



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-0578]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; General Licensing Provisions: Biologics License Application, Changes to an Approved Application, Labeling, Revocation and Suspension, Postmarketing Studies Status Reports, and Form FDA 356h

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or we) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, Fax: 202-395-7285, or emailed to oir_submission@omb.eop.gov. All comments should be identified with the OMB control number 0910-0338. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

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 Number 0910-0338--Extension

Under section 351 of the Public Health Services 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 (Pub. L. 105-115) amended the Federal Food, Drug, and Cosmetic Act (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 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 postmarketing studies 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 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.

A summary of the collection of information requirements follows:

Section 601.2(a) (21 CFR 601.2(a)) requires a manufacturer of a biological product to submit an application on forms prescribed for such purposes with accompanying data and 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 610.65 (21 CFR 610.60 through 610.65). The estimate for these regulations is included in the estimate under § 601.2(a) in table 1.

Section 601.5(a) (21 CFR 601.5(a)) requires a manufacturer to submit to FDA notice of its intention to discontinue manufacture of a product or all products. Section 601.6(a) (21 CFR 601.6(a)) requires the manufacturer to notify selling agents and distributors upon suspension of its license, and provide FDA of such notification.

Section 601.12(a)(2) (21 CFR 601.12(a)(2)) requires, generally, that the holder of an approved biologics license application (BLA) must assess the effects of a manufacturing change before distributing a biological product made with the change. Section 601.12(a)(4) requires, generally, that the applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling changes implemented. Section 601.12(a)(5) 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. The burden estimates for §

601.12(a)(2) are included in the estimates for supplements (§§ 601.12(b) and (c)) and annual reports (§ 601.12(d)). The burden estimates for § 601.12(a)(4) are included in the estimates under 601.12(f)(4) in table 1.

Sections 601.12(b)(1) and (3), (c)(1), (3), and (5), and (d)(1) and (3) 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. Under § 601.12(b)(4), 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. The burden estimate for § 601.12(b)(4) is minimal and included in the estimate under § 601.12(b)(1) and (3) in table 1.

Section 601.12(e) requires applicants to submit a protocol, or change to a protocol, as a supplement requiring FDA approval before distributing the product. Section 601.12(f)(1) through (3) requires applicants to follow specific procedures to report certain labeling changes to FDA. Section 601.12(f)(4) requires applicants to report to FDA advertising and promotional labeling and any changes.

Under § 601.14 (21 CFR 601.14), 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. This requirement is in addition to the provisions of §§ 601.2(a) and 601.12(f). The burden estimate for § 601.14 is minimal and included in the estimate under §§ 601.2(a) (BLAs) and 601.12(f)(1) through (3) (labeling supplements and annual reports) in table 1.

Section 601.45 (21 CFR 601.45) requires applicants of biological products for serious or life-threatening illnesses to submit to the Agency for consideration, during the preapproval review period, copies of all promotional materials, including promotional labeling as well as advertisements.

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) (21 CFR 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 table 1, 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 paragraph 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 (4) for Source Plasma Liquid; § 640.84(a) and (c) (21 CFR 640.84(a) and (c)) for Albumin; § 640.94(a) (21 CFR 640.94(a)) for Plasma Protein Fraction; § 660.2(c) (21 CFR 660.2(c)) for Antibody to Hepatitis B Surface Antigen; § 660.28(a) through (c) (21 CFR 660.28(a) through (c)) for Blood Grouping Reagent; § 660.35(a) through (d) (21 CFR 660.35(a) through (d)) for Reagent Red Blood Cells; § 660.45 (21 CFR 660.45) for Hepatitis B Surface Antigen; and § 660.55(a) and (b) (21 CFR 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. The burden estimates associated with § 809.10 are approved under OMB control number 0910-0485.

Section 601.27(a) (21 CFR 601.27(a)) 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. Section 601.27(b) 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. Section 601.27(c) provides that an applicant may request a full or partial waiver of the requirements under § 601.27(a) with adequate justification. The burden estimates for § 601.27(a) are included in the burden estimate under § 601.2(a) in table 1 because these regulations deal with information to be provided in an application.

Section 601.28 (21 CFR 601.28) requires sponsors of licensed biological products to submit the information in § 601.28(a) through (c) to the Center for Biologics Evaluation and Research (CBER) or to the Center for Drug Evaluation and Research (CDER) each year, within 60 days of the anniversary date of approval of the license. Section 601.28(a) 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. Section 601.28(b) 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. Section 601.28(c) 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. If the postmarketing studies were required or agreed to, the status of these studies is to be reported under § 601.70 (21 CFR 601.70) rather than under this section.

Sections 601.33 through 601.35 (21 CFR 601.33 through 601.35) clarify the information 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. The burden estimates for §§ 601.33 through 601.35 are included in the burden estimate under § 601.2(a) in table 1 because these regulations deal with information to be provided in an application.

Section 601.70(b) 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 (Form FDA 2252 approved under OMB control number 0910-0001). Under § 601.70(d), two copies of the annual report shall be submitted to FDA.

Sections 601.91 through 601.94 (21 CFR 601.91 through 601.94) concern biological products for which human efficacy studies are not ethical or feasible. Section 601.91(b)(2) requires, in certain circumstances, such postmarketing restrictions as are needed to ensure the safe use of the biological product. Section 601.91(b)(3) requires applicants to prepare and provide labeling with relevant information to patients 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 in animals). Section 601.93 provides that biological products approved under part 601, subpart H are subject to the postmarketing

recordkeeping and safety reporting applicable to all approved biological products. Section 601.94 requires applicants under part 601, subpart H to submit to the Agency for consideration during the preapproval review period copies of all promotional materials including promotional labeling as well as advertisements. 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 (OMB control number 0910-0308). Therefore, any burdens associated with these requirements would be reported under the AER information collection requirements (OMB control number 0910-0308). The burden estimate for § 601.91(b)(3) is included in the estimate under §§ 610.60 through 610.65.

Section 610.9(a) (21 CFR 610.9(a)) 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 under which it is conducted under the biologics regulations. The burden estimate for § 610.9(a) is included in the estimate under §§ 601.2(a) and 601.12(b) and (c) in table 1.

Under § 610.15(d) (21 CFR 610.15(d)), the Director of CBER or the Director of 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.

Section 640.120 (21 CFR 640.120) 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. For licensed establishments, a request for an exception or

alternative must be submitted in accordance with § 601.12; therefore, the burden estimate for § 640.120 is included in the estimate under § 601.12(b) in table 1.

Section 680.1(c) requires manufacturers to update annually their license file with the list of source materials and the suppliers of the materials. Section 680.1(b)(3)(iv) requires manufacturers to notify FDA when certain diseases are detected in source materials.

Sections 600.15(b) and 610.53(b) (21 CFR 600.15(b) and 610.53(b)) require 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. Section 606.110(b) (21 CFR 606.110(b)) 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. Under §§ 600.15(b), 610.53(b), and 606.110(b), a request for an exemption or modification to the requirements would be submitted as a supplement. Therefore, the burden hours for any submissions under §§ 600.15(b), 610.53(d), and 606.110(b) are included in the estimates under § 601.12(b) in table 1.

Form FDA 356h, "Application to Market a New or Abbreviated New Drug or Biologic for Human Use," is used for the applicable submissions to both CBER and CDER. The application form serves primarily as a checklist for firms to gather and submit certain information to FDA and 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. FDA estimates an average of 24 hours to complete the application form, which is included in the average burden per response. The estimated burden hours for

nonbiological product submissions to CDER using Form FDA 356h are approved under OMB control number 0910-0001 (an estimated 16,650 submissions × 24 hours = 399,600 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. Form FDA 2253 can also be submitted electronically. Form FDA 2253 is approved under OMB control number 0910-0001.

Respondents to this collection of information are manufacturers of biological products. Under table 1, 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 2018. Based on information obtained from FDA's database systems, there are an estimated 424 licensed biologics manufacturers. The total annual responses are based on the estimated number of submissions (i.e., 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 section 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, the estimate is based on the number of submissions received using Form FDA 2253 for advertising and promotional labeling.

Under §§ 601.28 and 601.70(b), FDA estimates that it takes an applicant approximately 24 hours (8 hours per study × 3 studies) annually to gather, complete, and submit the appropriate information for each postmarketing status report (approximately 2 to 4 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 § 610.15(d), FDA has received no submissions since the implementation of the final rule ("Revision of the Requirements for Constituent Materials") in April 2011 (76 FR 20513, April 13, 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).

There were a total of 3,398 amendments to an unapproved application or supplement and resubmissions submitted using Form FDA 356h.

In the *Federal Register* of September 19, 2019 (84 FR 49310), we published a 60-day notice requesting public comment on the proposed collection of information. No comments were received.

We estimate the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden¹

21 CFR Section	Form FDA No.	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours ¹⁰
601.2(a) ² , 610.60 through 610.65 ³	356h	36	1.28	46	860	39,560
601.5(a)	NA	8	1.13	9	0.33 (20 minutes)	3
601.6(a)	NA	1	1	1	0.33 (20 minutes)	1
601.12(a)(5)	NA	430	4.158	1,788	1	1,788
601.12(b)(1) and (3) and (e) ⁴	356h ²	166	4.843	804	80	64,320
601.12(c)(1) and (3) ⁵	356h ²	149	4.58	682	50	34,100
601.12(c)(5)	356h ²	7	1.14	8	50	400
601.12(d)(1) and (3) ⁶ and (f)(3) ⁸	356h ²	245	3.575	876	24	21,024
601.12(f)(1) ⁷	2253	65	3.169	206	40	8,240
601.12(f)(2) ⁷	2253	43	2.05	88	20	1,760
601.12(f)(4)/601.45 ⁹	2253	134	145.86	19,545	10	195,450
601.27(b)	NA	12	1.08	13	24	312
601.27(c)	NA	2	1	2	8	16
601.70(b) and (d)/601.28	2252	65	3.169	206	24	4,944
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	136	24.985	3,398	20	67,960
Total						439,899

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

²The reporting requirements under §§ 601.14, 601.27(a), 601.33, 601.34, 601.35, 610.9(a), 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).

³The 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) through (c), 660.35(a) through (d), 660.45, and 660.55(a) and (b) are included under §§ 610.60 through 610.65.

⁴The reporting requirements under §§ 601.12(a)(2) and (b)(4), 600.15(b), 610.9(a), 610.53(b), 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).

⁵The 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).

⁶The reporting requirement under § 601.12(a)(2) is included in the estimate under § 601.12(d).

⁷The reporting requirement under § 601.14 is included in the estimate under § 601.12(f)(1) and (2).

⁸The reporting requirement under §§ 601.12(a)(4) and 601.14 is included in the estimate under § 601.12(f)(3).

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

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

Table 2.--Estimated Annual Third-Party Disclosure Burden¹

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours ²
601.6(a)	1	20	20	0.33 (20 minutes)	7

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

²The number in this column has been rounded to the nearest whole number.

Our estimated burden for the information collection reflects an overall increase of 105,948 hours and a corresponding decrease of 2,671 responses. We attribute this adjustment in the total hours to an increase in the number of submissions we have received under §§ 601.12(b)(1) and (3), (e), and (f)(4), and 601.45 over the last few years. We attribute the decrease in total annual responses to a decrease in responses received under §§ 601.12(a)(5) and 601.27(b) over the last few years.

Dated: January 8, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

[FR Doc. 2020-00729 Filed: 1/16/2020 8:45 am; Publication Date: 1/17/2020]