Supporting Statement for
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
Existing OMB # 0910-0338

JUSTIFICATION

1. Need and Legal Basis

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 (Tab A). The information collection provisions are listed below (Tab B):

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), 610.60, 610.61, 610.62	Reporting	Require manufacturers 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.
601.5(a)	Reporting	Requires licensees to submit to FDA notice of its intention to discontinue manufacture of a product or all products.
601.6(a)	Reporting	Requires licensees 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 applicants must promptly review all promotional labeling and advertising to make it consistent with certain labeling changes implemented.
601.12(a)(5)	Reporting	Requires applicants 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 inform FDA of each change, in the product, production process, quality controls, equipment, facilities, responsible personnel or labeling

		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 product as they may relate to the safety or effectiveness of the product.
601.12(b)(4)	Reporting	Applicants may request 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 in reporting 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 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)(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	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, accompanied by Form FDA 2252 to FDA on the status of postmarketing studies for each approved application. Two copies of each 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 the subpart when human efficacy studies are not ethical or feasible (or based on efficacy studies conducted in animals alone).
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 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 applicants to submit requests for approval to perform plasmapheresis of donors who do not meet certain donor requirements for the collection of plasma containing rare antibodies.
610.11(g)(2)	Reporting	Provides that manufacturers of certain biological products may request an exemption from the general safety test requirements.
610.67	Reporting	Requires certain biological products to comply with

		the bar code requirements at § 201.25.
680.1(c)	Reporting	Requires manufacturers to update annually their license file with 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.
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 (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*:* §§ 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), 680.1(b)(2)(iii), and 680.1(d). In the table 1 of section 12 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: § 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) and (b) 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 610.62 or § 809.10. Therefore, the burden estimates for these regulations are included in the estimate under §§ 610.60 through 610.62 in table 1 of this document. The burden estimates associated with § 809.10 are approved under OMB Control No. 0910-0485 (expires June 30, 2008).

Under section 351 of the Public Health Services Act (the PHS Act) (42 U.S.C. 262) (Tab C), 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 part 601 (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) (Tab D), requiring reports of postmarketing studies (PMSs) for approved human drugs and licensed biological product. Section 506B of the act provides FDA with additional authority to monitor the progress of PMSs 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 PMS 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 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 submissions using FDA Form 356h to CDER are reported under OMB Control No. 0910-0001 (expires May 31, 2008.)

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, expires May 31, 2008) 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. Information Users

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 use the

information submitted from PMS 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. Improved Information Technology

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. Duplication 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 FDA or other government agencies requires similar information or data to be submitted. This information is not available from any other source.

5. Small Businesses

Although FDA must apply the statutory and regulatory requirements equally to all enterprises, 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. Less Frequent Collection

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 information that FDA needs to evaluate the safety, purity, potency, and effectiveness of a biological product and properly monitor the progress of PMSs.

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

7. Special Circumstances

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, or an annual report. 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. *Federal Register* Notice/Outside Consultation

In accordance with 5 CFR 1320.8(d), FDA published a 60-day notice requesting public comment on the information collection provisions in the *Federal Register* on November 2, 2006 (71 FR 64536). No comments were received from the public.

9. Payment/Gift to Respondent

No payment or gift was provided to respondents.

10. Confidentiality

The confidentiality of information received by FDA would be consistent with the Freedom of Information Act and FDA's regulations under 21 CFR Part 20, 21 CFR 601.51, and 601.70(e). Proprietary or trade secret information is deleted from any information released by FDA under the Freedom of Information Act and FDA regulations.

11. Sensitive Questions

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

12. Burden Estimate (Total Hours and Wages)

The total annual estimated burden imposed by this collection of information is 335,807.5 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)[1], 610.60, 610.61, and 610.62[2]	2567/356h	14	2	28	860	24,080
601.5(a)	NA	16	3.13	50	.33	17
601.6(a)	NA	1	21	21	.33	7
601.12(a)(5)	NA	190	15.7	2,983	1	2,983
601.12(b)(1)/(b)(3)[3]	356h[1]	190	4.75	903	80	72,240
601.12(c)(1)/(c)(3)[4]	356h[1]	98	2.60	255	50	12,750
601.12(c)(5)	356h[1]	34	1.38	47	50	2,350
601.12(d)(1)/(d)(3)	356h[1]	166	1.37	227	22.5	5,107.5
601.12(e)	356h[1]	14	1.43	20	120	2,400
601.12(f)(1)[5]	2567	12	1	12	40	480
601.12(f)(2)[5]	2567	10	1	10	20	200

601.12(f)(3)[6]	2567	70	1.43	100	10	1,000
601.12(f)(4)/601.45	2567	15	36	540	10	5,400
601.25(b)(3)	NA	0	0	0	0	0
601.26(f)	NA	0	0	0	0	0
601.27(b)	NA	3	1	3	24	72
601.27(c)	NA	7	1	7	8	56
601.28(a), (b), and (c)	NA	44	3.27	144	33.5	4,824
601.70(b) and (d)	2252	19	1.58	30	24	720
601.91(b)(3), 601.94	NA	1	1	1	240	240
610.67	NA	174	31	5,400	24	129,600
680.1(c)	NA	10	1	10	2	20
Amendments/Resubmissions	356h	306	11.6	3,563	20	71,260
Total						335,807

[1] The reporting requirements under §§ 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).

[2] 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) and (b), 660.35(a), (c through g), and (i through m), 660.45, and 660.55(a) and (b) are included under §§ 610.60 through 610.62.

[3] The reporting requirements under §§ 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), and 680.1(d) are included in the estimate under §§ 601.12(b).

[4] The reporting requirements under §§ 640.17, 640.25(c), 640.56(c), and 640.74(b)(2) are included in the estimate under §§ 601.12(c).

[5] The reporting requirements under § 601.14 is included in the estimates under §§ 601.12(f)(1) and (f)(2).

[6] The reporting requirements under § 601.14 is included in the estimates 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 received. Based on information obtained from FDA's database systems, there are an estimated 306 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) for a particular product 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 §§ 601.2 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 3,600 submissions of advertising and promotional labeling in fiscal year 2004. FDA estimates that approximately 15 percent of those submissions were received with Form FDA 2567 resulting in an estimated 540 submissions. The burden hours for the remaining submissions received using Form FDA 2253 are reported under OMB Control No. 0910-0001.

Under § 601.70(b), FDA estimates that it takes an applicant approximately 24 hours (8 hours per study x 3) annually to gather, complete, and submit the appropriate information for each PMS report (approximately two to four studies per report) and the accompanied transmittal Form FDA 2252 (approved under OMB Control No. 0910-0001, expires May 31, 2008). Included in these 24 hours is the time necessary to prepare and submit two copies of the annual progress report of PMSs to FDA under § 601.70(d).

Under §§ 601.91 through 601.94, FDA expects to receive very few applications of this nature; however, for calculation purposes, FDA is estimating the submission of one application annually. 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). Under § 601.93, any potential postmarketing reports and/or recordkeeping burdens would be included under the adverse experience reporting (AER) requirements under part 601 (21 CFR part 600) (OMB Control No. 0910-0308; expires July 31, 2008). Therefore, any burdens associated with these requirements would be reported under the AER information collection requirements.

There were also 3,540 amendments to an unapproved application or supplement and 23 resubmissions (total of 3,563 submissions) submitted using Form FDA 356h.

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 $14,105,571.

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting	335,806.5	$42	$14,103,873
Reporting	24	$69	$1,656
Recordkeeping	1	$42	$42

The cost estimate is based on a regulatory affairs specialist, at a pay rate of $42/hour, who would be responsible for filling out the form, and preparing an application, supplement, PMS report, or other similar submission, and recordkeeping. The cost estimate is also based on a medical director at a pay rate of $69/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 (50 notices of products(s) discontinuance and 21 notices of license suspension with an average of 20 minutes per notification). The estimated average hourly pay rate includes benefits but no overhead costs.

13. Capital Costs (Maintenance of Capital Costs)

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

14. Cost to Federal Government

The estimated annualized cost to FDA is $15,920,432. This estimate is based on full-time equivalents (FTEs) associated with the review of license applications including supplemental applications or other similar submissions, and PMS reports. 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, and PMS 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, patient information, and PMS. 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 is $110,176 that includes benefits but no overhead costs.

Activity	Number of FTEs	Average Annual Reviewer Salary	Total Cost
Application/Supplement Review	103	$110,176	$11,348,128
License Processing	36	$110,176	$3,966,336
Advertisement/Promotional Labeling	4.5	$110,176	$495,792
Review PMS Report	1	$110,176	$110,176
Total			$15,920,432

15. Program or Burden Changes

The burden estimate for 0910-0338 was 335,087.5. The slight increase in burden to 335,807.5 is attributed to the consolidation of OMB packages: 0910-0433, and 0910-0530 (biologics regulations only).

Section 601.25(b) 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. Section 601.26(f) 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. Under § 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 § 601.12. Since there is no further burden, we will no longer request OMB approval for these two regulations.

16. Publication and Tabulation Dates

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

17. Display of OMB Approval Date

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"

Not applicable.