OMB INFORMATION COLLECTION
INVESTIGATIONAL NEW DRUG (IND) REGULATIONS
21 CFR PART 312
0910-0014
SUPPORTING STATEMENT

A. Justification

1. Circumstances of Information Collection

The Food and Drug Administration (FDA) is requesting OMB approval under the Paperwork Reduction Act (44 U.S.C. 35) for the reporting and recordkeeping requirements contained in FDA regulation "Investigational New Drug Application" (21 CFR 312). This regulation implements provisions 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, includes unapproved biological drugs, 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. The act provides in 21 U.S.C. 355(a) 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). In addition,
section 351 of the Public Health Service Act (21 U.S.C. 262 et.seg) requires that biological products be licensed prior to marketing in interstate commerce. FDA approves an NDA **or** Biologics License Application (BLA) only if the sponsor of the application first demonstrates that the drug or biological drug product 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 is dictated by the scientific procedures and human subject safeguards that must be followed in the clinical tests of investigational new drugs.

There are 2 forms that are required under 21 CFR 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: (a) A cover sheet containing background information on the sponsor and investigator, (b) a table of contents, (c) an introductory statement and general investigational plan, (d) an investigator's brochure describing the drug substance, (e) a protocol for each planned study, (f) chemistry, manufacturing, and control information for each investigation, (g) pharmacology and toxicology information for each

investigation, and (h) 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 21 CFR part 312:

REPORTING REQUIREMENTS

21 CFR 312.7(d)	Applications for permission to sell an investigational new drug.
21 CFR 312.10(a)	Applications for waiver of requirements under 21 CFR 312. Only emergency requests are estimated under this section; other requests are included under 21 CFR 312.23 and 21 CFR 312.31.
21 CFR 312.20(c)	Applications for investigations involving an exception from informed consent under 21 CFR 50.24. Estimates for this requirement are included under 21 CFR 312.23.
21 CFR 312.23	Investigational New Drug Applications (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.

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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),(c)	Notification of withdrawal of an IND.
21 CFR 312.44(c),(d)	Opportunity for sponsor response to FDA when IND is terminated.
21 CFR 312.45(a),(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; financial disclosure information.
21 CFR 312.54(a),(b)	Sponsor submissions concerning investigations involving an exception from informed consent under 21 CFR 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 21 CFR 312.23.
21 CFR 312.56(b),(c),(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.
.64(d)	-Financial disclosure reports.
21 CFR 312.66	Investigator reports to IRB. Estimates for this requirement are included under 21 CFR 312.53.
21 CFR 312.70	Investigator disqualification; opportunity to respond to FDA. Estimates for this requirement

	are not included in the estimates for part 312.
21 CFR 312.83	Sponsor submission of treatment protocol. Estimates for this requirement are included under 21 CFR 312.34 and 21 CFR 312.35.
21 CFR 312.85	Sponsors conducting phase 4 studies. Estimates for these postmarketing studies are not included in the estimates for 21 CFR 312.
21 CFR 312.110(b)	Request to export an investigational drug.
21 CFR 312.120(b),(c)(2)	Sponsor's submission to FDA for use of foreign clinical study to support an IND.
21 CFR 312.120(c)(3)	Sponsor's report to FDA on findings of independent review committee on foreign clinical study.
21 CFR 312.130(d)	Request for disclosable information for investigations involving an exception from informed consent under 21 CFR 50.24.

RECORDKEEPING REQUIREMENTS

21 CFR 312.52(a)	Transfer of obligations to a contract research organization.
21 CFR 312.57(a),(b)	Sponsor recordkeeping.
21 CFR 312.59	Sponsor recordkeeping of

	disposition of unused supply of drugs. Estimates for this requirement are included under 21 CFR 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 312.160(a)	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 Information

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

A continuing objective of FDA is to improve the speed and quality of its drug review and approval program. The Act requires persons who wish to market new drug products to demonstrate that those drug products are both safe and effective for the labeled indications before introducing them into interstate commerce. This is achieved through the submission of an IND and a new drug application (NDA) **or** biologics license application (BLA**) for** biological drug products to FDA, and these applications ordinarily contain thousands of pages of reports, analyses, tabulations, and case reports that must be reviewed by agency officials.

In the mid-1980's, FDA began working with pharmaceutical

sponsors to develop Computer-Assisted New Drug Applications (CANDA). CANDAs were designed to provide information (text, data, image) electronically to facilitate the review of applications. These efforts yielded valuable information but were limited because for each new drug review division sponsors tended to develop different hardware and software approaches. A reviewer might be confronted with an array of hardware, software, and review tools to conduct a review that differed between sponsors and applications. Also, CANDAs were never approved as a substitute for the archival copy, so firms were still required to submit copies.

One solution to limitations of CANDAs was an approach whereby staff responsible for a particular review discipline (eg, chemistry, clinical) worked directly with pharmaceutical sponsors to develop a consistent approach that would be applicable to all sponsors and to all review divisions. Focus on this approach has evolved into the Electronic Regulatory Submission and Review (ERSR) Program. This new initiative is intended to ensure both the electronic availability of information and the means to manipulate this information electronically to yield a review.

ERSR has been made possible by other developments. The harmonization of FDA Form 356h has ensured that NDAs, ANDAs, and BLA**s** would contain comparable information in the same sections of the submission. The promulgation of the "Electronic Records; Electronic Signatures" final rule allowed FDA to accept electronic submissions without an accompanying paper archival copy because electronic records are equivalent to paper records and electronic signatures are equivalent to

hand-written signatures provided the requirements of 21 CFR Part 11 are met and the document has been identified in the agency's public docket as being acceptable for filing. The Guidance for Industry on "Archiving Submissions in Electronic Format - NDAs" provides for the receipt and archival of electronic report forms and tabulations. Another guidance for industry on "Providing Regulatory Submissions in Electronic Format - NDAs" issued in January 1999. In addition, the Center for Biologics Evaluation and Research, issued the draft “Guidance for Industry Pilot Program for electronic Investigational New Drug (eIND) Application for Biological Products” in May 1998.

ERSR is made up of a variety of projects that are in different stages of development and implementation. These projects are categorized into 3 areas: First, "Electronic Submissions" includes standards-related projects to define the format and content of regulatory submissions; written guidance for industry to follow in preparing electronic submissions; an Electronic Document Room project to accommodate the receipt, archive, and storage of electronic transmissions; an Electronic Gateway project to provide an agency-level central point for receipt of secure electronic transmissions and routing to the Centers; and scientific databases that include structured databases, reference guides, and analytical tools used by reviewers. Second, "Corporate Databases, Documentbases and Applications" includes projects under the Electronic Document Management System and the Management Information System. Third, other electronic initiatives including technical infrastructure, technical support, and

training.
ERSR will impact the underlying business processes related to regulatory submissions and reviews. Document rooms will handle electronic media rather than paper copies. Reviewers will review submissions online and generate their review documents online. Reviewers will conduct data analysis using structured databases, which combine data extracted from the submission under review as well as historical data from earlier submissions. Industry sponsors and manufacturers will experience reduced paper costs and manpower to compile paper submissions and better access to application status information through electronic mail.

4. Efforts to Identify Duplication

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 U.S. information can be produced, maintained, or reported. An applicant may provide copies of information produced by another party with the agreement of that secondary source. Whether the respondent is providing primary or secondary information, only one information collection takes place. FDA is the only agency that collects this IND information.

5. Involvement of 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 If Information Collected 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. Consistency With the Guidelines in 5 CFR 1320.5(d)(2)

These regulations comply with 5 CFR 1320.6 except as follows: First, FDA requires submission of safety information (i.e., information on adverse reactions from a drug or licensed biological product as well as other information on new studies or modifications of existing studies) more often than quarterly (21 CFR 312.32). Timely submissions are crucial to FDA's safety monitoring role. 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. Consultations Outside the Agency

In accordance with 5 CFR 1320.8(d), in the Federal Register of May 6, 1999 (64 FR 24402), a 60-day notice was published for public comment on this information collection. There were no comments received.

In the past, there has been a great deal of interaction with the public concerning these regulations. The March 19, 1987, final rule continued the rulemaking efforts by the Department of Health and Human Services and FDA to revise Federal regulations governing the new drug approval process. That phase of the regulations (called the IND Rewrite) made final new procedures in 21 CFR Part 312 for FDA review of investigational new drug applications and for monitoring the

progress of investigational drug use. The IND Rewrite was issued as a proposal in the Federal Register of June 9, 1983 (48 FR 26720). The first phase of these regulatory revision efforts (called the NDA Rewrite) covered FDA procedures in 21 CFR Part 314 for FDA review of new drug applications for marketing. This first phase was completed with publication of final regulations in the Federal Register of February 22, 1985 (50 FR 7452). Collectively, the IND and NDA Rewrites conclude an effort begun when FDA made concept papers available for public comment (44 FR 58919; October 12, 1979) and held a public meeting on November 9, 1979, to discuss them.

In preparing the final rule, FDA carefully reviewed more than 50 comments received from pharmaceutical manufacturers, trade associations, health professionals, professional societies, and consumer organizations. In addition, FDA managers met with agency employees in order to gain their views as part of the internal decisionmaking process. The agency also considered the recommendations of the Congressionally-sponsored Commission on the Federal Drug Approval Process. In preparing the final rule, therefore, the agency had considered views of persons representing virtually all groups having an interest in the investigational drug process. FDA's publication of the proposed IND regulations (June 9, 1983; 48 FR 26720) was the primary means for obtaining public comments on the IND information requirements. The preamble to the final rule of
March 19, 1987, provides a summary of hundreds of public comments.

In October of 1988 (53 FR 41516), FDA proposed an amendment to the IND regulations by proposing procedures designed to speed the availability of new therapies to desperately ill patients, while preserving appropriate guarantees for safety and effectiveness. These procedures intended to facilitate the development, evaluation, and marketing of such products, especially where no satisfactory alternative therapies exist. The procedures would apply to products intended to treat AIDS, cancer, and other such diseases. Several comments were received on this proposal. In April of 1992, FDA finalized this proposal (57 FR 13244) and discussed all comments received.

9. Remuneration of Respondents

No remuneration has been provided.

10. Assurance of Confidentiality

The release of information submitted to FDA under an IND **is** governed by the provisions of 21 CFR 312.5 and 314.430,and for investigatonal bilogical drug products, 21 CFR 601.50. 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. Questions of a Sensitive Nature

There are no questions of a sensitive nature.

12. Estimates of Annualized Hour Burden

Estimated Annual Reporting and Recordkeeping Burden for Human Drugs

21 CFR Section	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours Per Response	Total Hours
312.7(d)	7	1	7	24	168
312.10(a)	0	0	0	0	0
312.23(a),(f)	1,601	1.25	1,996	1,600	3,193,600
312.30(a)-(e)	918	14.85	13,629	284	3,870,636
312.31(b)	760	8.87	6,738	100	673,800
312.32(c),(d)	459	14.33	6,576	32	210,432
312.33(a)-(f)	1,841	2.35	4,318	350	1,511,300
312.35(a),(b)	1	1	1	300	300
312.36	643	1.2	720	16	11,520
312.38(b)	621	1.24	773	28	21,644
312.38(c)	621	1.24	773	160	123,680
312.44(c),(d)	710	1.10	780	16	12,480
312.45(a),(b)	294	1.32	389	12	4,668
312.47(b)	252	1	252	160	40,320
312.53(c)	4500	1	4500	80	360,000
312.54(a),(b)	4	1	4	48	192
312.55(b)	4500	1	4500	48	216,000
312.56(b),(c),(d)	5	1	5	80	400

312.58(a)	**337**	**1**	**337**	**8**	**2,696**
312.64(a)-(d)	**8200**	**1**	**8200**	**24**	**196,800**
312.110(b)	**150**	**2**	**303**	**75**	**22,725**
312.120(b), (c)(2)	**100**	**2**	**200**	**168**	**33,600**
312.120(c)(3)	**100**	**2**	**200**	**40**	**8,000**
312.130(d)	**4**	**1**	**4**	**8**	**32**
312.52(a) RECORDKEEPING	**360**	**1**	**360**	**2**	**720**
312.57(a),(b) RECORDKEEPING	**4000**	**2.05**	**8200**	**100**	**820,000**
312.62(a) RECORDKEEPING	**8200**	**1**	**8200**	**40**	**328,000**
312.62(b) RECORDKEEPING	**8200**	**12.2**	**100,000**	**40**	**4,000,000**
312.160(a) RECORDKEEPING	**3400**	**7.35**	**25,000**	**30 min.**	**12,500**
312.160(c) RECORDKEEPING	**3400**	**2.35**	**8,000**	**30 min.**	**4,000**
Human Drugs Total					**15,680,213**

Estimated Annual Reporting Burden for Biologics-Table 3

21 CFR Section	Number of Respondents	Number of Responses Per Response	Total Annual Responses	Hours per Response	Total Hours
312.7(d)	9	1.3	12	24	288
312.10(a)	1	1	1	40	40
312.23(a),(f) and 312.120(b), (c)(2), (c)(3)	278	1.8	492	1,600	787,200
312.30(a) and (e)	975	6.5	6,411	284	1,820,724
312.31(b)	975	9.2	9,005	100	900,500
312.32(c),(d) and 312.56(c)	602	6.7	4,034	32	129,088
312.33(a), (f) and 312.56(c)	1,253	1.6	1,989	350	696,150
312.35(a), (b)	1	1	1	300	300
312.36	22	5.5	122	16	1,952
312.38(b)	128	1.7	212	28	5,936
312.38(c)	128	1.7	212	160	33,920
312.44(c),	55	1.9	107	16	1,712

(d)					
312.45(a), (b)	74	1.4	105	12	1,260
312.47(b)	150	1.8	274	160	43,840
312.53(c)	672	6.6	4,421	80	353,680
312.54(a), (b)	4	1	4	48	192
312.55(b)	374	6.1	2288	48	109,824
312.56(b),(d)	12	1.6	20	80	1,600
312.58(a)	10	1	10	8	80
312.64(a) and (d)	5,014	1	5,014	24	120,336
312.110(b)	10	1.3	13	75	975
312.130(d)	1	1	1	0.5	0.5
Total Reporting Burden					**5,009,597.5**

Estimated Annual Recordkeeping for Biologics-Table 4

21 CFR Sections	Number of Recordkeepers	Annual Frequency Per Recordkeepi	Total Annual Records	Hours Per Recordkeeper	Total Hours

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312.52(a)	27	2.5	67	5	135
312.57(a), (b)	1,253	2	2,506	100	125,300
312.62(a)	5,014	1	5,014	40	200,560
312.62(b)	**8,200**	**12.2**	**100,000**	**40**	**328,000**
312.160(a)	**3400**	**7.35**	**25,000**	**30 min**	**1,700**
312.160(c)	320	1	320	0.5	160
Total Biologic Recordkeeping Hours					**655,855**
Total Biologi Burden Hours					**5,665,452.5**
Total Human Drugs Burden Hours					**11,575,113**
Total Combined Burden					**17,240,565.5**

13. Estimate of Annualized Cost Burden to Respondents

FDA's Economics Staff estimates an average industry wage rate of $50.00 per hour for preparing and submitting the information collection requirements under 21 CFR Parts 312, 314 and 601. This figure is an average of the following wage rates (based on the percentage of time required for each type of employee): Upper management at $70.00 per hour; middle management at $35.00 per hour; and clerical assistance at $23.00 per hour. Using the averaged wage rate of $50.00 per hour, and multiplied times the total hour burden estimated above, the total cost burden to respondents is $862,028,250.00 (17,240,565 x $50).

14. Estimates of Annualized Cost Burden to the Government

Based on data obtained for the second quarter of 1999 from the Center for Drug Evaluation and Research's Human Resource Allocation Report, approximately 513 FTEs are devoted to "new drug evaluation." Approximately 40% of New Drug Evaluation review is devoted to INDs. If each FTE equals approximately

$100,000.00, the total cost burden to the Federal Government would be $20,500,000 (513 x 40% x $100,000).

15. Changes In Burden

The total burden estimate currently approved for 0910-0014 is 6,238,858 hours. The increase in burden is a result of (1) the inclusion of burden estimates for biological drug products and (2) an increase in the burden hours estimated for "hours per response" for human drug products.

16. Time Schedule, Publication, and Analysis Plans

There are no publications.

17. Displaying of OMB Expiration Date

The agency is not seeking to not display the expiration date for OMB approval of the information collection.

B

18. Exception to the Certification Statement - Item 19

There are no exceptions to the certification statement identified in Item 19, "Certification for Paperwork Reduction Act Submission," of OMB Form 83-I.