

OMB INFORMATION COLLECTION
SUPPORTING STATEMENT

Biological Products Regulated Under Section 351 of the Public Health Services Act;
Implementation of Biologics License; Elimination of Establishment License and Product License
FINAL RULE

JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) is requesting OMB approval of the information collection requirements contained in 21 CFR 601.2 and other regulations listed below (Tab A).

21 CFR 601.2 -- Reporting: Requires a manufacturer of a biological product to submit an application with accompanying information to the Center for Biologics Evaluations and Research, FDA, for approval to market the product in interstate commerce.

21 CFR 600.15(b) -- Reporting: Requires submission of a request for an exemption or modification regarding the temperature requirements during shipment for certain biological products.

21 CFR 610.53(d) -- Reporting: Requires submission of a request for an exemption or modification regarding dating periods for certain biological products.

21 CFR 640.6 -- Reporting: Requires that an applicant submit a request to make a certain modification of Whole Blood.

21 CFR 601.5(a) -- Reporting: Requires a licensee to give notice of its intention to discontinue manufacture of a product or all products.

21 CFR 601.6(a) -- Reporting: Requires the licensee to notify selling agents and distributors upon suspension of its license. In addition, the licensee is to provide FDA with the records of such notification.

21 CFR 601.26(f) -- Reporting: Requests that licensees submit to the Commissioner a written statement intended to show that studies adequate and appropriate to resolve questions raised about a biological product have been undertaken for the product if designated as requiring further study under the reclassification procedures.

In addition to the requirements in 21 CFR 601.2, there are regulations in 21 CFR part 640 (Tab A) that require additional standards relating to certain information submitted in a license application including §§ 640.21(c), 640.22(c), 640.65(a), and 660.21(a)(3) and (d). The information collection burden for these regulations is included in the burden estimate for 21 CFR 601.2, as described in section 12.

In accordance with section 123 of the Food and Drug Administration Modernization Act of 1997

(P.L. 105-115)(Tab B) and the President's "Reinventing Government" initiatives, FDA is amending the regulations regarding the application for approval to market a biological product regulated under Section 351 of the PHS Act (42 U.S.C. 262 et seq.) (Tab C). Currently, most manufacturers must submit an establishment license application (ELA) and a product license application (PLA) when requesting approval to market a biological product in interstate commerce. Under the final regulations, a manufacturer will submit to FDA the appropriate establishment and product information in a single Biologics License Application (BLA) in lieu of filing a separate ELA and PLA. Upon approval of the BLA, a manufacturer will receive a single biologics license to market the product in interstate commerce.

Manufacturers of certain biological products are already required to submit a BLA and obtain FDA approval of the BLA before the product may be introduced into interstate commerce. In the **Federal Register** of May 14, 1996 (61 FR 24227)(Tab D), FDA issued a final rule to amend the biologics regulations by eliminating the ELA requirement for specified biotechnology and synthetic biological products licensed under section 351 of the PHS Act. An interim form was also made available (61 FR 24313, May 14, 1996)(Tab D) for use by manufacturers of these biological products. These actions were part of the President's "Reinventing Government" initiative to harmonize regulations administered by the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER), to reduce unnecessary burdens on industry without diminishing public health.

In the **Federal Register** of July 8, 1997 (62 FR 36558)(Tab E), FDA announced the availability of a revised FDA Form 356h (0910-0338). FDA Form 356h was revised as part of FDA continuing effort to achieve the objectives of the President's "Reinventing Government" initiative to harmonize application procedures with the Center for Drug Evaluation and Research (CDER) as outlined in the President's November 1995 National Performance Review Report, "Reinventing the Regulation of Drugs Made From Biotechnology" (Tab F). FDA intended that applicants for biologics licenses for products specified in 601.2(c) as well as autologous somatic cell therapy products could begin to use FDA Form 356h immediately and were required to do so beginning January 8, 1998. The revised form replaced the interim form and, when fully implemented, the revised form will replace the many different ELAs and PLAs currently in use. FDA intends to advise applicants for licenses for other biological products when they can voluntarily begin and will be required to use FDA Form 356h.

With the consolidation of the establishment and product license applications into a single biologics license application, the amount of information formerly included in the establishment license application will be reduced but not eliminated. Much of the information previously reviewed in an ELA at FDA will be reviewed by FDA investigators at the manufacturing site during a preapproval inspection. Some information formerly included in the ELA will now be submitted as "chemistry, manufacturing, and controls" (CMC) information or under the "establishment description" section of FDA Form 356h. The type and amount of information related to the establishment will vary according to the specific biological product for which licensure is being requested. To describe what information should be included for each type of biological product, CBER has prepared a series of

guidance documents. The following final documents are available: (1) “Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use” (61 FR 56243, October 31, 1996); (2) “Guidance for the Submission of Chemistry, Manufacturing, and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products” (62 FR 1460, January 10, 1997); (3) “Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls Information for Synthetic Peptide Substances” (issued on the internet, November 1994); (4) “Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls and Establishment Description Information for a Vaccine or Related Product (63 FR 518, January 5, 1999) and (5) “Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Product or Animal Plasma or Serum-Derived Products” (64 FR 7896, February 17, 1999); (6) “Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls and Establishment Description Information for a Biological In Vitro Diagnostic Product” (64 FR 11023, March 8, 1999); (7) “Guidance for Industry: On the Content and Format of Chemistry, Manufacturing and Controls and Establishment Description Information for Allergenic Extract or Allergen Patch Test (64 FR 20006; April 23, 1999); and (8) “Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the FDA Form 356h ‘Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use (64 FR 25049; May 10, 1999).’” (All guidance documents, Tab H).

In the **Federal Register** of July 31, 1998 (63 FR 40858)(Attachment G), FDA published the proposed rule to implement section 122 of FDAMA. The information collection package for the proposed rule was submitted for approval to OMB on 7/22/98. The package was not approved by OMB citing concerns regarding the burden of this collection. OMB stated that the burden should be assessed in light of public comments received in response to the proposed rule. FDA received one letter of comment on the information collection provisions of the proposed rule. Comments in response to the proposed rule are discussed in Section 8 of this supporting statement.

2. Purpose and Use of the Information

FDA has the responsibility to ensure the safety, purity, potency, and effectiveness of biological products. The PHS Act and FDA regulations require manufacturers to submit a license application for review and approval prior to marketing a biological product in interstate commerce. In addition, manufacturers are required to submit changes to an approved application. The information submitted to FDA in a biologics license application or supplement to an approved application is used to determine if a product is safe, pure, potent, and effective. If a license application is approved by FDA, a single biologics license will be issued to the manufacturer for that product.

3. Use of 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, the Center for Biologics Evaluation and Research (CBER) is utilizing electronic information systems technology. CBER currently accepts "Computer Assisted Product License Applications" (CAPLA's). CBER intends to continue this trend by accepting electronic biologics license applications and plans to issue guidance to assist manufacturers in this area (e.g., Draft Guidance for Industry: Electronic Submissions of a Biologics License Application (BLA) or Product License Application (PLA)/Establishment License Application (ELA) to the Center for Biologics Evaluation and Research (6/1/98; 63 FR 29741)). 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. Efforts to Identify Duplication and Use of Similar Information

FDA is the only agency that requires the filing of an application for the marketing of biological products for human use. No other component of the agency or other government agencies require similar information or data to be filed. This information is not available from any other source.

5. Impact on Small Businesses or Other Entities

FDA believes that its duty requires the equal application of the regulations to all enterprises. While FDA does not believe it can apply different standards with respect to statutory requirements, FDA does provide special help to small businesses. The Center for Biologics Evaluation and Research, Office of Communication, Training, and Manufacturer's Assistance provides assistance to small businesses subject to FDA's regulatory requirements.

6. Consequences of Collecting the Information Less Frequently

Manufacturers submit applications for approval of biological products only prior to marketing such products in interstate commerce. In addition, manufacturers are required to submit changes to an approved application. Less frequent collection of information will not provide the necessary information needed by FDA to properly evaluate the safety, purity, potency, and effectiveness of a biological product.

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

7. Special Circumstances Relating to the Guideline of 5 CFR 1320.5

An applicant may be required to submit to FDA proprietary trade secret or other confidential information when submitting a biologics license application. FDA has instituted security measures to protect confidential information received from manufacturers and will, to the extent permitted by law, protect the information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In the Federal Register of July 31, 1998 (63 FR 40858), FDA published the proposed rule and provided a 30-day notice requesting comments from the public on the information collection provisions. FDA received one letter of comment on these provisions.

A comment pointed out that few new BLAs for blood and blood components will be submitted to the agency. More frequently, changes to already approved applications are submitted as supplements. These supplements will now use the FDA Form 356h for submission to the agency. The comment stated if FDA Form 356h is merely substituted for the current forms and manufacturers must continue to file a supplement for each product at each location, the paperwork will actually increase because of the increased CMC and establishment requirements.

FDA agrees that few new BLAs for blood and blood components are submitted to the agency. However, FDA disagrees that the burden will increase. Previously, manufacturers desiring to make a single manufacturing change that would affect multiple products were required to submit a supplement to each individual product and establishment application. Under this final rule a manufacturer would only need to submit one supplement to the BLA. For example, under the current PLA/ELA system, if a manufacturer desired to make a single change to the irradiation procedure for its Whole Blood, Red Blood Cells, Platelets, and Plasma products manufactured at 3 locations, the manufacturer would be required to submit 12 supplements to 4 PLA's. Under the proposed BLA system, the manufacturer would only be required to submit one supplement to the BLA describing the change for all of the products and locations involved. Therefore, fewer supplements should be submitted by applicants. The size of the decrease in supplements will depend on how the applicant bundles the submissions. At the time of submission of a supplement, FDA expects that all data and information pertinent to the supplement be present or FDA may refuse to file the application (see Center for Biologics Evaluation and Research (CBER):Refusal to File (RTF) Guidance for Product License Applications (PLAs) and Establishment License Applications (ELAs) (58 FR 58770; 7/20/93)). Therefore, if an applicant wishes to submit a change affecting multiple locations in one supplement, and all data and information supporting the change at those locations are present in the supplement, FDA will accept such a submission. FDA, therefore, estimates that there will be an overall reduction in burden associated with this final rule. Another comment stated that the number of respondents and supplement submissions, and the hours per submission were severely underestimated by FDA. The comment expressed concern that FDA was unable to specifically enumerate the number of submissions made under §640.6 and suggested that this was "indicative of a larger problem." The comment described FDA's approach to burden estimates as disturbing for other reasons such as not addressing supplements for products other than Whole Blood, and because the agency's internal tracking, accounting and documentation systems may be inadequate. The comment stated that FDA had trouble distinguishing between supplemental license applications submitted under §§ 640.6 and 601.12. For the purposes of burden hour development, the distinction between supplements submitted under § 640.6 and those under § 601.12 is somewhat artificial because the burden for the regulated community to prepare the supplement is identical regardless of the section under which such information is submitted.

The comment has misinterpreted the estimate. In preparing this burden estimate, FDA estimated the burden for those sections of the regulations being amended, including § 640.6. No changes in § 601.12 were included in this rulemaking, therefore FDA has not estimated the burden of this subsection which already has an approved OMB collection of information number (0910-0315). The burden associated with the preparation of supplemental applications is also included in the estimate for §601.12 and is outside the scope of this rule. Since §640.6 applies specifically to Whole Blood, an estimate below is limited to only Whole Blood submissions and the associated reporting burden hours. The number of respondents reflects the number of fiscal year 1997 supplements submitted specifically for Whole Blood, and the 8 hours is an accurate estimate for this type of submission. For purposes of carrying out its obligations for the review of applications, FDA continues to believe that it is unnecessary to keep separate track of those applications submitted under §640.6. Because FDA’s current tracking system does not allow a search of the database which would identify accurately the number of Whole Blood supplements submitted pursuant to §640.6, FDA looked at the number of all supplements related only to Whole Blood (which is the scope of this regulation) and conservatively estimated the burden to account for more rather than fewer burden hours. Therefore, the estimated burden hours are likely to be higher than those that may actually occur.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift was 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 and the agency’s regulations under 21 CFR Part 20. Manufacturers seeking to market a biological product in interstate commerce may be required to include proprietary or trade information in a license application submitted for FDA approval. However, such proprietary or trade information is deleted from any information released by FDA under the Freedom of Information Act and FDA regulations.

11. Justification for Sensitive Questions

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

12. Estimate of Hour Burden Including Annualized Hourly Costs

The estimated annual burden for this information collection is **96,626** hours.

Estimated Annual Reporting Burden

21 CFR Section	No. of Respondents	Annual Frequency	Total Annual	Hours per Response	Total Hours
----------------	--------------------	------------------	--------------	--------------------	-------------

		per Response	Responses		
601.2	60	1	60	1,600	96,000
600.15(b)	1	1	1	8	8
601.5(a)	33	1	33	.33	11
601.6(a)	2	11	21	.33	7
610.53(d)	1	1	1	8	8
640.6	74	1	74	8	592

The final rule amends the regulations for filing an application to market a biological product under section 601.2 (21 CFR 601.2) to eliminate references to establishment licenses and product licenses for all products regulated under the Public Health Service Act. The final rule will require biologics manufacturers to file a single BLA, rather than either an ELA or PLA, to market a biological product. The agency estimates that the total paperwork burden for manufacturers filing one application that consolidates the information currently required under both the PLA and ELA will net a decrease of approximately 10%. The estimate reduces the number of annual responses from a combined PLA/BLA/ELA total of 76 to a BLA total of 60. This estimate is derived from the total number of license applications received by FDA in fiscal year 1997 (76) minus the total number of ELAs filed in the same period (17). Based on information provided by industry, the time estimated to prepare an application for FDA approval to market a product is approximately 1,600 hours. In addition to §601.2, there are other regulations included in the final rule that relate to certain information to be included in a license application including §§ 640.21(c), 640.22(c), 640.65(a), and 660.21(a)(3) and (d). The information collection requirements in the preceding regulations are included in the burden estimate below for § 601.2.

The final regulation also makes several technical amendments to conform the language throughout the biological product regulations to the changes for section 601.2. Specifically, the final rule makes the following technical term changes: references to product and establishment license, and product and establishment applications are replaced with “biologics license” or “biologics license application;” and “licensee” is replaced with “licensed manufacturer.” These technical changes impact neither the substantive requirements nor the paperwork burden of these regulations, each of which carry separate OMB clearance numbers as follows: §§ 207.20(c) and 207.21(a) (0910-0045); 600.80(c)(2) (0910-0308); 601.25(b)(3) (0910-0039); 607.20(b) and 607.21(0910-0052); 610.63 and 640.71(b)(1) (0910-0116).

The following regulations relate to the submission of additional information in a supplement to a biologics license application. Sections 600.15(b) and 610.53(d) require submission of a request for an exemption or modification regarding the temperature requirements during shipment and from dating periods, respectively, for certain biological products. The preparation of an exemption

request is estimated to be 8 hours; however, no requests were received by the agency under either regulations in fiscal year 1997. To account for the rare instance in which a request for an exemption may be made, the agency has estimated one respondent per year in the chart below. Section 640.6 requires that an applicant submit a request to make a certain modification of Whole Blood. The number of any supplement relating to Whole Blood filed by an applicant in fiscal year 1997 totaled 74. Because the agency could not determine the number of supplements filed specific to section 640.6, the estimate below is based on last year's total number of supplements related to Whole Blood.

The remaining regulations, sections 640.21(c), 640.22(c), 640.64(c), and 640.74(a) and (b)(2), refer to information that is collected pursuant to section 601.12, under which the collection of information burden is calculated. Moreover, the final rule will make only technical changes to these regulations. For example, the term "product license" is changed to "biologics licence, and the term "product licensee" is changed to "licensed manufacturer."

In addition, section 601.5(a) requires a licensee to give notice of its intention to discontinue manufacture of a product or all products. Upon such notice, FDA would revoke the license or licenses. In fiscal year 1999, an estimated 33 manufacturers submitted notice to discontinue either its establishment and/or products licenses. FDA estimates 20 minutes to prepare a letter of discontinuance. Section 601.6(a) requires the licensee to notify selling agents and distributors upon suspension of its license. In addition, the licensee is to provide FDA with the records of such notification. In fiscal year 1998/1999, FDA suspended 3 establishments licenses and is estimating 2 suspensions annually. FDA estimates that establishments would need to notify an average of 20 selling agents and distributors of such suspension, and estimates 20 minutes to prepare a notification letter and submit record of notification to FDA. Section 601.26(f) requests that licensees submit to the Commissioner a written statement intended to show that studies adequate and appropriate to resolve questions raised about a biological product have been undertaken for the product if designated as requiring further study under the reclassification procedures. There are no products that fall under this requirement and none are predicted in the future, therefore, FDA estimates no burden for this regulation.

Cost to Respondents

The estimated annual cost to respondents is **\$3,010,312.**

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting	96,000	\$31.15	\$2,990,400
Reporting	608	\$31.15	\$18,940
Reporting	18	\$54.00	\$ 972

FDA estimates that it should require an average of 1,600 hours of staff time per applicant to prepare and submit the required application information. FDA estimates that 60 license applications will be submitted annually. FDA estimates approximately 76 supplements to an approved application will be submitted annually with an average of 8 hours of staff time to prepare and submit the supplement. The cost estimate is based on a regulatory affairs specialist, at a pay rate of \$31.15/hour, who would be responsible for preparing the application or supplement.

In addition, FDA estimates approximately 33 notices of product(s) discontinuance and 21 notices of license suspension with an average of 20 minutes per notification. The cost estimate is based on a medical director at a pay rate of \$54.00/hour who would be responsible for the preparing notification to FDA of discontinuance of a product(s), and notification to industry of license suspension.

13. Estimate of Other Total Annual Cost Burden to Respondents or Recordkeepers

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

14. Annualized Cost to the Federal Government

The estimated annualized cost to the Federal Government is **\$14,612,130**. This estimate is based on full-time equivalents (FTEs) associated with the review of applications and supplemental applications and the average annual salaries for CBER reviewers.

The amount of time and expense incurred by the Federal government is due to the review of all material submitted with an application. 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 FTE’s associated with the processing of license revocations and suspensions, and the average annual salaries for CBER reviewers.**

Activity	Number of FTEs	Average Annual Reviewer Salary	Total Cost
Application Review	168	\$65,160.00	\$10,946,880
License Processing	7.5	\$65,160.00	\$ 3,655,250

15. Explanation of Program Changes or Adjustments

Changes in burdens is not applicable as this is the first submission for the final rule.

Page 10 - BLA

16. Plans for Tabulation and Publication and Program Time Schedule

There are no tabulated results for this information collection.

17. Reason(s) Display of 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 Submission

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