OMB INFORMATION COLLECTION
SUPPORTING STATEMENT

New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted; Proposed Rule

JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) is requesting OMB approval of the information collection requirements contained in the following regulations in 21 CFR Part 314, Subpart I; and Part 601, Subpart G (Tab A).

21 CFR 314.610(b)(3); 21 CFR 314.630; and 21 CFR 601.61(b)(3); 21 CFR 601.63	Reporting/ Recordkeeping	Provides that postmarketing recordkeeping and safety reporting requirements are applicable to a drug or biological products approved under this subpart.
21 CFR 314.610(c); 21 CFR 314.640; and 21 CFR 601.61(c); 21 CFR 601.64	Reporting	Provides that patient labeling information and promotional materials be submitted to FDA for approval for a drug or biological product approved under this subpart.
21 CFR 314.610(c); and 21 CFR 601.61(c)	Recordkeeping	Provides that labeling be provided to the patient or potential patient.

FDA approves new drugs under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 355) and biological products under section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262) (Tab B). FDA is proposing to amend its new drug and biological product regulations to identify the information needed to provide substantial evidence of the efficacy of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances when adequate and well-controlled efficacy studies in humans cannot be ethically conducted because they would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers without a proven treatment and because field trials (assessment of use of the product after accidental or hostile exposure to the substance) are not feasible. The agency is proposing that, in these situations, certain new drug and biological products that are intended to reduce or prevent serious or life-threatening conditions could be approved for marketing based on evidence of effectiveness derived from appropriate studies in animals, without adequate and well-controlled efficacy studies in humans (21 CFR 314.126). Under the proposed rule, FDA could rely on the evidence from animal studies where: (1) There is a reasonably well understood pathophysiological mechanism for the toxicity of the chemical, biological, radiological, or nuclear substance and its amelioration or prevention by the product; (2) the effect is independently substantiated in multiple animal species, including species expected to react with a response predictive for humans; (3) the animal

study endpoint is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity; and (4) the data or information on the kinetics and pharmacodynamics of the product or other relevant data or information in animals and humans allows selection of an effective dose in humans, and it is therefore reasonable to expect the effect of the product in animals to be a reliable indicator of its efficacy in humans. It is also expected that the data or information on the kinetics and pharmacodynamics of the drug or biological product will be sufficiently well understood in both animals and humans or there will be some other relevant data or information in animals and humans to allow selection of an effective dose in humans.

2. Purpose and Use of the Information

Information about the effectiveness of a new drug or biological product is necessary to enable FDA to properly evaluate the data along with other required information to determine if a new drug or biological product is safe and effective prior to marketing in interstate commerce, as required by section 505 of the FD&C Act and section 351 of the PHS Act. For the limited types of products within the scope of this proposal, FDA would grant marketing approval for a new drug or biological product on the basis of adequate and well-controlled animal trials when it is scientifically reasonable to expect that the effect of the drug or biological product in animals is reasonably likely to predict clinical benefit in humans. Safety evaluation is not discussed in this proposed rule because the safety of these products can be studied in human volunteers. In order to provide for the safe and effective use of these products, similar restrictions, withdrawal procedures, postmarketing safety reporting requirements, and requirements pertaining to promotional materials contained in the accelerated approval regulations in subpart H of part 314 and in subpart E of part 601 are included in this proposal, with appropriate modifications.

3. Use of Information Technology and Burden Reduction

One of FDA's continuing objectives is to improve the speed and quality of its review and approval programs. In order to reach a decision to approve an application, the agency must evaluate all information and data provided by applicants on the safety and efficacy of the proposed product. To make the review process more efficient for industry and FDA, the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) is utilizing electronic information systems technology.

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 among 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 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. CDER has issued the following Guidance for Industry documents entitled “Regulatory Submissions in Electronic Format - NDAs” and “ Regulatory Submissions in Electronic Format - General Considerations”.

CBER currently accepts “Computer Assisted Product License Applications” (CAPLA’s). CBER intends to continue this trend by accepting electronic biologics license applications and plans to issue guidance to assist manufacturers in this area (e.g., Draft Guidance for Industry: Electronic Submissions of a Biologics License Application (BLA) or Product License Application (PLA)/Establishment License Application (ELA) to the Center for Biologics Evaluation and Research (6/1/98; 63 FR 29741)).

FDA believes the increased use of computer assisted license applications will enhance the timeliness, effectiveness, and efficiency of the review process and reduce burdensome, nonessential hard-copy handling and storage. FDA is not aware of any other improved technology to reduce the burden.

4. Efforts to Identify Duplication and Use of Similar Information

FDA is the only agency that requires the filing of an application for the marketing of a new drug or biological product for human use. No other component of the agency or other government agencies require similar information or data to be filed. This information is not available from any other source.

5. Impact on Small Businesses or Other Entities

FDA believes that its duty requires the equal application of the regulations to all enterprises. While FDA does not believe it can apply different standards with respect to statutory requirements, FDA does provide special help to small businesses. The Center for Biologics Evaluation and Research, Office of Communication, Training, and Manufacturer’s Assistance, and the Center for Drug Evaluation and Research, Office of Training and Communications provide assistance to small businesses subject to FDA’s regulatory requirements.

6. Consequences of Collecting the Information Less Frequently

Manufacturers submit applications for approval of a new drug or biological product only prior to marketing such products in interstate commerce. Less frequent collection of information will not provide the necessary information needed by FDA to properly evaluate the safety and effectiveness of a new drug or biological product.

There are no technical or legal obstacles to reducing the burden.

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

An applicant may be required to submit to FDA proprietary trade secret or other confidential information when submitting a biologics license application. FDA has instituted security measures to protect confidential information received from manufacturers and will, to the extent permitted by law, protect the information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A notice requesting comments on the information collection provisions will be provided in the proposed rule published in the Federal Register.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift was provided to respondents.

10. Assurance of Confidentiality Provided to Respondents

The confidentiality of information received by FDA would be consistent with the Freedom of Information Act and the agency's regulations under 21 CFR Part 20, as well as 21 CFR 314.430 or 601.51. Manufacturers seeking to market a biological product in interstate commerce may be required to include proprietary or trade information in a license application submitted for FDA approval. However, such proprietary or trade information is deleted from any information released by FDA under the Freedom of Information Act and FDA regulations.

11. Justification for Sensitive Questions

Questions of a sensitive nature are not applicable to this information collection.

12. Estimate of Hour Burden Including Annualized Hourly Costs

The estimated annual burden for this information collection is 247 hours.

Estimated Annual Reporting Burden[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
314.610(b)(3); 314.630; 601.61(b)(3); 601.64	1	1	1	5	5
314.610(c); 314.640; 601.61(c); 601.64	1	1	1	240	240
Total					245

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

Estimated Annual Disclosure/Recordkeeping Burden[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
314.610(b)(3); 314.630; 601.61(b)(3); 601.64	1	1	1	1	1
314.610(c); 601.61(c)	1	1	1	1	1
Total					2

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

FDA estimates that only one application of this nature may be submitted every 3 years; however, for calculation purposes, FDA is estimating the submission of one application annually. FDA estimates 240 hours for a manufacturer of a new drug or biological product to develop patient labeling, and to submit the appropriate information and promotional labeling to FDA. At this time, FDA cannot estimate the number of postmarketing reports for adverse drug or biological experiences associated with a newly approved drug or biological product. Therefore, FDA is using one report for purposes of this information collection. These reports are required under 21 CFR parts 310, 314, and 600. Any burdens associated with these requirements will be reported under the adverse experience reporting (AER) information collection requirements. The estimated hours for postmarketing reports range from 1 to 5 hours based on previous estimates for adverse experience reporting; however FDA is estimating 5 hours for the purpose of this information collection.

The majority of the burden for developing the patient labeling is included under the reporting requirements, therefore, minimal burden is calculated for providing the guide to patients. As discussed previously, no burden can be calculated at this time for the number of AER reports that

may be submitted after approval of a new drug or biologic, therefore, the number of records that may be maintained also cannot be determined. Any burdens associated with these requirements will be reported under the AER information collection requirements. The estimated recordkeeping burden of 1 hour is based on previous estimates for the recordkeeping requirements associated with the AER system.

Cost to Respondents

The estimated annual cost to respondents is $ 12,320.00.

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting	245	$50.00	$12,250.00
Recordkeeping/Disclosure	2	$35.00	$70.00

The cost estimate is based on an average pay rate of $50.00/hour. This average is based on the salaries of an upper level manager, mid-level professional, and clerical support that may be involved in the preparation and submission of the required labeling information. The cost estimate is also based on a mid-level professional, at a pay rate of $35.00/hour, who has the training and skills to handle the recordkeeping/disclosure requirements.

13. Estimate of Other Total Annual Cost Burden to Respondents or Recordkeepers

There are no capital start-up, operation, maintenance, or purchase costs associated with the information collection.

14. Annualized Cost to the Federal Government

The estimated annualized cost to the Federal Government is $34,109,598.00. This estimate is based on full-time equivalents (FTEs) associated with the review of applications including supplemental applications and the average annual salaries for CBER and CDER reviewers.

The amount of time and expense incurred by the Federal government is due to the review of all material submitted with an application. This information is essential to determine the safety and effectiveness of products in support of FDA's mission to protect the public health. This information may include clinical data, safety updates, samples submitted for evaluation by the agency, case report tabulations, case report forms, and patient information.

Activity	Number of FTEs	Average Annual Reviewer Salary	Total Cost
Application Review/CBER	168	$65.160.00	$23,162,718.00

Application Review/CDER	327	$70,834.00	$10,946,880.00
Total			$34,109,598.00

15. Explanation of Program Changes or Adjustments

Changes in burdens is not applicable as this is the first submission for the proposed rule.

16. Plans for Tabulation and Publication and Program Time Schedule

There are no tabulated results for this information collection.

17. Reason(s) Display of Expiration Date is Inappropriate

FDA is not seeking approval to exempt the display of the expiration date of the OMB approval.

18. Exceptions to Certification for Paperwork Reduction Act Submission

There are no exceptions to Item 19 of OMB Form 83-I.