

**General Licensing Provisions: Biologics License Application, Changes to an Approved Application, Labeling, Revocation and Suspension, Postmarketing Studies Status Reports, and Forms FDA 356h and 2567**

**OMB# 0910-0338**

**SUPPORTING STATEMENT**

**Justification**

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) is requesting an 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. A summary of the information collection provisions are listed below:

21 CFR Section	Category	Description
600.15(b), 610.53(d)	Reporting	Require the submission of a request for an exemption or modification regarding the temperature requirements during shipment and regarding dating periods, respectively, for certain biological products.
601.2(a); and 610.60 through 610.65	Reporting	Requires manufacturers of a biological product to submit an application on forms prescribed for such purposes with accompanying information, including certain labeling information, to FDA for approval to market a product in interstate commerce. The container and package labeling requirements are provided under §§ 610.60 through 601.65.
601.5(a)	Reporting	Requires a manufacturer to submit to FDA notice of its intention to discontinue manufacture of a product or all products.
601.6(a)	Reporting	Requires the manufacturer to notify selling agents and distributors upon suspension of its license, and provide FDA with records of such notification.
601.12(a)(2)	Reporting	Requires, generally, that the holder of an approved biologics license application must assess the effects of a manufacturing change before distributing a biological product made with the change.
601.12(a)(4)	Reporting	Requires, generally, that the applicant must promptly revise all promotional labeling and advertising to make it consistent with certain labeling changes implemented.

601.12(a)(5)	Reporting	Requires the applicant to include a list of all changes contained in the supplement or annual report; for supplements, this list must be provided in the cover letter.
601.12(b)(1)/(b)(3), 601.12(c)(1)/(c)(3), 601.12(c)(5), and 601.12(d)(1)/(d)(3)	Reporting	Require applicants to follow specific procedures to submit information to FDA of any changes, in the product, production process, quality controls, equipment, facilities, or responsible personnel established in an approved license application. The appropriate procedure depends on the potential for the change to have a substantial, moderate, or minimal adverse effect on the identity, strength, quality, purity, or potency of the products as they may relate to the safety or effectiveness of the product.
601.12(b)(4)	Reporting	An applicant may ask FDA to expedite its review of a supplement for public health reasons or if a delay in making the change described in it would impose an extraordinary hardship of the applicant.
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	Require applicants to follow specific procedures to report certain labeling changes to FDA.
601.12(f)(4)	Reporting	Requires applicants to report to FDA advertising and promotional labeling and any changes.
601.14	Reporting	Requires that the content of labeling required in § 201.100(d)(3) must be in electronic format and in a form that FDA can process, review, and archive.
601.25(b)	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	Requires 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) until after licensing the product for use in adults.
601.27(c)	Reporting	Provides that an applicant may request a full or partial waiver of the requirements under § 601.27(a) with adequate justification.
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	Clarify the information required to be submitted in an application to FDA to evaluate the safety and effectiveness of in vivo radiopharmaceuticals.
601.45	Reporting	Requires applicants of biological products for serious or life-threatening illnesses 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.
601.70(b) and (d)	Reporting	Requires each applicant of a licensed biological product to submit annually a report to FDA on the status of postmarketing studies for each approved product application. Each annual postmarketing status report must be accompanied by a completed transmittal Form FDA 2252. Two copies of the annual report must be submitted.
601.91(b)(3)	Reporting	Requires applicants to prepare and provide labeling with relevant information to patient or potential patient for biological products approved under part 601, subpart H when human efficacy studies are not ethical or feasible (or based on evidence of effectiveness from studies conducted in animals).
601.93	Reporting/ Recordkeeping	Provides that biological products approved under subpart H are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.
601.94	Reporting	Requires applicants under subpart H to submit to

		the agency for consideration during preapproval review period copies of all promotional materials including promotional labeling as well as advertisements.
606.110(b)	Reporting	Requires the submission of a request for approval to perform plasmapheresis of donors who do not meet certain donor requirements for the collection of plasma containing rare antibodies.
610.9(a)	Reporting	Requires the applicant to present certain information, in the form of a license application or supplement to the application, for a modification of any particular test method or manufacturing process or the conditions which it is conducted under the biologics regulations.
610.11(g)(2)	Reporting	Provides that a manufacturer of certain biological products may request an exemption from the general safety test (GST) requirements contained in subpart H.
610.67	Reporting	Requires certain biological products to comply with the bar code requirements at § 201.25.
640.120	Reporting	Requires licensed establishments to submit a request for an exception or alternative to any requirement in the biologics regulations regarding blood, blood components, or blood products. A request for an exception or alternative must be submitted in accordance with § 601.12.
680.1(c)	Reporting	Requires manufacturers to update annually their license file with the list of source materials and the suppliers of the materials.
680.1(b)(3)(iv)	Reporting	Requires manufacturers to notify FDA when certain diseases are detected in <b>animals intended for use or used as</b> source materials.
Amendments/ Resubmissions	Reporting	Includes amendments to an unapproved application or supplement or resubmission of a license application.
601.91(b)(2)(iii)	Recordkeeping	Requires, in certain circumstances, postmarketing restrictions as needed to ensure the safe use of the biological products distribution conditioned on specified recordkeeping requirements.

In addition to §§ 601.2 and 601.12, there are other regulations in 21 CFR Parts 640, 660, and 680 that relate to information to be submitted in a license application or supplement for certain blood or allergenic products as follows: §§ 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 (d). In the table 1 of this document, the burden associated with the information collection requirements in these regulations is included in the burden estimate for §§ 601.2 and/or 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.

There are also additional container and/or package labeling requirements for certain licensed biological products including: § 640.70(a) for Source Plasma; § 640.74(b)(3) and (b)(4) for Source Plasma Liquid; § 640.84(a) and (c) for Albumin; § 640.94(a) for Plasma Protein Fraction; § 660.2(c) for Antibody to Hepatitis B Surface Antigen; § 660.28(a), (b), and (c) for Blood Grouping Reagent; § 660.35(a), (c) through (g), and (i) through (m) for Reagent Red Blood Cells; § 660.45 for Hepatitis B Surface Antigen; and § 660.55(a) and (b) for Anti-Human Globulin. The burden associated with the additional labeling requirements for submission of a license application for these certain biological products is minimal because the majority of the burden is associated with the requirements under §§ 610.60 through 610.65 or § 809.10 (21 CFR 809.10). Therefore, the burden estimates for these regulations are included in the estimate under §§ 610.60 through 610.65 in table 1 of this document. The burden estimates associated with § 809.10 are approved under OMB Control No. 0910-0485.

Under section 351 of the Public Health Services Act (the PHS Act) (42 U.S.C. 262), 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.

Section 130(a) of the Food and Drug Administration Modernization Act (Public Law 105-115) amended the Federal Food, Drug, and Cosmetic Act (the act,) by adding a new provision, section 506B of the act (21 U.S.C. 356b), requiring reports of postmarketing studies for approved human drugs and licensed biological products. Section 506B of the act provides FDA with additional authority to monitor the progress of postmarketing studies that applicants have made a commitment to conduct and requires FDA to make publicly available information that pertains to the status of these studies. Under section 506B(a) of the act, applicants that have committed to conduct a postmarketing study for an approved human drug or licensed biological product must submit to FDA a status report of the progress of the study or the reasons for the failure of the applicant to conduct the study. This report must be submitted within 1 year after the U.S. approval of the application and then annually until the study is completed or terminated.

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 certain information to FDA. 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 FDA for efficient handling and distribution to the appropriate staff for review. The estimated burden hours for nonbiological product submissions using FDA Form 356h to CDER are approved 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. 0910-0001) was previously used only by drug manufacturers regulated by the CDER. In August 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. Purpose and Use of the Information Collection

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. The recordkeeping requirements serve preventative and remedial purposes to ensure safe use of the biological products. The regulations also describe the types of postmarketing studies that require status reports, the information to be included in the reports, and the type of information that FDA would consider appropriate for public disclosure. FDA uses the information submitted from postmarketing study reports to meet its reporting obligations under section 506B of the act and section 130(b) of the Modernization Act. 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 Improved 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 and CDER utilize electronic information systems technology. CBER and CDER currently accept the submission of electronic license applications and other similar submissions. FDA believes the increased use of computer-assisted license applications enhances 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. Effects 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 biological product for human use, any changes to an approved application, and other required information. No other government agency requires similar information or data to be submitted. This information is not available from any other source.

## 5. Impact on Small Businesses or Other Small Entities

Although FDA must apply the statutory and regulatory requirements equally to all enterprises, the agency does provide special help to small businesses. CBER's Office of Communication, Outreach, and Development, Division of Manufacturers Assistance and Training, provides assistance to small businesses subject to FDA's regulatory requirements. CDER's Office of Communication, Division of Drug Information, also provides assistance to small businesses.

## 6. Consequences of Collecting the Information Less Frequently

Manufacturers are required to submit applications to FDA for approval of biological products prior to marketing such products in interstate commerce. In addition, manufacturers are required to submit to FDA 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 information that FDA needs to evaluate the safety, purity, potency, and effectiveness of a biological product and properly monitor the progress of postmarketing studies.

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, change to an approved application, an annual report, or other related information. FDA protects confidential information received from manufacturers to the extent permitted by law. 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 the Agency

In accordance with 5 CFR 1320.8(d), FDA published a 60-day notice for public comment in the Federal Register of January 26, 2010 (75 FR 4081). No comments were received from the public.

## 9. Explanation of Any Payment or Gift to the Respondents

No payment or gift has been or will be 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 (FOIA) and FDA's published regulations under 21 CFR Part 20, 21 CFR 601.51, and 601.70(e).

## 11. Justification for Sensitive Questions

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

## 12. Estimates of Annualized Burden Hours and Costs

The total annual estimated burden imposed by this collection of information is 341,698 hours annually.

Table 1. – Estimated Annual Reporting Burden

21 CFR Section	Form FDA No.	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
601.2(a) <sup>1</sup> and 610.60 through 610.65 <sup>2</sup>	2567/356h	23	2	46	860	39,560
601.5(a)	NA	11	3	33	20 minutes (1/3)	11
601.6(a)	NA	1	21	21	20 minutes (1/3)	7
601.12(a)(5)	NA	802	9	7,218	1	7,218
601.12(b)(1), (b)(3) <sup>2</sup> , and (e) <sup>3</sup>	356h <sup>1</sup>	166	5	830	80	66,400
601.12(c)(1) and (c)(3) <sup>4</sup>	356h <sup>1</sup>	141	5	705	50	35,250
601.12(c)(5)	356h <sup>1</sup>	42	5	210	50	10,500
601.12(d)(1), (d)(3), and (f)(3) <sup>6</sup>	356h <sup>1</sup>	246	3	738	23	16,974
601.12(f)(1) <sup>5</sup>	2567	112	2	224	40	8,960
601.12(f)(2) <sup>5</sup>	2567	53	3	159	20	3,180
601.12(f)(4) and 601.45	2567/2253	42	106	4,452	10	44,520
601.26(f)	NA	1	1	1	1	1
601.27(b)	NA	6	1	6	24	144
601.27(c)	NA	10	1	10	8	80
601.70(b), (d), and 601.28	2252	39	2	78	24	1,872
601.91(b)(3), and 601.94	NA	1	1	1	240	240
680.1(c)	NA	9	1	9	2	18
680.1(b)(3)(iv)	NA	1	1	1	2	2
Amendments/Resubmissions	356h	314	17	5,338	20	106,760
<b>Total</b>						<b>341,697</b>

<sup>1</sup> The reporting requirements under §§ 610.9(a), 601.14, 601.27(a), 601.33, 601.34, 601.35, 610.11(g)(2), 640.17, 640.25(c), 640.56(c), 640.74(b)(2), 660.51(a)(4), and 680.1(b)(2)(iii) are included in the estimate under § 601.2(a).

<sup>2</sup> The reporting requirements under §§ 640.70(a), 640.74(b)(3) and (b)(4), 640.84(a) and (c), 640.94(a), 660.2(c), 660.28(a), (b), and (c), 660.35(a), (c) through (g), and (i) through (m), 660.45, and 660.55(a) and (b) are included under §§ 610.60 through 610.65.

<sup>3</sup> The reporting requirements under §§ 610.9(a), 600.15(b), 610.11(g)(2), 610.53(d), 606.110(b), 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), 640.120, and 680.1(d) are included in the estimate under §§ 601.12(b).



<sup>4</sup> The reporting requirements under §§ 610.9(a) 640.17, 640.25(c), 640.56(c), and 640.74(b)(2) are included in the estimate under §§ 601.12(c).

<sup>5</sup> The reporting requirement under § 601.14 is included in the estimates under §§ 601.12(f)(1) and (f)(2).

<sup>6</sup> The reporting requirement under § 601.14 is included in the estimate under 601.12(f)(3).

The number of respondents is based on the estimated annual number of manufacturers that submitted the required information to FDA or the number of submissions FDA received in fiscal year 2008. Based on information obtained from FDA's database systems, there are an estimated 301 licensed biologics manufacturers. 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) for a particular product received annually by FDA. 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 §§ 601.2 and 601.12, the estimated hours per response are based on the average number of hours to submit the various submissions. The estimated average number of hours is based on the range of hours to complete a very basic application or supplement and a complex application or supplement.

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

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. Based on information obtained from FDA's database system, there were an estimated 4,452 submissions of advertising and promotional labeling. FDA estimates that approximately 15 percent of those submissions were received with Form FDA 2567 and 85 percent were received with Form FDA 2253.

Under §§ 601.28 and 601.70(b), FDA estimates that it takes an applicant approximately 24 hours (8 hours per study x 3 studies) annually to gather, complete, and submit the appropriate information for each postmarketing study report (approximately two to four studies per report) and the accompanied transmittal Form FDA 2252. Included in these 24 hours is the time necessary to prepare and submit two copies of the annual progress report of postmarketing studies to FDA under § 601.70(d).

Under §§ 601.91 through 601.94, FDA expects to receive very few applications for these products; however, for calculation purposes, FDA is estimating the annual submission of one application. Under §§ 601.91(b)(3) and 601.94, FDA estimates 240 hours for a manufacturer of a new biological product to develop patient labeling, and to submit the appropriate information and promotional labeling to FDA. The majority of the burden for developing the patient labeling is included under the reporting requirements for § 601.94, therefore minimal burden is calculated for providing the guide to patients under § 601.91(b)(3).

There were a total of 5,338 amendments to an unapproved application or to a supplement, and resubmissions submitted using Form FDA 356h.

Under § 601.25(b), FDA estimates no PRA burden for this regulation because the time period to submit data and information for review by an advisory review panel has expired and therefore this regulation is not included in table 1 of this document. Under section 601.26(f), based on the possible reclassification of one or more products, FDA is using an estimate of one for calculation purposes. 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 the appropriate paragraph of § 601.12.

Under 601.67, we are not requesting the burden (129,600 hours) be extended by OMB because the label redesign had to be completed by the final rule compliance date of April 26, 2006 (2/26/2004; 69 FR 9120).

Table 2. - Estimated Annual Recordkeeping Burden

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
601.91(b)(2)(iii)	1	1	1	1	1

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 \$ 15,718,648.

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting	341,679	\$46	\$15,717,234
Reporting	18	\$76	\$1,368
Recordkeeping	1	\$46	\$46
Total			\$15,718,648

The cost estimate is based on a regulatory affairs specialist, at a pay rate of \$46/hour, who would be responsible for filling out the form, and preparing an application, supplement, postmarketing study report, or other similar submission, and recordkeeping. The cost estimate is also based on a medical director at a pay rate of \$76/hour who would be responsible for preparing notification to FDA of discontinuance of a product(s), and notification to industry of a license suspension. The estimated average hourly pay rate includes benefits but no overhead costs.

13. Estimates of Other Total Annual Cost Burden to Respondents and Record Keepers

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

14. Annualized Cost to the Federal Government

The estimated annualized cost to FDA is \$17,573,130. This estimate is based on full-time equivalents (FTEs) associated with the review of license applications including supplemental applications or other similar submissions, and postmarketing study reports. The amount of time and expense incurred by the Federal government includes the time to the review of all material submitted with an application, supplement, or other similar submission, and postmarketing study reports. 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 estimated average annual salary for CBER reviewers includes benefits but no overhead costs.

Activity	Number of FTEs	Average Annual Reviewer Salary	Total Cost
Application/Supplement Review	103	\$121,194	\$12,482,982
License Processing	36	\$121,194	\$4,362,984
Advertisement/Promotional Labeling	5	\$121,194	\$605,970
Review Postmarketing Study Report	1	\$121,194	\$121,194
Total			\$17,573,130

15. Explanation for Program Changes or Adjustments

The change in burden hours is a result of updated data on the number of submissions received by FDA as a result of §§ 601.2 and 601.12(a), (c), (d), and (f).

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 the display of the expiration date of the OMB approval.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

N/A.