

OMB INFORMATION COLLECTION  
SUPPORTING STATEMENT  
0910-0315

General Licensing Provisions: Changes to an Approved Application; Labeling; and Revocation and Suspension

**JUSTIFICATION**

**1. Circumstances Making the Collection of Information Necessary**

The Food and Drug Administration (FDA) is requesting an extension of OMB approval for OMB Control No. 0910-0315 and the information collection requirements for Form FDA 2567 and the regulations listed below (Tab A). This information collection package 0910-0315 consolidates OMB Control Nos. 0910-0039 and 0910-0124.

21 CFR 600.15(b)	Reporting	Requires the submission of a request for an exemption or modification regarding the temperature requirements during shipment of certain biological products.
21 CFR 601.2	Reporting	Requires a manufacturer of a biological product to submit an application with accompanying information, including labeling information, to FDA for approval to market a product in interstate commerce.
21 CFR 601.5(a)	Reporting	Requires a licensee to give notice of its intention to discontinue manufacture of a product or all products.
21 CFR 601.6(a)	Reporting	Requires the licensee to notify selling agents and distributors upon suspension of its license, and provide FDA with records of such notification.
21 CFR 601.12 (b), (c), & (d)	Reporting	Require applicants to follow specific procedures in informing FDA of each change, established in an approved license application, in the product, production process, quality controls, equipment, facilities, or responsible personnel depending on the potential for the change to have a substantial, moderate, minimal or no adverse effect on the safety or effectiveness of the product.
21 CFR 601.12(e)	Reporting	Requires an applicant to submit a protocol, or change to a protocol, as a supplement requiring FDA approval prior to distributing the product.
21 CFR 601.12(f)(1), (2), & (3)	Reporting	Requires applicants to follow specific procedures in reporting labeling changes to FDA.
21 CFR 601.12 (f)(4)	Reporting	Requires applicants to report advertising and promotional labeling and any changes to FDA.

21 CFR 601.25(b)	Reporting	Requires interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of biological products that have been licensed prior to July 1, 1972.
21 CFR 601.26(f)	Reporting	Requires licensee submit to FDA a written statement intended to show that studies adequate and appropriate to resolve questions raised about a biological product have been undertaken for a product if designated as requiring further study under the reclassification procedures
21 CFR 601.45	Reporting	Requires applicants to submit to the agency for consideration, during the preapproval review period, copies of all promotional materials, including promotional labeling as well as advertisements.
21 CFR 610.53(d)	Reporting	Requires the submission of a request for an exemption or modification regarding the dating periods for certain biological products.

In addition to §§ 601.2 and 601.12, there are other regulations that relate to certain information submitted in a license application or supplement: §§ 640.6, 640.17, 640.21(c), 640.22(c), 640.25(c), 640.56(c), 640.64(c), 640.74(a), and (b)(2), 660.51(a)(4), and 680.1(b)(2)(iii) and (c). The burden associated with the information collection requirements in these regulations is included in the burden estimate for § 601.2 reported under OMB Control No. 0910-0427, and § 601.12 reported in this information collection package (0910-0315).

Form FDA 2567 is used by manufacturers of licensed biological products to submit labeling, e.g., circulars, package labels, container labels, etc., and labeling changes for FDA review and approval. The labeling information is submitted with the form for license applications, supplements, or as part of an annual report. Form FDA 2567 is also used for the transmission of advertisements and promotional labeling. Form FDA 2567 serves as an easy guide to assure that the manufacturer has provided the information required for expeditious handling of their labeling by the Center for Biologics Evaluation and Research (CBER). For advertisements and promotional labeling, manufacturers of licensed biological products may submit to CBER either Form FDA 2567 or 2253 (Tab B). Form FDA 2253 was previously used only by drug manufacturers regulated by the Center for Drugs Evaluation and Research (CDER). In August of 1998, FDA revised and harmonized Form FDA 2253 to enable the form to be used to transmit specimens of promotional labeling and advertisements for biological products as well as for prescription drugs and antibiotics. The revised, harmonized form updates the information about the types of promotional materials and the codes that are used to clarify the type of advertisement or labeling submitted; clarifies the intended audience for the advertisements or promotional labeling, e.g., consumers, professionals, news services; and helps ensure that the submission is complete. Form FDA 2253 is approved under OMB Control No. 0910-0376.

Under Section 351 of the Public Health Services Act (PHS Act, 42 U.S.C. 262, Tab C), manufacturers of biological products must submit a license application for FDA review and approval prior to marketing a biological product in interstate commerce. Licenses may be issued

only upon showing that the establishment and the products for which a license is desired meets standards prescribed in regulations designed to insure the continued safety, purity, and potency of such products. All such licenses are issued, suspended, and revoked as prescribed by regulations.

## **2. Purpose and Use of the Information**

FDA has the responsibility to ensure the safety, purity, potency, and effectiveness of biological products. The PHS Act and FDA regulations require manufacturers to submit a license application for review and approval prior to marketing a biological product in interstate commerce. In addition, manufacturers must submit to FDA advertising and promotional labeling. Manufacturers are also required to submit changes, including labeling, changes to an approved application, as well as advertising and promotional labeling changes. The information submitted to FDA in a biologics license application (BLA), supplement to an approved application, or other similar submission is used to determine if a product is safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use. Without this information, FDA could not monitor industry procedures and discharge its statutory responsibility for protecting the nation's health.

## **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, purity, potency, and efficacy of the proposed product. To make the review process more efficient for industry and FDA, CBER is utilizing electronic information systems technology. CBER currently accepts electronic license application, and has recently issued guidance to assist manufacturers in this area ("Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research in Electronic format - Biologics Marketing Applications [BLA, or PLA/ELA and NDA]" (64 FR 61647, November 12, 1999)).

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 biological product for human use, any changes to an approved application, and other required information. No other component of the agency or other government agencies requires similar information or data to be filed. This information is not available from any other source.

## **5. Impact on Small Businesses or Other Small 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. CBER's Office of Communication, Training, and Manufacturer's Assistance provides assistance to small businesses subject to FDA's regulatory requirements.

#### **6. Consequences of Collecting the Information Less Frequently**

Manufacturers are required to submit applications for approval of biological products prior to marketing such products in interstate commerce. In addition, manufacturers are required to submit a supplement to an approved application prior to implementing a change or in an annual report, depending on the significance of the change. Less frequent collection of information will not provide the necessary information needed by FDA to properly evaluate the safety, purity, potency, and effectiveness of a biological product.

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

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

An applicant may be required to submit to FDA proprietary trade secret or other confidential information when submitting a license application, or change to an approved application. FDA has instituted security measures to protect confidential information received from manufacturers and will, to the extent permitted by law, protect the information. In addition, certain changes to an approved application are required to be submitted each time a change is made. This information is necessary for FDA to ensure that the proposed changes do not have an adverse effect on the strength, quality, purity, or potency as they may relate to the safety and effectiveness of a product.

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

In accordance with 5 CFR 1320.8(d), a 60-day notice for public comment on the information collection provisions was published in the **Federal Register** of March 7, 2000 (65 FR 12011, Tab D). *No comments were received from the public.*

#### **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 and 21 CFR 601.51. Manufacturers submitting an application for FDA approval to market a biological product in interstate commerce, or any changes to an approved application, 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. Estimates of Hour Burden Including Annualized Hourly Costs**

The estimated annual burden for this information collection is 112,360 hours.

21 CFR Part	Form FDA No.	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
601.2(a)	2567/ 356h <sup>1</sup>	17	3.71	63	2	126
601.12(f)(1)	2567	12	1	12	40	480
601.12(f)(2)	2567	10	1	10	20	200
601.12(f)(3)	2567	70	1.43	100	10	1,000
601.12(f)(4)/601.45	2567	63	33.03	2,081	10	20,810
601.12(b)(1)/(b)(3)	356h <sup>1</sup>	190	4.75	903	80	72,240
601.12(c)(1)/(c)(3)	356h <sup>1</sup>	98	2.60	255	50	12,750
601.12(c)(5)	356h <sup>1</sup>	34	1.21	41	50	2,050
601.12(d)	356h <sup>1</sup>	166	1.37	227	10	2,270
601.12(e)	356h <sup>1</sup>	14	1.43	20	20	400
600.15(b)	356h <sup>1</sup>	1	1	1	8	8
610.53(d)	356h <sup>1</sup>	1	1	1	8	8
601.25(b)(3)	NA	0	0	0	0	0
601.26(f)	NA	0	0	0	0	0
601.5(a)	NA	33	1	33	.33	11
601.6(a)	NA	2	10.50	21	.33	7
<b>Total</b>						<b>112,360</b>

<sup>1</sup> The burden hours for the use of Form FDA 356h are reported under OMB Control No. 0910-0338.

The number of respondents is based on the estimated annual number of manufacturers who submitted the required information to FDA. There are an estimated 350 licensed biologics manufacturers. However, not all manufacturers will have any submissions in a given year and some may have multiple submissions. The total annual responses is based on the estimated number of submissions, i.e., license applications, labeling and other supplements, protocols, advertising and promotional labeling, and notifications, received annually by FDA. The rate of

submissions is not expected to change significantly in the next few years. The hours per response are based on past FDA experience with the various submissions or notifications. Additional information regarding these estimates is provided below as necessary.

Under  $\S$  601.2(a), the total annual response is based on the numbers of applications submitted to FDA for approval to market a biological product. The estimated burden hours include the time required to fill out the form and collate the documentation. The estimated burden hours to prepare the labeling information submitted with a license application are included in the burden hours to submit a license application which are reported under OMB Control No. 0910-0427.

Under  $\S$  601.12(f)(1), (f)(2), and (f)(3), the estimated burden hours include the time to prepare the supplement, fill out the form, and collate the documentation. Under  $\S$  601.12(f)(4) and  $\S$  601.45, manufacturers of biological products may use either Form FDA 2567 or Form FDA 2253 to submit advertising and promotional labeling. In fiscal year 1999, CBER received 3784 submissions of advertising and promotional labeling from 114 manufacturers. FDA estimates that approximately 55% of those submissions were received with Form FDA 2567 resulting in an estimated 2081 submissions by 63 manufacturers. The estimated burden hours include the time to prepare the submission, fill out the form, and collate the documentation. The burden hours for the remaining submissions received using Form FDA 2253 are reported under OMB Control No. 0910-0376.

Under sections 601.12(b) through (d), and section 601.12(e), the estimated burden hours include the time to prepare the appropriate supplement or protocol, respectively, and collate the documentation.

Under section 600.15(b) and 610.53(d), FDA receives very few requests for an exemption or modification to the requirements, therefore, FDA has estimated one respondent per year to account for the rare instance in which a request may be made. The estimated burden hours include the time to prepare the request for modification or exemption.

Under section 601.25(b)(3), FDA estimates no burden for this regulation since all requested data and information had been submitted by 1974. Under section 601.26(f), FDA estimates no burden for this regulation since there are no products designated to require further study and none are predicted in the future. However, based on the possible reclassification of a product, the labeling for the product may need to be revised, or a manufacturer, on its own initiative, may deem it necessary for further study. As a result, any changes to product labeling would be reported under  $\S$  601.12. The information collection requirements for  $\S$  601.12 are reported in this information collection package (0910-0315).

Under section 601.5(a), the total annual responses are based on the estimated annual number of notifications received by FDA to discontinue either an establishment and/or product license(s). The estimated burden hours include the time to prepare and submit a letter of discontinuance.

Under section 601.6(a), the total annual responses are based on FDA estimates that an establishment would need to notify an average of 20 selling agents and distributors of such suspension, and provide FDA with one notification of delivery of such records. The number of

respondents is based on the estimated annual number of suspensions by FDA of an establishment or product license(s). The estimated burden hours includes the time to prepare a notification letter and submit record of such notification to FDA.

Cost to Respondents

The estimated annual cost to respondents is \$3,932,942.

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting	112,342	\$35.00	\$3,931,970
Reporting	18	\$54.00	\$972

The cost estimate is based on a regulatory affairs specialist, at a pay rate of \$35.00/hour, who would be responsible for filling out the form, and preparing an application, supplement, or other similar submission. In addition, FDA estimates approximately 33 notices of products(s) discontinuance and 21 notices of license suspension with an average of 20 minutes per notification. The cost estimate is based on a medical director at a pay rate of \$54.00/hour who would be responsible for the preparing notification to FDA of discontinuance of a product(s), and notification to industry of license suspension.

**13. Estimate of Other Total Annual Cost Burden to Respondents or Record-keepers**

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

**14. Annualized Costs to the Federal Government**

The estimated annualized cost to the Federal Government is \$11,806,992.00. This estimate is based on full-time equivalents (FTEs) associated with the review of applications including supplemental applications or other similar submissions, and the average annual salaries for CBER reviewers.

The amount of time and expense incurred by the Federal government is due to the review of all material submitted with an application, supplement, or other similar submission. 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. In addition, the estimate is based on the number of FTEs associated with the processing of license revocations and suspensions, and the average annual salaries for CBER reviewers.

Activity	Number of FTEs	Average Annual Reviewer Salary	Total Cost
Application/Supplement Review	168	\$65,160.00	\$10,946,880.00
License Processing	7.5	\$65,160.00	\$488,700.00
Advertisement/Promotional Labeling	5.7	\$65,160.00	\$371,412.00
Total			\$11,806,992.00

**15. Explanation of Program Changes or Adjustments**

The estimated total annual burden for this information collection requirement was 100,200 hours in 1997. The slight increase in burden to 112,360 is mostly attributed to revised estimates and the consolidation of OMB Control Nos. 0910-0039 and 0910-0124 into this information collection package (0910-0315).

**16. Plans for Tabulation and Publication and Project Time Schedule**

There are no tabulated results to publish for this information collection.

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

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

**18. Exception to Certification for Paperwork Reduction Act Submissions**

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