INVESTIGATIONAL NEW DRUG (IND) REGULATIONS

21 CFR Part 312

0910-0014

SUPPORTING STATEMENT

Terms of Clearance: None.

A. Justification

1. Circumstances Making the Collection of Information Necessary

FDA is requesting OMB approval for the reporting and recordkeeping requirements contained in FDA regulations entitled, "Investigational New Drug Application" in 21 CFR part 312 (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 FD&C 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 FD&C 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 monitor the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products, including 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 as required under 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 312.6 – Labeling of an investigational new drug. Estimates for the information collection in this requirement are included under § 312.23(a)(7)(iv)(*d*).

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 the information collection in this requirement are included under §§ 312.23 and 312.31. In addition, other waiver 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 the information collection in this requirement are included under § 312.23.

21 CFR 312.23 -- IND (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 312.41 – Comment and advice on an IND. Estimates for the information collection inthis requirement are included under § 312.23.

21 CFR 312.42 -- 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, an inactive status determination of an IND.

21 CFR 312.47 – Meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings.

21 CFR 312.48 – Dispute resolution. Estimates for the information collection in this requirement are included under § 312.47.

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 and others.

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.
.64(d) – Financial disclosure reports.

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

21 CFR 312.70 -- 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 the information collection in this requirement are included under § 312.23, and under §§ 314.50, 314.70, and 314.81 in OMB Control Number 0910-0001.

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

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

21 CFR 312.130 -- Requests for disclosable information in an IND and from 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 a 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 on the investigational drug.

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

21 CFR 312.160(a)(3) – Records pertaining to the 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 estimates that approximately 76% of all IND submissions under 21 CFR part 312 are submitted electronically. FDA has developed several guidance documents to assist industry in the use of information technology in the submission of applications for human drugs. These guidance documents and others are available at FDA's web site:

http://www.fda.gov/cder/guidance/index.htm.

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), FDA published a 60-day notice for public comment in the FEDERAL REGISTER of November 5, 2014 (79 FR 65663). No comments were received that pertained to this information collection burden.

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

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

21 CFR Part 312 Subpart	FDA Form	No. of respondents	No. of responses per respondent	Total annual responses	Average burden per response	Total Hours
Subpart A – General Provisions; including applicability of requirements and requests for waivers – 312.1 – 312.10		906	1.05	958	25.75	24,672
Subpart B – Investigational New Drug Application; including content and form, safety reports, and annual reports – 312.20 – 312.38	1571	14,459	4.64	67,226	228.96	15,392,380

Table 1 -- Estimated Annual Reporting Burden for Human Drugs

21 CFR Part 312 Subpart	FDA Form	No. of respondents	No. of responses per respondent	Total annual responses	Average burden per response	Total Hours
Subpart C – Administrative Actions; including sponsor requests to FDA – 312.40 – 312.48		655	1.65	1,087	120.39	130,864
Subpart D – Responsibilities of Sponsors and Investigators; including investigator reports and sponsor notifications – 312.50 – 312.70	1572	7,730	5.32	41,126	74.68	3,071,104
Subpart F – Miscellaneous provisions including import & export requirements and foreign clinical studies – 312.110 – 312.145		1,463	8.59	12,572	32.93	414,003
Subpart I – Expanded Access to Investigational Drugs for Treatment Use; including emergency use of IND – 312.300 – 312.320		694	2.54	1,763	57.01	100,512
TOTAL		25,907		124,732		19,133,535

Table 2-- Estimated Annual Recordkeeping Burden for Human Drugs

21 CFR Section	No. of record-keepers	No. of records per record-keeper	Total annual records	Average burden per record-keeping	Total hours
312.52(a) Sponsor records for the transfer of obligations to a contract research organization.	335	1.50	503	2	1,006
312.57 Sponsor recordkeeping showing the receipt, shipment, or other disposition of the investigational drug, and any financial interests.	1,689	1	1,689	100	168,900
312.62(a) Investigator recordkeeping of the disposition of drugs.	1,444	1	1,444	40	57,760
312.62(b) Investigator recordkeeping of case histories of individuals.	1,444	1	1,444	40	57,760
312.160(a)(3) Records pertaining to the shipment of drugs for	547	1.40	782	30 minutes	391

investigational use in laboratory research animals or in vitro tests.					
312.160(c) Shipper records of alternative disposition of unused drugs.	547	1.40	782	30 minutes	391
TOTAL					286,208

Table 3 -- Estimated Annual Reporting Burden for Biologics

21 CFR Part 312 Subpart	FDA Form	No. of respondents	No. of responses per respondent	Total annual responses	Average burden per response	Total Hours
Subpart A – General Provisions; including applicability of requirements and requests for waivers – 312.1 – 312.10		239	1.20	287	26.51	7,608
Subpart B – Investigational New Drug Application; including content and form, safety reports, and annual reports – 312.20 – 312.38	1571	2,146	3.69	7,932	317.46	2,518,128
Subpart C – Administrative Actions; including sponsor requests to FDA – 312.40 – 312.48		244	1.45	356	142.93	50,884
Subpart D – Responsibilities of Sponsors and Investigators; including investigator reports and sponsor notifications – 312.50 – 312.70	1572	3,785	4.01	15,193	38.08	578,536
Subpart F – Miscellaneous provisions; including import & export requirements and foreign clinical studies – 312.110 – 312.145		655	4.96	3,254	28.73	93,494
Subpart I – Expanded Access to Investigational Drugs for Treatment Use; including emergency use of IND – 312.300 – 312.320		164	1.85	304	17.80	5,412
TOTAL		7,287		27,326		3,254,062

Table 4-- Estimated Annual Recordkeeping Burden for Biologics

21 CFR Section	No. of record-	No. of records	Total annual	Average burden per	Total hours

	keepers	per record-keeper	records	record-keeping	
312.52(a) Sponsor records for the transfer of obligations to a contract research organization.	75	1.40	105	2	210
312.57 Sponsor recordkeeping showing the receipt, shipment, or other disposition of the investigational drug, and any financial interests.	335	2.70	904	100	90,400
312.62(a) Investigator recordkeeping of the disposition of drugs.	453	1	453	40	18,120
312.62(b) Investigator recordkeeping of case histories of individuals.	453	1	453	40	18,120
312.160(a)(3) Records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests.	111	1.40	155	0.5 (30 minutes)	78
312.160(c) Shipper records of alternative disposition of unused drugs.	111	1.40	155	0.5 (30 minutes)	78
TOTAL					127,006

12b. Annualized Cost Burden Estimate

FDA estimates an average industry wage rate of $85.00 per hour x total number of hours in the 4 tables for preparing and submitting the information collection requirements under 21 CFR Parts 312 and 601 is a total of $1,938,068,935.

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

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

CDER estimates that approximately 715 FTEs are devoted to the review of INDs and related submissions under part 312. CDER also estimates that each FTE equals approximately $171,000.00. Thus, the annualized cost burden for CDER is $122,265,000.00.

15. Explanation for Program Changes or Adjustments

This ICR contains significant estimate adjustments due to agency discretion. The CDER 2015 total hours is 22,800,811. The CDER 2011 total hours is 141,870,849. Overall, there is a cumulative decrease of 119,070,038 burden hours.

The reason for these large estimate adjustments is because the data used for the 2015 extension was generated by CDER's Office of Strategic Programs using their Document Archiving, Reporting & Regulatory Tracking System (DARRTS). This system was not available to us for the 2011 request for extension and therefore we relied on data estimates derived from the IND Review Divisions. Going forward, we plan to use the same DARRTS tracking system for future extensions so that there will be more consistency. In addition, we plan to use the data from this extension as the baseline for new data, and any fluctuations will be investigated and revised to ensure consistency.

Details on the two largest decreases are as follows:

The largest decrease may be found within the CDER program in administering 21 CFR 312.55(b) (*sponsor reports to investigators on new observations, especially adverse reactions and safe use*) reflecting a drop in burden hours from 109,027,680 in 2011 to 99,216 in 2015, a difference of 108,928,464; and a corresponding drop in respondents from 985 to 590, a difference of 395 (approximately a 40% drop).

The next largest reduction can be found in the annual recordkeeping estimate for CDER where, under 21 CFR 312.62(a) (*disposition of drug*) and (b) (*case histories*), the number of recordkeepers dropped collectively by over 90%, resulting in a decrease of 9,837,244 burden hours.

Generally, during the years preceding the data we used for our 2009 extension request, we had to use "best estimates" for much of the information collection that was not submitted directly to us. With our new system, we are better able to estimate this information collection based on the reports that are submitted to us.

In addition, we have revised the IC list found at www.reginfo.gov by consolidating the previously itemized regulatory provisions by their corresponding subpart in the CFR. We believe this will assist the reader by more easily identifying the summary of fluctuations for this collection. Readers may still view burden associated with individual provisions by referring to the tables found in item12, "*Estimates of Annualized Burden Hours and Costs"* found in this document.

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.