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

OMB Control No. 0910-0338

SUPPORTING STATEMENT

Justification

1. Circumstances Making the Collection of Information Necessary

This information collection supports Food and Drug Administration (FDA) regulations regarding biologics license applications, changes to approved applications, labeling, revocation and suspension postmarketing studies status reports, and agency form FDA 356h. The regulations include:

21 CFR 600.15(b), 610.53(d); Reporting: requires the submission of a request for an exemption or modification regarding the temperature requirements during shipment and from dating periods, respectively, for certain biological products.

21 CFR 601.2(a) and 610.60 through 610.65; Reporting: requires a manufacturer 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.

21 CFR 601.5(a); Reporting: requires a manufacturer to submit to FDA notice of its intention to discontinue manufacture of a product or all products.

21 CFR 601.6(a); Reporting/Disclosure: requires the manufacturer to notify selling agents and distributors upon suspension of its license, and provide FDA of such notification.

21 CFR 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.

21 CFR 601.12(a)(4); Reporting: requires, generally, that the applicant must promptly review all promotional labeling and advertising to make it consistent with any labeling changes implemented.

21 CFR 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.

21 CFR 601.12(b)(1)/(b)(3), 601.12(c)(1)/(c)(3), 601.12(c)(5), and 601.12(d)(1)/(d)(3); Reporting: requires 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.

21 CFR 601.12(b)(4); Reporting: 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.

21 CFR 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.

21 CFR 601.12(f)(1), 601.12(f)(2), 601.12(f)(3); Reporting: requires applicants to follow specific procedures to report certain labeling changes to FDA.

21 CFR 601.12(f)(4); Reporting: requires applicants to report to FDA advertising and promotional labeling and any changes.

21 CFR 601.14; Reporting: requires the content of labeling required in 21 CFR 201.100(d)(3) must be in electronic format and in a form that FDA can process, review, and archive.

21 CFR 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 subpopulations, and to support dosing and administration information.

21 CFR 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.

21 CFR 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.

21 CFR 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.

21 CFR 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.

21 CFR 601.28(c); Reporting: requires sponsors to submit to FDA a statement on the current status of any postmarketing studies in the pediatric population performed by, on or behalf of, the applicant.

21 CFR 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 radiopharmaceuticals intended for in vivo administration for diagnostic and monitoring use.

21 CFR 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.

21 CFR 601.70(b) and (d); Reporting: requires each applicant of a licensed biological product to submit annually a report to FDA, accompanied by a completed transmittal Form FDA 2252, on the status of postmarketing studies for each approved product application. Two copies of each annual report must be submitted to FDA.

21 CFR 601.91(b)(3); Reporting: requires applicants to prepare and provide labeling with relevant information to patient or potential patients 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).

21 CFR 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.

21 CFR 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.

21 CFR 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.

21 CFR 610.15(d); Reporting: the Director of the Center for Biologics Evaluation and Research (CBER) or the Director of the Center for Drug Evaluation and Research (CDER) may approve, as appropriate, a manufacturer's request for exceptions or alternatives to the regulation for constituent materials. Manufacturers seeking approval of an exception or alternative must submit a request in writing with a brief statement describing the basis for the request and the supporting data.

21 CFR 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.

21 CFR 680.1(c); Reporting: requires manufacturers to update annually their license file with the list of source materials and the suppliers of the materials.

21 CFR 680.1(b)(3)(iv); Reporting: requires manufacturers to notify FDA when certain diseases are detected in source materials.

Amendments/ Resubmissions; Reporting: includes amendments to an unapproved application or supplement or resubmission of a license application.

In addition to §§ 601.2 and 601.12, other regulations in parts 640, 660, and 680 (21 CFR Parts 640, 660, and 680) 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 (d). In table 1 of this document, the burden associated with the information collection requirements in the applicable 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: § 640.74(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). Section 601.91(b)(3) is also included under §§ 610.60 through 610.65. 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 §§ 601.91(b)(2) and 601.93, any potential postmarketing reports and/or recordkeeping burdens would be included under the adverse experience reporting (AER) requirements under 21 CFR Part 600. Therefore, any burdens associated with these requirements would be reported under the AER information collection requirements (OMB control number 0910-0308).

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 part 601 (21 CFR Part 601).

Section 130(a) of the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115) amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act,) by adding a new provision, section 506B of the FD&C Act (21 U.S.C. 356b), requiring reports of

postmarketing studies (PMSs) for approved human drugs and licensed biological products. Section 506B of the FD&C Act provides FDA with additional authority to monitor the progress of PMSs that applicants have made a commitment to conduct and requires the Agency to make publicly available information that pertains to the status of these studies. Under section 506B(a) of the FD&C 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 CBER and CDER. The application form serves primarily as a checklist for firms to gather and submit certain information to FDA. As such, the form, now entitled "*Application to Market a New or Abbreviated New Drug or Biologic for Human Use*" 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. In addition, the form provides key information to FDA for efficient handling and distribution to the appropriate staff for review. The estimated burden hours for other product submissions to CDER using FDA Form 356h are approved under OMB control number 0910-0001 (an estimated 3,200 submissions x 24 hours = 76,800 hours).

For advertisements and promotional labeling, (e.g., circulars, package labels, container labels, etc.) and labeling changes, manufacturers of licensed biological products may submit to CBER or CDER Form FDA 2253, "*Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use*." 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. Form FDA 2253 can be submitted electronically. Form FDA 2253 is approved under OMB control number 0910-0001.

2. Purpose and Use of the Information Collection

The collection of information will be used by FDA to monitor industry procedures and discharge its statutory responsibility for protecting the nation's health. 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, applicants must submit to FDA advertising and promotional labeling. Manufacturers or applicants or 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 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 PMS reports to meet its reporting obligations under section 506B of the FD&C Act and section 130(b) of the Food and Drug Administration Modernization Act.

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 are utilizing electronic information systems technology. CBER and CDER currently accept 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. Effects to Identify Duplication and Use of Similar Information

We are unaware of duplicative information collection.

5. Impact on Small Businesses or Other Small Entities

This collection of information applies to small as well as large establishments. Although FDA must apply the statutory and regulatory requirements equally to all enterprises, the agency does provide special help to small businesses. The Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development, Division of Manufacturers Assistance and Training as well as other agency components provide 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 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, or an annual report. 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 July 11, 2016 (81 FR 44868). No comments were received from the public in response to the notice.

9. Explanation of Any Payment or Gift to the Respondents

No payment or gift is 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 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 information collection.

12. Estimates of Annalized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

We estimate the burden for this information collection as follows:

Table 1 – Estimated Annual Reported Burden

21 CFR Section	Form FDA No.	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Avg. Burden per Response	Total Hours[10]
601.2(a)[2], 610.60 through 610.65[3]	356h	28	1.36	38	860	32,680
601.5(a)	NA	12	0.75	9	0.33	3
601.6(a)	NA	1	1	1	0.33	1
601.12(a)(5)	NA	537	24.41	13,106	1	13,106
601.12(b)(1)/(b)(3)/(e)[4]	356h[2]	164	3.66	600	80	48,000
601.12(c)(1)/(c)(3)[5]	356h[2]	120	4.78	574	50	28,700
601.12(c)(5)	356h[2]	7	1.14	8	50	400
601.12(d)(1)/(d)(3)[6]/(f)(3)[8]	356h[2]	246	3.34	822	24	19,728
601.12(f)(1)[7]	2253	72	1.93	139	40	5,560
601.12(f)(2)[7]	2253	60	1.82	109	20	2,180
601.12(f)(4)/601.45[9]	2253	114	102.42	11,676	10	116,760
601.27(b)	NA	20	16.50	330	24	7,920
601.27(c)	NA	12	1.08	13	8	104
601.70(b) and (d)/601.28	2252	82	1.70	139	24	3,336
610.15(d)	NA	1	1	1	1	1
680.1(c)	NA	9	1	9	2	18
680.1(b)(3)(iv)	NA	1	1	1	2	2
Amendments/Resubmissions	356h	125	22.22	2,777	20	55,540
TOTAL						334,039

[1] The reporting requirements under §§ 601.14, 601.27(a), 601.33, 601.34, 601.35, 610.9(a) 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 §§ 601.93(b)(3), 640.74(b)(3) and (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.

[3] The reporting requirements under §§ 601.12(a)(2) and (b)(4), 600.15(b), 610.9(a), 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).

[4] The reporting requirements under §§ 601.12(a)(2), 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).

[5] The reporting requirement under § 601.12(a)(2) is included in the estimate under 601.12(D).

[6] The reporting requirement under § 601.14 is included in the estimate under § 601.12(f)(1) and (2).

[7] The reporting requirement under §§ 601.12(a)(4) and 601.14 is included in the estimate under 601.12(f)(3).

[8] The reporting requirement under §601.94 is included in the estimate under § 601.45.

[9] The reporting requirement under § 601.94 is included in the estimate under § 601.45.

[10] The numbers in this column have been rounded to the nearest whole number.

Table 2 – Estimated Annual Third-Party Disclosure Burden

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours[1]
601.6(a)	1	20	20	0.33 (20 minutes)	7

In tables 1 and 2, the numbers of respondents are 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 (FY) 2015. Based on information obtained from FDA's database systems, there are an estimated 391 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. In Table 1, FDA is estimating one in case a suspension occurs.

Under §§ 601.12(f)(4) and 601.45, manufacturers of biological products may use Form FDA 2253 to submit advertising and promotional labeling (which can include multiple pieces). Based on information obtained from FDA's database system, there were an estimated 11,676 submissions of advertising and promotional labeling using Form FDA 2253 from 114 manufacturers.

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 status 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). Form FDA 2252 is approved under OMB control number 0910-0001.

Under § 610.15(d), FDA has received no submissions since the implementation of the final rule in April 2011. Therefore, FDA is estimating one respondent and one annual request to account for a possible submission to CBER or CDER of a request for an exception or alternative for constituent materials under § 610.15(d).

Under §§ 600.15(b), 601.53(d), 606.110(b), and 640.120, the burden estimate is included in the estimate under § 601.12(b).

There were 2,777 amendments to an unapproved application or supplement, and resubmissions submitted using Form FDA 356h.

12b. Annualized Cost Burden Estimate

Activity	Total Burden Hours	Hourly Wage Rate	Total Cost
Reporting	333,949	$50	$16,697,450
Reporting/Disclosure	11	$80	$880

The cost estimate is based on a regulatory affairs specialist, at a wage rate of $50/hour, who would be responsible for filling out the form, and preparing an application, supplement, PMS report, or other similar submission. The cost estimate is also based on a medical director at a wage rate of $80/hour who would be responsible for preparing notification to FDA of discontinuance of a product(s) (3 hours), and notification to industry of a license suspension (1 notice of product discontinuance (1 hour) and 21 notices of license suspension with an average of 20 minutes per notification) (1 report to FDA and 20 notices of suspension to selling agents and distributors) (7 hours). The estimated average hourly pay rate includes benefits but no overhead costs.

13. Estimates of Other Total Annual Costs to Respondents and/or Record/keepers/Capital Costs

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 $18,035,100. 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 $121,194 that includes benefits but no overhead costs.

Activity	Number of FTEs	Average Annual Reviewer Salary	Total Cost
Application/Supplement Review	103	$124,380	$12,811,140
License Processing	36	$124,380	$4,477,680
Advertisement/Promotional Labeling	5	$124,380	$621,900
Review PMS Report	1	$124,380	$124,380
Total			$18,035,100

15. Explanation for Program Changes or Adjustments

The information collection reflects nominal adjustments. We attribute these to normal variations associated with industry submissions. These fluctuations have resulted in an overall decrease to the collection of 1,568 responses and 9,286. Also, we have removed 21 CFR 601.25 (§ 601.25(b)) and 601.26 (§ 601.26(f)) (February 12; 2016, 81 FR 7445); 21 CFR 610.11 (§ 610.11(g)(2)) (July 2, 2015; 80 FR 37971) from the Code of Federal Regulations. While there were minimal burden hours associated with these regulations removing the ICs resulted in an additional reduction of 21 responses and 8 hours.

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

There are no exceptions to the certification.