

OMB INFORMATION COLLECTION
SUPPORTING STATEMENT

General Licensing Provisions: Biologics License Application, Changes to an Approved
Application, Labeling; and Revocation and Suspension
0910-0338

JUSTIFICATION

1. Circumstances Which Make this Collection of Information Necessary

The Food and Drug Administration (FDA) is requesting the extension of Office of Management and Budget (OMB) Control No. 0910-0338 and OMB approval of the information collection provisions including Forms FDA 356h and 2567 (Tab A). The information collection provisions are listed below:

601.2(a) 610.60, 610.61, 610.62	Reporting	Requires a manufacturer of a biological product to submit an application with accompanying information, including container and package labeling information, to FDA for approval to market a product in interstate commerce.
601.12(b)(1)/(b)(3), 601.12(c)(1)/(c)(3), 601.12(c)(5), and 601.12(d)	Reporting	Requires 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. The appropriate procedure depends on the potential for the change to have a substantial, moderate, minimal, or no adverse effect on the safety or effectiveness of the product.
601.12(e)	Reporting	Requires applicants to submit a protocol, or change to a protocol, as a supplement requiring FDA approval before distributing the product.
601.12(f)(1), 601.12(f)(2), 601.12(f)(3)	Reporting	Requires applicants to follow specific procedures in reporting labeling changes to FDA. The appropriate procedure depends on the potential for the change to have a substantial, moderate, minimal, or no adverse effect on the safety or effectiveness of the product.
601.12(f)(4)	Reporting	Requires applicants to report to FDA advertising and promotional labeling and any changes.
601.45	Reporting	Requires applicants to submit to the agency for consideration, during the pre-approval review period, copies of all promotional materials, including promotional labeling as well as advertisements.
600.15(b)	Reporting	Requires the submission of a request for an exemption or modification regarding the temperature requirements during shipment for certain biological products.

610.53(d)	Reporting	Requires the submission of a request for an exemption or modification regarding dating periods for certain biological products.
601.25(b)(3)	Reporting	Requests 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.
601.26(f)	Reporting	Requests that licensees 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.
601.27(a)	Reporting	Requires that applications for new biological products contain data that are adequate to assess the safety and effectiveness of the biological product for the claimed indications in pediatric sub-populations, and to support dosing and administration information.
601.27(b)	Reporting	Provides that an applicant may request a deferred submission of some or all assessments of safety and effectiveness required under 601.27(a).
601.27(c)	Reporting	Provides that an applicant may request a full or partial waiver of the requirements under 601.27(a).
601.28(a)	Reporting	Requires sponsors to submit to FDA a brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated.
601.28(b)	Reporting	Requires sponsors to submit to FDA an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information.
601.28(c)	Reporting	Requires sponsors to submit to FDA a statement on the current status of any post-marketing studies in the pediatric population performed by, on or behalf of, the applicant.
601.33, 601.34, 601.35	Reporting	Clarifies the information required to be submitted in an application to FDA to evaluate the safety and effectiveness of in vivo radiopharmaceuticals.
601.5(a)	Reporting	Requires a licensee to submit to FDA notice of its intention to discontinue manufacture of a product or all products.
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.
680.1(c)	Reporting	Requires manufacturers to update annually the list of source materials and the suppliers of the materials.

Amendments/ Resubmissions	Reporting	Includes amendments to an unapproved application or supplement or resubmission of a license application.
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In addition to §§ 601.2 and 601.12, there are other regulations that relate to information to be submitted in a license application or supplement for certain blood or allergenic products: §§ 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). In the chart in section 12, the burden associated with the information collection requirements in these regulations is included in the burden estimate for §§ 601.2 and 601.12. A regulation may be listed under more than one section of § 601.12 due to the type of category under which a change to an approved application may be submitted. In addition, the burden associated with the information collection requirements in §§ 601.27(a) and 601.33 -601.35 is included in the burden estimate for § 601.2 since these regulations deal with information to be provided in an application.

Under Section 351 of the Public Health Services Act (PHS Act, 42 U.S.C. 262, Tab B), manufacturers of biological products must submit a license application for FDA review and approval before 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 ensure the continued safety, purity, and potency of such products. All such licenses are issued, suspended, and revoked as prescribed by regulations in 21 CFR Part 601.

In July 1997, FDA revised Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use" to harmonize application procedures between Center for Biologics Evaluation and Research (CBER) and the Center for Drugs Evaluation and Research (CDER). The application form serves primarily as a checklist for firms to gather and submit to the agency studies and data that have been completed. The checklist helps to ensure that the application is complete and contains all the necessary information, so that delays due to lack of information may be eliminated. The form provides key information to the agency for efficient handling and distribution to the appropriate staff for review. The estimated burden hours for submissions using FDA Form 356h to CDER are reported under OMB Control No. 0910-0001.

Form FDA 2567 "Transmittal of Labels and Circulars" 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 CBER. For advertisements and promotional labeling, manufacturers of licensed biological products may submit to CBER either Form FDA 2567 or 2253. Form FDA 2253 (approved under OMB Control No. 0910-0376) was previously used only by drug manufacturers regulated by the CDER. In August of 1998, FDA revised and harmonized Form FDA 2253 so the form may 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.

2. How, By Whom, and the Purpose for Collecting this 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 and other information, FDA could not monitor industry procedures and discharge its statutory responsibility for protecting the nation's health.

3. Use of Information Technology to Reduce Burden on the Public

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 the submission of electronic license applications. 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. Identification and Use of Duplicate 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. FDA's Efforts to Reduce burden on Small Businesses

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 (CBER), Office of Communications, Training, and Manufacturers Assistance provides assistance to small businesses subject to FDA's regulatory requirements.

6. Impact of Not Collecting This Information or Collecting 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 this and other 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 That Occur When Collecting This Information

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. Identification of FDA Outside Sources

In accordance with 5 CFR 1320.8(d), FDA published a notice in the Federal Register of February 8, 2002 (67 FR 6036, Tab C) providing for a 60-day comment period on the information collection. We received one comment on the proposed information collection.

The comment stated that we should revise various regulations to harmonize regulations between the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). The comment cited many specific provisions, with none of the cited provisions being affected by the proposed information collection, and recommended specific changes to those provisions. For example, the comment asked that we delete 21 CFR 610.12 regarding sterility for bulk materials, that we revise 21 CFR 610.11, 610.12, 610.13, and 610.30 to delete references to specific tests, and that we redefine “manufacturer” in 21 CFR 600.3(t). The comment also asked us to address “outdated” safety reporting regulations; to permit multiple product facilities (citing 21 CFR 600.11(e)(3)); and to expedite follow-up actions after inspections.

The comment’s suggested regulatory revisions pertain to provisions or matters that are outside the scope of the proposed information collection. Consequently, we decline to adopt the comment’s recommendations.

One comment relevant to the information collection in the 60-day notice stated that Form FDA 2567 is only used to submit labels to CBER and that CDER does not use this form. The comment stated that the requirement to use only one form for one Center imposes an additional burden (but did not describe the additional burden), and suggested that CBER and CDER use the same form or not use the form at all.

We are considering whether to retain Form FDA 2567 for labeling purposes, but because the issue of eliminating the form is complex, we won't have a decision on the matter before the OMB approval expires. Therefore, we are renewing the form until a final decision is reached on the use of the form. Manufacturers already have the option of submitting to CBER and CDER Form FDA 2253 for the submission of advertising and promotional labeling. However, any additional burden of submitting the form with a BLA is minimal since the time required to fill out this form is estimated to average 10 minutes.

9. Payment or Gifts Offered to Respondents

No payment or gift was provided to respondents.

10. Method of Ensuring Respondent Confidentiality

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. Use of Sensitive Questions

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

12. Burden Hours and Cost Associated With This Information Collection

The total estimated burden for the reporting burdens is 301,751.75 hours.

Estimated Annual Reporting Burden						
21 CFR Part ¹	Form FDA No.	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
601.2(a) 610.60, 610.61, 610.62	2567/ 356h	22	3.64	80	1,600	128,000
601.12(b)(1)/(b)(3)	356h	168	4.98	837	80	66,960
601.12(c)(1)/(c)(3)	356h	119	6.63	789	50	39,450
601.12(c)(5)	356h	58	3.52	204	50	10,200
601.12(d)	356h	83	1.72	143	10	1,430
601.12(e)	356h	70	1	70	20	1,400
601.12(f)(1)	2567	37	2.08	77	40	3,080
601.12(f)(2)	2567	45	1	45	20	900
601.12(f)(3)	2567	20	1	20	10	200

601.12(f)(4)/ 601.45	2567	42	36.88	1,549	10	15,490
600.15(b)	356h	1	1	1	8	8
610.53(d)	356h	1	1	1	8	8
601.25(b)(3)	NA	0	0	0	0	0
601.26(f)	NA	0	0	0	0	0
601.27(b)	NA	5	1	5	24	120
601.27(c)	NA	3	1.33	4	8	32
601.28(a)	NA	69	1	69	8	552
601.28(b)	NA	69	1	69	24	1,656
601.28(c)	NA	69	1	69	1.5	103.5
601.5(a)	NA	5	1	25	.33	8.25
601.6(a)	NA	2	21	42	.33	14
680.1(c)	NA	10	1	10	2	20
Amendments/ Resubmissions	356h	350	4.59	1,606	20	32,120
Total						301,751.75

¹ The reporting requirement under sections 601.27(a), 601.33, 601.34, 601.35, and 680.1(b)(2)(iii) is included in the estimate under section 601.2(a). The reporting requirement under sections 606.110(b), 640.6, 640.17, 640.21(c), 640.22(c), 640.25(c), 640.56(c), 640.64(c), 640.72(a) and (b)(2) is included in the estimate under section 601.12(b). The reporting requirement under sections 640.25(c) and 640.56(c) is also included in the estimate under section 601.12(c)(3).

The number of respondents is based on the estimated annual number of manufacturers that submitted the required information to FDA in fiscal year (FY) 2000, or the number of submissions received in FY 2000. Based on information obtained from CBER's database system, there is 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 are based on the estimated number of submissions (e.g., license applications, labeling and other supplements, protocols, advertising and promotional labeling, notifications) received annually by FDA. Based on previous estimates, the rate of submissions is not expected to change significantly in the next few years. The hours per response are based on information provided by industry and past FDA experience with the various submissions or notifications. The hours per response include the time estimated to prepare the various submissions or notifications to FDA, and, as applicable, the time required to fill out the appropriate form and collate the documentation. Additional information regarding these estimates is provided below as necessary.

Under §§ 601.12(f)(4) and 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 2000, CBER received 4,302 submissions of advertising and promotional labeling from 117 manufacturers. FDA estimates that approximately 36% of those submissions were received with Form FDA 2567 resulting in an estimated 1,549 submissions by 42 manufacturers. The burden hours for the remaining submissions received using Form FDA 2253 are reported under OMB Control No. 0910-0376.

Under §§ 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 in Table 1 to account for the rare instance in which a request may be made.

Under § 601.25(b)(3), FDA estimates no burden for this regulation since all requested data and information had been submitted by 1974. Under § 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 § 601.12.

Under §601.6(a), the total annual responses is based on FDA estimates that establishments may notify an average of 20 selling agents and distributors of such suspension and provide FDA with the records of such notification. The number of respondents is based on the estimated annual number of suspensions by FDA of a biologics license.

There were also 1,585 amendments to an unapproved application or supplement and 21 resubmissions (total of 1,606 submissions) submitted in FY 2000 using Form FDA 356h.

Cost to Respondents

The estimated annual cost to respondents is \$11,466,922.50.

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting	301,729.50	\$38.00	\$11,465,721.00
Reporting	22.25	\$54.00	\$1201.50

The cost estimate is based on a regulatory affairs specialist, at a pay rate of \$38.00/hour, who would be responsible for filling out the form, and preparing an application, supplement, or other similar submission. The cost estimate is also 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 a license suspension (25 notices of products(s) discontinuance and 42 notices of license suspension with an average of 20 minutes per notification).

FDA is estimating the operating costs for postage and handling associated with the submissions sent to FDA.

Activity	No. of Submissions	Average Cost per Submission	Total Cost
Postage and Handling	5,715	\$60.00	\$342,900.00

Based on our burden estimates, there were 5,715 submissions sent to FDA. FDA estimates that most of the application, supplements, and other submissions are submitted from industry to FDA/CBER by private courier. Submissions in this information collection package can range

from a regular letter to several boxes of data with the majority of supplements received containing less than a box of data. Based on past FDA experience, FDA estimates that an average of 1 box of data is submitted to FDA taking into account the various submissions. FDA estimates that each box weighs approximately 20 pounds. Based on cost estimates of a major private courier, the cost for a 20 lb. box shipped Standard Overnight is \$60.00; this shipping cost is based on an average distance within the continental U.S.

13. Annual Cost Estimate to Respondents

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

14. Annual Cost to FDA

The estimated annualized cost to the Federal Government is \$20,152,029.00. This estimate is based on full-time equivalents (FTEs) associated with the review of license applications including supplemental applications or other similar submissions. 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 advertising and promotional labeling. The average annual salary and benefits for CBER reviewers is \$99,418.00.

Activity	Number of FTEs	Average Annual Reviewer Salary	Total Cost
Application/Supplement Review	189.5	\$99,418.00	\$18,839,711.00
License Processing	7.5	\$99,418.00	\$745,635.00
Advertisement/Promotional Labeling	5.7	\$99,418.00	\$566,683.00
Total			\$20,152,029.00

15. Changes From Previous Approval

The burden estimate for 0910-0338 was 602, 856. The decrease in burden is attributed to the estimated burden hours for submissions using FDA Form 356h to the Center for Drug Evaluation and Research being reported under OMB Control No. 0910-0001.

FDA is consolidating into 0910-0338 the following information collection packages: 0910-0315, 0910-0409, and 0910-0427.

16. Publishing the Results of This Information Collection

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

17. Reason for Not Displaying the OMB Approval Date

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

18. Explanations to Section 19, "Certification for Paperwork Reduction Act Submissions"

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