 1. -- Estimated Annual Reporting Burden for Human Drugs[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response (in Hours)[2]	Total Hours
312.2(e)	455	1.03	469	24	11,256
312.8	30	1.13	34	48	1,632
312.10	4	1	4	10	40
312.23(a) through (f)	2,496	1.26	3,156	1,600	5,032,000
312.30(a)	2,030	8.91	18,089	284	5,134,436

through (e)					
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	6,000	360	2,160,000
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)	44	1	44	16	704
312.45(a) and (b)	254	1.43	362	12	4,344
312.47(b)	281	1.8	506	160	80,960
312.53(c)	21,194	1	21,194	80	1,695,520
312.54(a) and (b)	1	1	1	48	48
312.55(b)	985	2,305	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	31,791	1	31,791	24	762,984
312.70(a)	4	1	4	40	160
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
312.310(b) and 312.305(b)	988	1	988	8	7,904
312.310(d)	525	1.23	646	16	10,336
312.315(c) and 312.305(b)	68	1	68	120	8,160
312.320	9	1.11	10	300	3,000
Total					124,833,496

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

[2] Burden estimates of less than 1 hour are expressed as a fraction of an hour in the format "[number of minutes per response]/60".

Table 2. -- Estimated Annual Recordkeeping Burden for Human Drugs[1]

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping (in Hours)[2]	Total Hours
312.52(a)	335	1.5	503	2	1,006
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	30/60	391
312.160(c)	547	1.4	782	30/60	391
Total					10,123,468

1 There are no capital costs or operating and maintenance costs associated with this collection of information.

2 Burden estimates of less than 1 hour are expressed as a fraction of an hour in the format "[number of minutes per response]/60".

Table 3. – Estimated Annual Reporting Burden for Biologics[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response (in Hours)[2]	Total Hours
312.8	41	1.4	57	24	1,368
312.23(a) through (f) and 312.120(b), (c)(2), and (c) (3)	433	1.3	563	1,808	1,017,904
312.30(a) through (e)	590	6.8	4,012	284	1,139,408
312.31(b)	263	29.3	7,706	100	770,600
312.32(c) and (d) and 312.56(c)	294	13.7	4,028	32	128,896
312.33(a) through	647	2.3	1,488	360	535,680

(f) and 312.56(c)					
312.38(b) and (c)	117	1.3	152	28	4,256
312.42(e)	74	1.5	111	284	31,524
312.44(c) and (d)	17	1.1	18	16	304
312.45(a) and (b)	60	1.8	108	12	1,296
312.47(b)	43	1.5	65	160	10,400
312.53(c)	348	6.6	2,297	80	183,760
312.54(a) and (b)	1	1	1	48	48
312.55(b)	138	2.5	345	48	16,560
312.56(b) and (d)	14	1.6	22	80	1,760
312.58(a)	8	1	8	8	64
312.64	6,003	3.5	21,010	24	504,240
312.70(a)	6	1	6	40	240
312.110(b)	21	1	21	75	1,575
312.130(d)	1	1	1	8	8
Total					4,349,891

1 There are no capital costs or operating and maintenance costs associated with this collection of information.

2 Burden estimates of less than 1 hour are expressed as a fraction of an hour in the format "[number of minutes per response]/60".

Table 4. – Estimated Annual Recordkeeping Burden for Biologics

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping (in Hours)[2]	Total Hours
312.52(a)	139	1.4	195	2	390
312.57(a) and (b)	433	2.6	1,126	100	112,600
312.62(a)	5,570	1	5,570	40	222,800
312.62(b)	5,570	10	55,700	40	2,228,000
312.160(a)(3)	146	1.4	204	30/60	102
312.160(c)	146	1.4	204	30/60	102
Total					2,563,994

1 There are no capital costs or operating and maintenance costs associated with this collection of information.

2 Burden estimates of less than 1 hour are expressed as a fraction of an hour in the format "[number of minutes per response]/60".

Costs –

FDA estimates an average industry wage rate of $75.00 per hour (including overhead and benefits) for preparing and submitting the information collection requirements under 21 CFR

Parts 312 and 601.

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, associated with this ICR extension.

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 hour changes in this ICR are the result of burden hours associated with new rulemaking that have been added to this extension. The final rules that have been incorporated into this extension are as follows: Expanded Access to Investigational Drugs for Treatment Use (*RIN 0910-AF14*), Charging for Investigational Drugs Under an Investigational New Drug Application (*RIN 0910—AF13*), and Human Subject Protection; Foreign Clinical Studies Not Conducted Under and Investigational New Drug Application (*RIN 0910-AF15*)

These new burden hours are indicated in the following "21 CFR sections" of the table below:

21 CFR Section	No. of Respondents	No. of Responses Per Respondent	Total Annual Responses	Average Burden Per Response	Total Hours
312.2(e)	455	1.03	469	24	11,280
312.8	30	1.13	34	48	1,632
312.10	4	1	4	10	40
312.120	115	5	575	32	18,400
312.310(b) and 312.305(b)	988	1	988	8	7,904

312.310(d)	525	1.23	646	16	10,336
312.315(c) and 312.305(b)	68	1	68	120	8,160
312.320	9	1.11	10	300	3,000
TOTAL	*2,234*				*60,752*

The other 21 CFR Section burden changes in the Information Collection package are due to changes in the actual reporting estimates FDA received from the Program Office over the past two years.

These changes in estimates, may at times, cause the Information Collection package, specially the Part II, to have negative numbers in the "Due to Adjustment in Agency Estimate". The negative number (-60,377) of Annual Number of Responses that appears in the Due to Adjustment in Agency Estimate is a result of the electronic database systems - ICRAS and ROCIS – keeping a record of the all information since 2006. Once an Information Collection (IC) line item's annual responses and/or annual hour burden is modified, the result can cause an increase (positive number) in the "Due to Adjustment in Agency Estimate" or a decrease (negative 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.