UNITED STATES FOOD & DRUG ADMINISTRATION

Investigational New Drug (IND) Regulations
21 CFR Part 312

OMB Control No. 0910-0014

SUPPORTING STATEMENT **Part A: Justification**

1. Circumstances Making the Collection of Information Necessary

This information collection supports Food and Drug Administration (FDA, us or we) regulations. Section 505(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act (21 U.S.C. 355(a)) provides that a new drug may not be introduced or delivered for introduction into interstate commerce in the United States unless we have previously approved a new drug application (NDA). We approve 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. We are also charged, under section 505(i) of the FD&C Act (21 U.S.C. 355(i)), with promulgating regulations governing the investigational use of drugs by qualified experts, including regulations to ensure that clinical investigation of the safety and effectiveness of unapproved new drugs and biological products can be conducted.

Accordingly, we have issued regulations in 21 CFR part 312 (*Investigational New Drug Application*) that establish "*procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, [FDA] of investigational new drug applications (IND's)*." The regulations set forth information collection requirements covering the content and format of an initial application submission, as well as amendments to that application; the reporting on significant revisions of clinical investigation plans, as well as progress and safety reporting; and recordkeeping requirements pertaining to the disposition of drugs, individual case histories, and certain other documentation verifying the fulfillment of responsibilities by clinical investigators.

To assist respondents to the information collection, we have developed the following collection instruments:

- **Form FDA 1571** entitled, "*Investigational New Drug Application (IND)*"; and
- **Form FDA 1572**, "*Statement of Investigator*."

Instructions for completing the forms are available on our website at www.fda.gov. We have also issued procedural draft guidance for industry entitled, "*Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators*," also available from our website at https://www.fda.gov/downloads/Drugs/Guidances/UCM446695.pdf. The guidance document provides details of the informational content of an IND as well as information needed to complete required forms.

Anyone intending to conduct a clinical investigation must submit *Form FDA 1571* as instructed. The reporting elements include: (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 is completed, signed, and submitted by the IND sponsor before an investigator may participate in an investigation. It includes background information on the investigator as well as the investigation, and a general outline of the planned investigation and study protocol.

We therefore request OMB approval of the information collection provisions found in 21 CFR part 312, as well as Forms FDA 1571 and 1572 and associated instructions found on our website and in agency guidance.

2. Purpose and Use of the Information Collection

The IND applications (and any supplements thereto) are reviewed by FDA medical officers and other agency staff responsible for overseeing a specific study. The details and complexity of the review requirements are dictated by the scientific procedures and human subject safeguards that must be followed when conducting clinical tests of investigational new drugs. The IND application enables us to monitor clinical investigations of unapproved new drugs and biological products with regard to: (1) the safety of ongoing clinical investigations; (2) whether clinical testing of a drug should be authorized; (3) the likelihood of reliable data on the metabolism and pharmacological action of the drug in humans; (4) the timeliness of reporting information on adverse reactions to the drug; (5) obtaining information on side effects associated with increasing doses; (6) obtaining information on the drug's effectiveness; (7) ensuring the design of well-controlled, scientifically valid studies; and (8) obtaining any other information pertinent to determining whether clinical testing should be continued, and information related to the protection of human subjects.

Without the requisite information, we cannot authorize or monitor clinical investigations that must be conducted before authorizing the sale and general use of new drugs. The reporting and recordkeeping requirements set forth in the regulations enable us to monitor a study's progress, ensure the safety of subjects, ensure that a study will be conducted ethically, and increase the likelihood that sponsors will conduct studies that will be useful in determining whether a drug should be marketed and available for use in medical practice.

Upon receipt of the IND by FDA, an IND number will be assigned, and the application will be forwarded to the appropriate reviewing division. The reviewing division will send a letter to the Sponsor-Investigator providing notification of the IND number assigned, date of receipt of the original application, address where future submissions to the IND should be sent, and the name and telephone number of the FDA person to whom questions about the application

should be directed. Studies shall not be initiated until 30 days after the date of receipt of the IND by FDA unless you receive earlier notification by FDA that studies may begin.

3. Use of Improved Information Technology and Burden Reduction

Even though we are moving toward electronic IND submissions, paper submissions are acceptable but must be submitted in triplicate (the original and two photocopies are acceptable). We estimate 76% of all INDs will be submitted electronically. We are unaware of any legal or technological obstacles to reducing burden.

4. Efforts to Identify Duplication and Use of Similar Information

Regulations under 21 CFR part 312; subpart I provide for expanded access to investigational drugs for treatment use, including emergency use by individual patients in certain instances. We have established a separate information collection to support these requirements, which is currently approved under OMB Control No. 0910-0814. We are currently reviewing the latter collection and will consolidate the information collections, if appropriate. We are otherwise unaware of duplicative or similar information collection.

5. Impact on Small Businesses or Other Small Entities

The IND regulations provide for certain waivers and exemptions but are otherwise intended to enable FDA to fulfill its mandate to ensure the safe study and use of investigational drugs. At the same time, we assist small businesses in complying with our regulations through our Regional Small Business Representatives and through the scientific and administrative staffs within the agency. We also provide a Small Business Guide on our website at http://www.fda.gov/

6. Consequences of Collecting the Information Less Frequently

The timing of an IND application is determined by the respondent. Subsequently, however, information collection schedules are consistent with those prescribed in the applicable regulations. To effectively monitor the progress of ongoing studies and ensure the safety of study participants, we must obtain timely information regarding adherence to regulatory responsibilities, as well as any serious adverse effects or other safety issues. Less frequent reporting or fewer recordkeeping requirements might compromise or unnecessarily risk the safety of investigation participants as well as the public health.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

The information collection requirements under 21 CFR § 312.32 (*IND safety reporting*) provide for more-than-quarterly reporting with regard to the submission of safety information (i.e., information on adverse drug reactions as well as other information on new studies or modifications of existing studies). However, we believe this is necessary for ensuring the safety of clinical investigations. The regulations also 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), we published a 60-day notice for public comment in the Federal Register of October 4, 2018 . No comments were received that pertaining to the information collection.

9. Explanation of Any Payment or Gift to Respondents

No remuneration is provided to respondents to the information collection.

10. Assurance of Confidentiality Provided to Respondents

In developing this proposed collection, staff from FDA's Center for Drug Evaluation and Research (CDER) consulted the FDA Privacy Officer to identify potential risks to the privacy of individuals whose information may be handled by or on behalf of FDA in association with the Individual Patient Expanded Access Applications: Form FDA 3926, if finalized as proposed. In this case, the subject information collection employing proposed Form FDA 3926 does solicit personally identifiable information (PII) that will be collected and maintained by FDA/CDER.

Although PII is collected, this collection is not subject to the Privacy Act and the particular notice and other requirements of the Act do not apply. Specifically, we do not use name or any other personal identifier to routinely retrieve records from the greater collection of Form FDA 3926 submissions.

The PII to be collected has been minimized to protect the privacy of the individuals. To ensure against the solicitation or submission of unnecessary PII, the form has been designed to provide fields only information required to meet the intended purpose behind the form. Within text fields, we provide example or lists of relevant information and this will inform submissions to include relevant information and not irrelevant information including unnecessary PII. We have also developed instruction that accompany Form FDA 3926 with direction that further supports privacy. For example, it specifies that full patient name should never be submitted. And, FDA has prepared guidance for physicians completing the form to further support the privacy and confidentiality of individuals and the accuracy, integrity, and relevancy of the information collected.

We also note that information submitted to FDA is protected from inappropriate disclosure under FDA disclosure regulations at 21 CFR part 20.

11. Justification for Sensitive Questions

There are no questions of a sensitive nature.

12. Estimates of Annualized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

Below, we estimate the burden of the information collection as reported by FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) as follows:

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

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
§ 312.2(e); Requests for FDA advice on the applicability of part 312 to a planned clinical investigation.	400	1	400	24	9,600
§ 312.8; Requests to charge for an investigational drug.	74	1.23	91	48	4,368
§ 312.10; Requests to waive a requirement in part 312.	86	1.84	158	24	3,792
§ 312.23(a) through (f); IND content and format (including Form FDA 1571)	2,187	1.7	3,718	1,600	5,948,800
§ 312.30(a) through (e); Protocol amendments.	4,418	5.52	24,387	284	6,925,908
§ 312.31(b); Information amendments.	6,691	3.32	22,214	100	2,221,400
§ 312.32(c) and (d); IND safety reports.	867	15.78	13,681	32	437,792
§ 312.33(a) through (f); IND annual reports.	3,376	2.86	9,655	360	3,475,800
§ 312.38(b) and (c); Notifications of withdrawal of an IND.	930	1.61	1,497	28	41,916
§ 312.42; Sponsor requests that a clinical hold be removed, including sponsor submission of a complete response to the issues identified in the clinical hold order.	198	1.38	273	284	77,532
§ 312.44(c) and (d); Sponsor responses to FDA when IND is terminated.	12	1.16	14	16	224
§ 312.45(a) and (b); Sponsor requests for or responses to an inactive status determination of an IND by FDA.	231	1.84	425	12	5,100
§ 312.47; Meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings.	122	1.51	184	160	29,440
§ 312.54(a); Sponsor submissions to FDA concerning investigations involving an	15	2.4	36	48	1,728

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

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
exception from informed consent under § 50.24.					
§ 312.54(b); Sponsor notifications to FDA and others concerning an IRB determination that it cannot approve research because it does not meet the criteria in the exception from informed consent in § 50.24(a).	2	1	2	48	96
§ 312.56(b), (c), and (d); Sponsor notifications to FDA and others resulting from: (1) the sponsor's monitoring of all clinical investigations and determining that an investigator is not in compliance with the investigation agreements; (2) the sponsor's review and evaluation of the evidence relating to the safety and effectiveness of the investigational drug; and (3) the sponsor's determination that the investigational drug presents an unreasonable and significant risk to subjects.	6,100	7	42,700	80	3,416,000
§ 312.58(a); Sponsor's submissions of clinical investigation records to FDA on request during FDA inspections.	73	1	73	8	584
§ 312.70; During the disqualification process of a clinical investigator by FDA, the number of investigator responses or requests to FDA following FDA's notification to an investigator of its failure to comply with investigation requirements.	4	1	4	40	160
§ 312.110(b)(4) and (b)(5); Written certifications and written statements submitted to FDA relating to the export of an investigational drug.	11	26.28	289	75	21,675
§ 312.120(b); Submissions to FDA of "supporting information" related to the use of foreign clinical studies not conducted under an IND.	1,414	8.62	12,189	32	390,048
§ 312.120(c); Waiver requests submitted to FDA related to the use of foreign clinical studies not conducted under an IND.	35	2.34	82	24	1,968
§ 312.130; Requests for disclosable information in an IND and for investigations involving an exception from informed consent under § 50.24.	3	1	3	8	24
§§ 312.310(b) and 312.305(b); Submissions related to expanded access and treatment of an individual patient.	935	2.77	2,590	8	20,720

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

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
§ 312.310(d); Submissions related to emergency use of an investigational new drug.	480	2.15	1,032	16	16,512
§§ 312.315(c) and 312.305(b); Submissions related to expanded access and treatment of an intermediate-size patient population.	118	2.52	297	120	35,640
§ 312.320(b); Submissions related to a treatment IND or treatment protocol.	10	12.9	129	300	38,700
Total					23,125,527

Table 2.--Estimated Annual Reporting Burden for Biologics (CBER)[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
312.2(e) Requests for FDA advice on the applicability of part 312 to a planned clinical investigation.	217	1.18	256	24	6,144
312.8 Requests to charge for an investigational drug.	20	1.50	30	48	1,440
312.10 Requests to waive a requirement in part 312.	2	1	2	24	48
312.23(a) through (f) IND content and format.	335	1.35	452	1,600	723,200
312.30(a) through (e) Protocol amendments.	694	5.84	4,053	284	1,151,052
312.31 (b) Information amendments.	77	2.43	187	100	18,700
312.32(c) and (d) IND Safety reports.	161	8.83	1,422	32	45,504
312.33(a) through (f) IND Annual reports.	745	2.14	1,594	360	573,840
312.38(b) and (c) Notifications of withdrawal of an IND.	134	1.69	226	28	6,328
312.42 Sponsor requests that a clinical hold be removed, including sponsor submission of a complete response to the issues identified in the clinical hold order.	67	1.30	87	284	24,708
312.44(c) and (d) Sponsor responses to FDA when IND is terminated.	34	1.15	39	16	624
312.45(a) and (b)	55	1.38	76	12	912

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Sponsor requests for or responses to an inactive status determination of an IND by FDA.					
312.47 Meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings.	88	1.75	154	160	24,640
312.53(c) Investigator reports submitted to the sponsor, including Form FDA-1572, curriculum vitae, clinical protocol, and financial disclosure.	453	6.33	2,867	80	229,360
312.54(a) Sponsor submissions to FDA concerning investigations involving an exception from informed consent under 21 CFR 50.24.	1	1	1	48	48
312.54(b) Sponsor notifications to FDA and others concerning an IRB determination that it cannot approve research because it does not meet the criteria in the exception from informed consent in 50.24(a).	1	1	1	48	48
312.55(a) Number of investigator brochures submitted by the sponsor to each investigator.	239	1.91	456	48	21,888
312.55(b) Number of sponsor reports to investigators on new observations, especially adverse reactions and safe use.	243	4.95	1,203	48	57,744
312.56(b), (c), and (d) Sponsor notifications to FDA and others resulting from: (1) The sponsor's monitoring of all clinical investigations and determining that an investigator is not in compliance with the investigation agreements; (2) the sponsor's review and evaluation of the evidence relating to the safety and effectiveness of the investigational drug; and (3) the sponsor's determination that the investigational drug presents an unreasonable and significant risk to subjects.	108	2.21	239	80	19,120
312.58(a) Number of sponsor's submissions of clinical investigation records to FDA on request during FDA inspections.	7	1	7	8	56

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
312.64 Number of investigator reports to the sponsor, including progress reports, safety reports, final reports, and financial disclosure reports.	2,728	3.82	10,421	24	250,104
312.70 During the disqualification process of a clinical investigator by FDA, the number of investigator responses or requests to FDA following FDA's notification to an investigator of its failure to comply with investigation requirements.	5	1	5	40	200
312.110(b)(4) and (b)(5) Number of written certifications and written statements submitted to FDA relating to the export of an investigational drug.	18	1	18	75	1,350
312.120(b) Number of submissions to FDA of "supporting information" related to the use of foreign clinical studies not conducted under an IND.	280	9.82	2,750	32	88,000
312.120(c) Number of waiver requests submitted to FDA related to the use of foreign clinical studies not conducted under an IND.	7	2.29	16	24	384
312.130 Number of requests for disclosable information in an IND and for investigations involving an exception from informed consent under § 50.24.	350	1.34	469	8	3,752
312.310(b) and 312.305(b) Number of submissions related to expanded access and treatment of an individual patient.	78	1.08	84	8	672
312.310(d) Number of submissions related to emergency use of an investigational new drug.	76	2.76	210	16	3,360
312.315(c) and 312.305(b) Number of submissions related to expanded access and treatment of an intermediate-size patient population.	9	1	9	120	1,080
312.320(b) Number of submissions related to a treatment IND or treatment protocol.	1	1	1	300	300
Total					3,254,606

Table 3.--Estimated Annual Recordkeeping Burden for Human Drugs (CDER)[1]

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
§ 312.52(a); Sponsor records for the transfer of obligations to a contract research organization.	1,300	1	1,300	2	2,600
§ 312.57; Sponsor recordkeeping showing the receipt, shipment, or other disposition of the investigational drug and any financial interests.	13,000	1	13,000	100	1,300,000
§ 312.62(a); Investigator recordkeeping of the disposition of drugs.	13,000	1	13,000	40	520,000
§ 312.62(b); Investigator recordkeeping of case histories of individuals.	13,000	1	13,000	40	520,000
§ 312.160(a)(3); Records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests.	547	1.43	782	0.50 (30 minutes)	391
§ 312.160(c); Shipper records of alternative disposition of unused drugs.	547	1.43	782	0.50 (30 minutes)	391
§ 312.53(c); Investigator reports submitted to the sponsor, including Form FDA 1572, curriculum vitae, clinical protocol, and financial disclosure.	1,732	7.94	13,752	80	1,100,160
§ 312.55(a); Investigator brochures submitted by the sponsor to each investigator.	995	4	3,980	48	191,040
§ 312.55(b); Sponsor reports to investigators on new observations, especially adverse reactions and safe use.	995	4	3,980	48	191,040
§ 312.64; Investigator reports to the sponsor, including progress reports, safety reports, final reports, and financial disclosure reports.	13,000	1	13,000	24	312,000
	58,116		76,576		4,137,622

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

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

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
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

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

12b. Annualized Cost Burden Estimate

We estimate an average pharmaceutical industry wage rate of $75.00 per hour for preparing and submitting the information collection requirements under 21 CFR part 314. Multiplied times the total hour burden estimated above, the total labor cost burden to respondents is $2,299,857,075.

13. Estimates of Other Total Annual Costs to Respondents and/or Recordkeepers/Capital Costs

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

14. Annualized Cost to the Federal Government

We allocate approximately 835 FTEs to the reviewing the submissions under 21 CFR part 312. Assuming each FTE costs approximately $175,000 for these review activities, the total cost burden to the Federal Government is approximately $146,125,000.

15. Explanation for Program Changes or Adjustments

Because we have received an increased number of IND submissions since last OMB approval of the information collection, we have increased our estimate of the associated burden accordingly. The information collection, therefore, reflects a cumulative increase in burden by 81,332 annual responses and 7,843,950 burden hours attributable to a growing number of investigational new drug applications and associated research.

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

FDA will display the OMB expiration date as required by 5 CFR 1320.5

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification statement.