4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-N-1721]

# Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Investigational New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202-395-7285, or emailed to oira_submission@omb.eop.gov. All comments should be identified with the OMB control number 0910-0014. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: JonnaLynn Capezzuto, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-3794, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Investigational New Drug Application--21 CFR Part 312

OMB Control Number 0910-0014--Extension

This information collection supports FDA regulations in 21 CFR Part 312 covering Investigational New Drugs. Part 312 implements provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(i)) requiring FDA 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 ensure drug products marketed in the United States are 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 investigational new drug application (IND) regulations under part 312 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. The regulations also include recordkeeping

requirements pertaining to the disposition of drugs, records pertaining to individual case histories, and certain other documentation verifying the fulfillment of responsibilities by clinical investigators.

Submissions are reviewed by medical officers and other Agency scientific reviewers assigned responsibility for overseeing a specific study. The details 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; and (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 that must be conducted before authorizing the sale and general use of new drugs. These reports enable FDA to monitor a study's progress, to ensure the safety of subjects, to ensure 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.

To assist respondents with certain reporting requirements under part 312, we have developed two forms: Form FDA 1571 entitled, "Investigational New Drug Application (IND)" and Form FDA 1572 entitled, "Statement of Investigator." Anyone who intends 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 executed 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.

In the *Federal Register* of October 4, 2018 (83 FR 50102) FDA published a 60-day notice requesting public comment on the proposed collection of information. We received one comment. The comment did not pertain to the regulations or estimates provided in the 60-day notice requesting that OMB extend its approval for the information collection in these regulations. Rather, the comment discussed issues that pertained to Docket No. FDA-2010-D-0503 for the "Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards (IRBs): Investigational New Drug Applications (INDs)--Determining Whether Human Research Studies Can Be Conducted Without an IND." Accordingly, we have submitted the comment to Docket No. FDA-2010-D-0503.

FDA estimates the burden of this collection of information 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 exception from informed consent under § 50.24. | 15 | 2.4 | 36 | 48 | 1,728 |
| § 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 | 6,100 | 7 | 42,700 | 80 | 3,416,000 |

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 |
|---|---|---|---|---|---|
| the investigational drug presents an unreasonable and significant risk to subjects. | | | | | |
| § 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 |
| § 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 |

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

Table 2.--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 |
| Total | | | | | 2,343,382 |

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

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

| 21 CFR Section | No. of Respondents | No. of Disclosures per Respondent | Total Annual Disclosures | Average Burden per Disclosure | Total Hours |
|---|---|---|---|---|---|
| § 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 |
| Total | | | | | 1,794,240 |

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

Table 4.--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); Sponsor requests for or responses to an inactive status determination of an IND by FDA. | 55 | 1.38 | 76 | 12 | 912 |
| § 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 § 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 |

| 21 CFR Section | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Average Burden per Response | Total Hours |
|---|---|---|---|---|---|
| § 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 |
| § 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 |

| 21 CFR Section | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Average Burden per Response | Total Hours |
|---|---|---|---|---|---|
| § 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 |

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

Table 5.--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.

Because we have received an increased number of IND submissions since the last OMB approval of the information collection, we have increased our estimate of the associated burden accordingly.

Dated:  February 6, 2019.

Lowell J. Schiller,

Acting Associate Commissioner for Policy.

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