## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. FDA–2009–N–0030]**

### Agency Information Collection Activities; Proposed Collection; Comment Request; Investigational New Drug Regulations

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing an opportunity for public comment on the proposed collection of certain information by the agency. Under the Paperwork Reduction Act of 1995 (the PRA), Federal agencies are required to publish notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on requirements under which the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products can be conducted.

**DATES:** Submit written or electronic comments on the collection of information by April 13, 2009.

**ADDRESSES:** Submit electronic comments on the collection of information to *http://www.regulations.gov*. Submit written comments on the collection of information to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

**FOR FURTHER INFORMATION CONTACT:** Elizabeth Berbakos, Office of Information Management (HFA–710), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–796–3792.

**SUPPLEMENTARY INFORMATION:** Under the PRA (44 U.S.C. 3501–3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. ''Collection of information'' is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

#### Investigational New Drug Regulations—21 CFR Part 312 (OMB Control Number 0910 0014)—Extension

FDA is requesting OMB approval for the reporting and recordkeeping requirements contained in FDA's regulations ''Investigational New Drug Application'' in part 312 (21 CFR part 312). Part 312 implements provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)) to issue regulations under which the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products can be conducted.

FDA is charged with implementing statutory requirements that drug products marketed in the United States be shown to be safe and effective, properly manufactured, and properly labeled for their intended uses. Section 505(a) of the act provides that a new drug may not be introduced or delivered for introduction into interstate commerce in the United States unless FDA has previously approved a new drug application (NDA). FDA approves an NDA only if the sponsor of the application first demonstrates that the drug is safe and effective for the conditions prescribed, recommended, or suggested in the product's labeling. Proof must consist, in part, of adequate and well-controlled studies, including studies in humans, that are conducted by qualified experts. The Investigational New Drug (IND) regulations establish reporting requirements that include an initial application as well as amendments to that application, reports on significant revisions of clinical investigation plans, and information on a drug's safety or effectiveness. In addition, the sponsor is required to give FDA an annual summary of the previous year's clinical experience. Submissions are reviewed by medical officers and other agency scientific reviewers assigned responsibility for overseeing the specific study. The IND regulations also contain recordkeeping requirements that pertain to the responsibilities of sponsors and investigators. The detail and complexity of these requirements are dictated by the scientific procedures and human subject safeguards that must be followed in the clinical tests of investigational new drugs.

The IND information collection requirements provide the means by which FDA can do the following: (1) Monitor the safety of ongoing clinical investigations; (2) determine whether the clinical testing of a drug should be authorized; (3) ensure production of reliable data on the metabolism and pharmacological action of the drug in humans; (4) obtain timely information on adverse reactions to the drug; (5) obtain information on side effects associated with increasing doses; (6) obtain information on the drug's effectiveness; (7) ensure the design of well-controlled, scientifically valid studies; 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 in response to the IND regulations, FDA cannot authorize or monitor the clinical investigations which must be conducted prior to authorizing the sale and general use of new drugs. These reports enable FDA to monitor a study's progress, assure subject safety, assure that a study will be conducted ethically, and 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:

The first form is 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.

The second form is 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:

TABLE 1—REPORTING AND RECORDKEEPING REQUIREMENTS IN 21 CFR PART 312

| REPORTING REQUIREMENTS | |
|---|---|
| 21 CFR Section | Requirements |
| 312.7(d) | Applications for permission to sell an investigational new drug |
| 312.80 | Charging for investigational drugs under an IND |
| 312.10 | Applications for waiver of requirements under part 312; as indicated in § 312.10(a), estimates for this requirement are included under §§ 312.23 and 312.31. In addition, separate requests under § 312.10 are estimated in table 2 of this document. |
| 312.20(c) | Applications for investigations involving an exception from informed consent under § 50.24 (21 CFR 50.24); estimates for this requirement are included under § 312.23. |
| 312.23 | INDs (content and format) |
| (a)(1) | Cover sheet FDA–1571 |
| (a)(2) | Table of contents |
| (a)(3) | Investigational plan for each planned study |
| (a)(5) | Investigator's brochure |
| (a)(6) | Protocols—Phases 1, 2, and 3 |
| (a)(7) | Chemistry, manufacturing, and control information |
| (a)(7)(iv)(*a*), (*b*), and (*c*) | A description of the drug substance, a list of all components, and any placebo used |
| (a)(7)(iv)(*d*) | Labeling: Copies of labels and labeling to be provided each investigator |
| (a)(7)(iv)(*e*) | Environmental impact analysis regarding drug manufacturing and use |
| (a)(8) | Pharmacological and toxicology information |
| (a)(9) | Previous human experience with the investigational drug |
| (a)(10) | Additional information |
| (a)(11) | Relevant information |
| (f) | Identification of exception from informed consent |
| 312.30 | Protocol amendments |
| (a) | New protocol |
| (b) | Change in protocol |
| (c) | New investigator |
| (d) | Content and format |
| (e) | Frequency |
| 312.31 | Information amendments |
| (b) | Content and format<br>Chemistry, toxicology, or technical information |
| 312.32 | Safety reports |
| (c)(1) | Written reports to FDA and to investigators |
| (c)(2) | Telephone reports to FDA for fatal or life-threatening experience |
| (c)(3) | Format or frequency |
| (d) | Followup submissions |
| 312.33 | Annual reports |
| (a) | Individual study information |
| (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 |
| (c) | Next year general investigational plan |
| (d) | Brochure revision |
| (e) | Phase I protocol modifications |
| (f) | Foreign marketing developments |
| 312.35 | Treatment use of investigational new drugs |
| (a) | Treatment protocol submitted by IND sponsor |
| (b) | Treatment IND submitted by licensed practitioner |

TABLE 1—REPORTING AND RECORDKEEPING REQUIREMENTS IN 21 CFR PART 312—Continued

| REPORTING REQUIREMENTS | |
|---|---|
| 21 CFR Section | Requirements |
| 312.36 | Requests for emergency use of an investigational new drug |
| 312.38(b) and (c) | Notification of withdrawal of an IND |
| 312.42(e) | Sponsor requests that a clinical hold be removed and submits a complete response to the issues identified in the clinical hold order |
| 312.44(c) and (d) | Opportunity for sponsor response to FDA when IND is terminated |
| 312.45(a) and (b) | Sponsor request for, or response to, inactive status determination of an IND |
| 312.47(b) | ''End-of-Phase 2'' meetings and ''Pre-NDA'' meetings |
| 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 |
| 312.54(a) and (b) | Sponsor submissions concerning investigations involving an exception from informed consent under § 50.24 |
| 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 |
| 312.56(b), (c), and (d) | Sponsor monitoring of all clinical investigations, investigators, and drug safety; notification to FDA |
| 312.58(a) | Sponsor's submission of records to FDA on request |
| 312.64<br>(a)<br>(b)<br>(c) | Investigator reports to the sponsor<br>Progress reports<br>Safety reports<br>Final reports |
| 312.66 | Investigator reports to Institutional Review Board; estimates for this requirement are included under § 312.53 |
| 312.70(a) | Investigator disqualification; opportunity to respond to FDA |
| 312.83 | Sponsor submission of treatment protocol; estimates for this requirement are included under §§ 312.34 and 312.35 |
| 312.85 | Sponsors conducting Phase 4 studies; estimates for this requirement are included under § 312.23 in 0910–0014, and §§ 314.50, 314.70, and 314.81 in 0910–0001 |
| 312.110(b) | Request to export an investigational drug |
| 312.120 | Submissions related to foreign clinical studies not conducted under an IND |
| 312.130(d) | Request for disclosable information for investigations involving an exception from informed consent under § 50.24 |

| RECORDKEEPING REQUIREMENTS | |
|---|---|
| 21 CFR Section | Requirements |
| 312.52(a) | Transfer of obligations to a contract research organization |
| 312.57 | Sponsor recordkeeping |
| 312.59 | Sponsor recordkeeping of disposition of unused supply of drugs; estimates for this requirement are included under § 312.57 |
| 312.62(a) | Investigator recordkeeping of disposition of drugs |
| 312.62(b) | Investigator recordkeeping of case histories of individuals |
| 312.120(d) | Recordkeeping requirements for submissions related to foreign clinical studies not conducted under an IND; estimates for this requirement are included under § 312.57 |
| 312.160(a)(3) | Records maintenance: shipment of drugs for investigational use in laboratory research animals or in vitro tests |
| 312.160(c) | Shipper records of alternative disposition of unused drugs |

In tables 2 and 3 of this document, the estimates for ''No. of Respondents,'' ''No. 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 for submissions received in 2007 and from other sources familiar with the number of submissions received under 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 2—ESTIMATED ANNUAL REPORTING BURDEN FOR HUMAN DRUGS AND BIOLOGICS (CDER)[1]

| 21 CFR Section | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Hours per Response | Total Hours |
|---|---|---|---|---|---|
| 312.7(d) | 28 | 1.58 | 44 | 24 | 1,056 |
| 312.10 | 4 | 1 | 4 | 10 | 40 |
| 312.23(a) through (f) | 2,496 | 1.26 | 3,156 | 1,600 | 5,049,600 |
| 312.30(a) through (e) | 2,030 | 8.91 | 18,079 | 284 | 5,134,436 |
| 312.31(b) | 153 | 2.97 | 454 | 100 | 45,400 |
| 312.32(c) and (d) | 985 | 23.06 | 22,713 | 32 | 726,816 |
| 312.33(a) through (f) | 2,564 | 2.34 | 5,994 | 360 | 2,157,840 |
| 312.35(a) and (b) | 9 | 1.11 | 10 | 300 | 3,000 |
| 312.36 | 525 | 1.23 | 645 | 16 | 10,320 |
| 312.38(b) and (c) | 654 | 1.34 | 874 | 28 | 24,472 |
| 312.42(e) | 149 | 1.10 | 164 | 284 | 46,576 |
| 312.44(c) and (d) | 159 | 1.13 | 179 | 16 | 2,864 |
| 312.45(a) and (b) | 254 | 1.43 | 362 | 12 | 4,344 |
| 312.47(b) | 281 | 1.8 | 529 | 160 | 84,640 |
| 312.53(c) | 900 | 26.51 | 23,855 | 80 | 1,908,400 |
| 312.54(a) and (b) | 1 | 1 | 1 | 48 | 48 |
| 312.55(b) | 985 | 2,306 | 2,271,300 | 48 | 109,022,400 |
| 312.56(b), (c), and (d) | 18 | 1 | 18 | 80 | 1,440 |
| 312.58(a) | 91 | 4.10 | 373 | 8 | 2,984 |
| 312.64 | 141,393 | 1 | 141,393 | 24 | 3,393,432 |
| 312.70(a) | 4 | 1.5 | 6 | 40 | 240 |
| 312.110(b) | 23 | 18.26 | 420 | 75 | 31,500 |
| 312.120[2] | 115 | 5 | 575 | 32 | 18,400 |
| 312.130(d) | 3 | 1 | 3 | 8 | 24 |

[1] There are no capital and startup, or operation, maintenance, and purchase costs associated with the collection of information requirements.
[2] Section 312.120 includes the burden estimate for both CDER and CBER.

TABLE 3—ESTIMATED ANNUAL RECORDKEEPING BURDEN FOR HUMAN DRUGS AND BIOLOGICS (CDER)[1]

| 21 CFR Section | No. of Recordkeepers | No. of Records per Recordkeeper | Total Annual Records | Hours per Record | Total Hours |
|---|---|---|---|---|---|
| 312.52(a) | 683 | 1 | 683 | 2 | 1,366 |
| 312.57 | 75 | 485.28 | 36,396 | 100 | 3,639,600 |
| 312.62(a) | 14,732 | 1 | 14,732 | 40 | 589,280 |
| 312.62(b) | 147,320 | 1 | 147,320 | 40 | 5,892,800 |

TABLE 3—ESTIMATED ANNUAL RECORDKEEPING BURDEN FOR HUMAN DRUGS AND BIOLOGICS (CDER)[1]—Continued

| 21 CFR Section | No. of Recordkeepers | No. of Records per Recordkeeper | Total Annual Records | Hours per Record | Total Hours |
|---|---|---|---|---|---|
| 312.160(a)(3) | 547 | 1.4 | 782 | .5 | 391 |
| 312.160(c) | 547 | 1.4 | 782 | .5 | 391 |

[1] There are no capital and startup, or operation, maintenance, and purchase costs associated with the collection of information requirements.

TABLE 4—ESTIMATED ANNUAL REPORTING BURDEN FOR BIOLOGICS (CBER)[1]

| 21 CFR Section | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Hours per Responses | Total Hours |
|---|---|---|---|---|---|
| 312.7(d) | 12 | 1.1 | 13 | 24 | 312 |
| 312.23(a) through (f)[2] | 168 | 1.5 | 256 | 1,600 | 409,600 |
| 312.30(a) through (e) | 372 | 6.4 | 2,369 | 284 | 672,796 |
| 312.31(b)[2] | 703 | 7.7 | 5,417 | 100 | 541,700 |
| 312.32(c) and (d) | 175 | 14.6 | 2,563 | 32 | 82,016 |
| 312.33(a) through (f) | 512 | 2.3 | 1,168 | 360 | 420,480 |
| 312.35(a) and (b) | 1 | 1 | 1 | 300 | 300 |
| 312.36 | 10 | 4 | 40 | 16 | 640 |
| 312.38(b) and (c) | 81 | 1.5 | 120 | 28 | 3,360 |
| 312.42(e) | 74 | 1.5 | 108 | 284 | 30,672 |
| 312.44(c) and (d) | 34 | 1.1 | 39 | 16 | 624 |
| 312.45(a) and (b) | 41 | 1.4 | 59 | 12 | 708 |
| 312.47(b) | 31 | 1.2 | 37 | 160 | 5,920 |
| 312.53(c) | 243 | 4.95 | 1,203 | 80 | 96,240 |
| 312.54(a) and (b) | 1 | 1 | 1 | 48 | 48 |
| 312.55(b) | 42 | 1 | 43 | 48 | 2,064 |
| 312.56(b), (c), and (d) | 10 | 1.6 | 16 | 80 | 1,280 |
| 312.58(a) | 7 | 1 | 7 | 8 | 56 |
| 312.64 | 2,728 | 3.82 | 10,411 | 24 | 249,864 |
| 312.70(a) | 5 | 1 | 5 | 40 | 200 |
| 312.110(b) | 18 | 1 | 18 | 75 | 1,350 |
| 312.130(d) | 1 | 1 | 1 | 8 | 8 |

[1] There are no capital and startup, or operation, maintenance, and purchase costs associated with the collection of information requirements.
[2] The reporting requirement for § 312.10 is included in the estimates for §§ 312.23 and 312.31.

TABLE 5—ESTIMATED ANNUAL RECORDKEEPING BURDEN FOR BIOLOGICS (CBER)[1]

| 21 CFR Section | No. of Recordkeepers | Annual Frequency per Recordkeeping | Total Annual Records | Hours per Record | Total Hours |
|---|---|---|---|---|---|
| 312.52(a) | 52 | 1.4 | 73 | 2 | 146 |
| 312.57 | 168 | 3.05 | 512 | 100 | 51,200 |
| 312.62(a) | 2,560 | 1 | 2,560 | 40 | 102,400 |
| 312.62(b) | 2,560 | 10 | 25,600 | 40 | 1,024,000 |
| 312.160(a)(3) | 55 | 1.4 | 77 | 0.5 | 38.5 |

TABLE 5—ESTIMATED ANNUAL RECORDKEEPING BURDEN FOR BIOLOGICS (CBER)[1]—Continued

| 21 CFR Section | No. of Recordkeepers | Annual Frequency per Recordkeeping | Total Annual Records | Hours per Record | Total Hours |
|---|---|---|---|---|---|
| 312.160(c) | 55 | 1.4 | 77 | 0.5 | 38.5 |

[1] There are no capital and startup, or operation, maintenance, and purchase costs associated with the collection of information requirements.

TABLE 6—TOTALS FOR ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDENS FOR CDER AND CBER

| | |
|---|---|
| Reporting Burden | 130,190,510 |
| Recordkeeping | 11,301,652 |
| Total | 141,492,162 |

Dated: February 4, 2009.

**Jeffrey Shuren,**

*Associate Commissioner for Policy and Planning.*

[FR Doc. E9–2846 Filed 2–10–09; 8:45 am]

**BILLING CODE 4160–01–S**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. FDA–2009–N–0031]**

### Agency Information Collection Activities; Proposed Collection; Comment Request; Substances Generally Recognized as Safe: Notification Procedure

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing an opportunity for public comment on the proposed collection of certain information by the agency. Under the Paperwork Reduction Act of 1995 (the PRA), Federal agencies are required to publish notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on the information collection provisions of the Notification Procedure for Substances Generally Recognized as Safe.

**DATES:** Submit written or electronic comments on the collection of information by April 13, 2009.

**ADDRESSES:** Submit electronic comments on the collection of information to *http://www.regulations.gov.* Submit written comments on the collection of information to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

**FOR FURTHER INFORMATION CONTACT:** Jonna Capezzuto, Office of Information Management (HFA–710), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–796–3794.

**SUPPLEMENTARY INFORMATION:** Under the PRA (44 U.S.C. 3501–3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. ''Collection of information'' is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

**Substances Generally Recognized as Safe: Notification Procedure—21 CFR 170.36 and 570.36 (OMB Control Number 0910–0342)—Extension**

Section 409 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348) establishes a premarket approval requirement for ''food additives;'' section 201(s) of the act (21 U.S.C. 321) provides an exemption from the definition of ''food additive'' and thus from the premarket approval requirement, for uses of substances that are Generally Recognized as Safe (GRAS) by qualified experts. In April 1997, FDA proposed a voluntary procedure whereby manufacturers would notify FDA about a view that a particular use (or uses) of a substance is not subject to the statutory premarket approval requirements based on a determination that such use is GRAS (62 FR 18938, April 17, 1997). Proposed §§ 170.36 and 570.36 provide a standard format for the voluntary submission of a notice. The notice would include a detailed summary of the data and information that support the GRAS determination, and the notifier would maintain a record of such data and information. FDA would make the information describing the subject of the GRAS notice, and the agency's response to the notice, available in a publicly accessible file; the entire GRAS notice would be publicly available consistent with the Freedom of Information Act and other Federal disclosure statutes.

*Description of Respondents*: Manufacturers of Substances Used in Food and Feed.

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