

Adverse Experience Reporting for Licensed Biological Products;
and General Records

0910-0308

SUPPORTING STATEMENT

Terms of Clearance: None.

A. Justification

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) is requesting an extension of Office of Management and Budget (OMB) Control No. 0910-0308 and OMB approval of the information collection requirements listed below:

21 CFR 600.80(c)(1)	Reporting	Requires licensed manufacturers or any person whose name appears on the label of a licensed biological product to report each adverse experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the licensed manufacturer (postmarketing 15-day Alert reports). Also requires licensed manufacturers to submit any follow-up reports within 15 calendar days of receipt of new information or as requested by FDA, and if additional information is not obtainable to maintain records of the unsuccessful steps taken to seek additional information. In addition, requires a person who submits an adverse action report to the licensed manufacturer, rather than FDA, to maintain a record of this action.
21 CFR 600.80(c)(2)	Reporting	Requires licensed manufacturers to report each adverse experience not reported in a postmarketing 15-day Alert report (21 CFR 600.80(c)(1)(i)) at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals.

21 CFR 600.80(e)	Reporting	Requires licensed manufacturers to submit a 15-day Alert report for an adverse experience obtained from a postmarketing clinical study only if the licensed manufacturer concludes that there is a reasonable possibility that the product caused the adverse experience.
21 CFR 600.81	Reporting	Requires licensed manufacturers to submit, at an interval of every 6 months, information about the quantity of the product distributed under the biologics license, including the quantity distributed to distributors.
21 CFR 600.90	Reporting	Licensed manufacturers may submit a waiver request for any requirement that applies to the licensed manufacturer under §§ 600.80 and 600.81. A waiver request must include supporting documentation.
21 CFR 600.12(a), (b) (1), (c), (d) & (e)	Recordkeeping	Requires, among other things, that records must be made concurrently with the performance of each step in the manufacture and distribution of a product and be retained for no less than 5 years after the records of manufacture have been completed or 6 months after the latest expiration date for the individual products, whichever represents a later date. In addition, manufacturers must maintain records relating to the sterilization of equipment and supplies, animal necropsy records, and records in cases of divided manufacturing responsibility with respect to a product.
21 CFR 600.12(b)(2)	Recordkeeping	Requires manufacturers to maintain complete records pertaining to the recall from distribution of any product.
21 CFR 600.80(i)	Recordkeeping	Requires licensed manufacturers to maintain for a period of 10 years records of all adverse experiences known to the licensed manufacturer, including raw data and any correspondence relating to the adverse experiences.
21 CFR 610.18(b)	Recordkeeping	Requires, in part, that the results of all periodic tests for verification of cultures and determination of freedom from extraneous organisms be recorded and maintained.

Under the Public Health Service (PHS) Act (42 U.S.C. 262), FDA may only approve a biologics license application for a biological product that is safe, pure, and potent. When a biological product is approved and enters the market, the product is introduced to a larger patient population in settings different from clinical trials. New information generated during the postmarketing period offers further insight into the benefits and risks of the product, and evaluation of this information is important to ensure its safe use. FDA issued the adverse experience reporting (AER) requirements in

21 CFR Part 600 to enable FDA to take actions necessary for the protection of the public health in response to reports of adverse experiences related to licensed biological products¹. The primary purpose of FDA's AER system is to identify potentially serious safety problems with licensed biological products, focusing especially on newly licensed products. Although the premarket approval process is meant to disclose a general safety profile of a biological product's comparatively common adverse effects, the larger and more diverse patient populations exposed to the licensed biological product provides the opportunity to collect information on rare, latent, and long-term effects. In addition, production and/or distribution problems have contaminated biological products in the past. AER reports are obtained from a variety of sources, including manufacturers, patients, physicians, foreign regulatory agencies, and clinical investigators. Identification of new and unexpected safety issues through the analysis of the data in the AER system contributes directly to increased public health protection. For example, evaluation of these safety issues enables FDA to take focused regulatory action. Such action may include, but is not limited to, important changes in the product's labeling (such as adding a new warning), coordination with manufacturers to ensure adequate corrective action is taken, and removal of a biological product from the market when necessary.

AER reports are filed using the MEDWATCH Form FDA-3500A (approved under OMB No.0910-0291) or the Vaccine Adverse Experience Reporting System Form (VAERS-1). Section 321 of the National Childhood Vaccine Injury Act (NCVIA, Public Law 99-660) specifically addresses the waiver of paperwork reduction in the implementation of this statute. Under § 600.80(f)(3), a manufacturer may also use an alternative report form provided the format is equivalent to all elements of information specified in the designated forms and the format is pre-approved by MEDWATCH or FDA.

The general recordkeeping provisions under 21 CFR 600.12 require manufacturers of licensed biological products for human use to maintain records of each step in the manufacture and distribution of products. These requirements provide FDA with the necessary information to help ensure the safety, purity, and potency of biological products. The recordkeeping requirements for §§ 610.12(g), 610.13(a)(2), 610.18(d), 680.2(f) and 680.3(f) are approved under OMB Control No. 0910-0139.

2. Purpose and Use of the Information Collection

The primary purpose of FDA's AER system is to identify potentially serious safety problems with licensed biological products, focusing especially on newly licensed products. Although premarket testing discloses a general safety profile of a new drug's comparatively common adverse effects, the larger and more diverse patient populations exposed to the licensed biological product provides, for the first time, the opportunity to collect information on rare, latent, and long-term effects. AER reports are obtained from a variety of sources, including manufacturers, patients, physicians, foreign regulatory agencies, and clinical investigators. Identification of new and unexpected safety issues through the analysis of the data in the AERS system contributes directly to increased public health protection. For example, evaluation of these safety issues enables FDA to take focused regulatory action. Such action may include, but not be limited to important changes in the product's labeling (such as adding a new warning), coordination with manufacturers to ensure adequate corrective action is taken, and removal of a biological product from the market where necessary.

¹ Please note that throughout the regulations referenced in relation to these information collections, licensed biological products refers to biologics licensed under any provision of section 351 of the PHS Act (42 U.S.C 262).

The semiannual distribution reports provide FDA with important information about products distributed under biologics licenses, including the quantity, certain lot numbers, labeled date of expiration, the fill lot numbers for the total number of dosage units of each strength or potency distributed (e.g., 50,000 per 10-milliliter vials), and date of release. This allows FDA to estimate more accurately the incidence of a product's adverse effects in relation to the volume of the product distributed.

The recordkeeping requirements serve preventative and remedial purposes by establishing accountability and traceability in the manufacture and distribution of products. These requirements also enable FDA to perform meaningful inspections. Without this information, FDA could not monitor industry procedures and discharge its statutory responsibility for protecting the nation's health.

3. Use of Improved Information Technology and Burden Reduction

Most of the information required under the AER regulations is submitted using FDA Form 3500A or VAERS-1. Both versions of the forms and instructions are available on the Internet. This information can be submitted electronically through MEDWATCH or VAERS. The forms can also be downloaded so that computers can be used to fill out and print the report, which can then be mailed or faxed to the agency.

Licensed manufacturers may use computers, discs, tapes, microfiche or microfilm in lieu of hard copy records for the purpose of maintaining records. Computers may be used for filing distribution records. 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 this information. The required information is not available from any other source.

5. Impact on Small Businesses or Other Small Entities

This collection of information applies to both small as well as large establishment. Although FDA must apply the statutory and regulatory requirements to all enterprises, FDA does provide special help to small businesses. The Center for Biologics Evaluation and Research (CBER), Office of Communications, Outreach, and Development, Division of Manufacturer's Assistance and Training, and the Center for Drug Evaluation and Research (CDER), Office of Communication, Division of Drug Information provides assistance to small businesses concerning FDA's regulatory requirements.

6. Consequences of Collecting the Information Less Frequently

Less frequent data collection would delay identification of biological products believed responsible for adverse reactions, including permanent injuries and fatalities. Appropriate FDA action such as withdrawal from the market or changes in labeling would also be delayed.

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

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

The licensed manufacturers are required to submit to FDA a 15-day Alert report for each serious and unexpected adverse experience as well as any follow-up reports within 15 calendar days of receipt of new information or as requested by FDA. This requirement enables FDA to promptly investigate and, when necessary, initiate corrective action to protect the public from potential adverse product interactions.

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 April 7, 2014 (79 FR 19097). FDA received one comment from the public. The comment was not responsive to the comment request on the four specified aspects of the collection of information and did not provide any data or explanation that would support a change regarding the information collection requirements.

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 is consistent with the Freedom of Information Act and FDA’s published regulations under 21 CFR Part 20, 21 CFR 312.130, 314.430, 601.50, and 601.51.

11. Justification for Sensitive Questions

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

12. Estimates of Annualized Burden Hours and Costs

The estimated annual burden for this information collection is 4,293,361 hours.

12a. Annualized Hour Burden Estimate

Table 1.--Estimated Annual Reporting Burden					
21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
600.80(c)(1) & 600.80(e)	131	705.88	92,470	1	92,470
600.80(c)(2)	131	1,012.73	132,667	28	3,714,676
600.81	131	2.55	334	1	334
600.90	35	1.83	64	1	64
Total					3,807,544

Respondents to this collection of information are manufacturers of biological products and any person whose name appears on the label of a licensed biological product. The number of respondents is based on the estimated number of manufacturers that are subject to those regulations or that submitted the required information to the CBER and CDER, FDA, in fiscal year (FY) 2013. Based on information obtained from the FDA's database system, there were 131 licensed biologics manufacturers. This number excludes those manufacturers who produce Whole Blood or components of Whole Blood and in-vitro diagnostic licensed products, because of the exemption under § 600.80(k). The total annual responses are based on the number of submissions received annually by FDA in FY 2013. There were an estimated 92,470 15-day Alert reports, 132,667 periodic reports, and 334 lot distribution reports submitted to FDA. The number of 15-day Alert reports for postmarketing studies under § 600.80(e) is included in the total number of 15-day Alert reports. FDA received 64 requests from 35 manufacturers for waivers under § 600.90, of which 63 were granted. The hours per response are based on FDA experience. The burden hours required to complete the MedWatch Form for § 600.80(c)(1), (e), and (f) are reported under OMB Control No. 0910-0291.

21 CFR Section	Number of Recordkeepers	Number of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
600.12 ¹	164	41.99	6,887	32	220,384
600.12(b)(2)	334	5.03	1,679	24	40,296
600.80(i)	131	1,718.60	225,137	1	225,137
TOTAL					485,817

¹The recordkeeping requirements in § 610.18(b) are included in the estimate for § 600.12.

The number of respondents is based on the number of manufacturers subject to those regulations. Based on information obtained from FDA's database system, there were 334 licensed manufacturers of biological products in FY 2013. However, the number of recordkeepers listed for § 600.12(a)-(e), excluding (b)(2), is estimated to be 164. This number excludes manufacturers of blood and blood components because their burden hours for recordkeeping have been reported/approved under § 606.160 in OMB Control No. 0910-0116. The total annual records is based on the annual average of lots released in 2013 (6,887), number of recalls made (1,679), and total number of adverse experience reports received (225,137) in FY 2013. The hours per record are based on FDA experience.

12b. Annualized Cost Burden Estimate

The estimated annualized cost to the respondents is \$249,342,771.

Activity	Total Burden Hours	Hourly Wage Rate	Total Respondent Cost
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Reporting	3,807,544	\$60	\$228,452,640
Recordkeeping	485,817	\$43	\$20,890,131
TOTAL			\$249,342,771

This cost is based on an average pay rate of \$60.00 per hour for an upper level manager, and mid-level professional that handle the various reporting requirements. This cost is also based on a pay rate of \$43 per hour for a mid-level professional that handles the various recordkeeping requirements. This salary estimate includes benefits but no overhead costs.

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

There are no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

The estimated annual cost to FDA is \$83,423,289.

Annual Cost to FDA				
Activity	Number of Reports	Hours per Report	Cost per Hour	Total Cost
Report Distribution	3,807,544	0.1	\$31	\$11,803,386
Report Review	3,807,544	0.33	\$57	\$71,619,903
TOTAL				\$83,423,289

The cost is based on two Regulatory Information Specialists, (GS-9/11), who are responsible for distributing the reports. The cost is also based on a GS-14 Reviewer who is responsible for reviewing the reports. The salaries include benefits but no overhead costs.

Annual Cost to FDA				
Activity	Number of Respondents	Hours per Inspection	Cost per Hour	Total Cost
Inspection	167	40	\$57	\$380,760

There are 334 licensed manufacturers of biological products that will be inspected on a biennial basis. Therefore it is estimated that approximately one-half (167 establishments) will be inspected annually. The cost estimate is based on a FDA inspector at an average grade of GS-13/5 who takes an average of 40 hours for each establishment to perform the on-site inspection, review the records, and write the report.

15. Explanation for Program Changes or Adjustments

The estimated total annual burden for this information collection in 2010 was 2,096,444 hours. The current increase to the total annual burden of 4,293,361 burden hours is mostly attributed to the

increase in the number of respondents and total annual responses (number of AER reports) submitted under 21 CFR 600.80(c)(2) and the corresponding recordkeeping requirements under 21 CFR 600.80(i). The increase under these requirements (~ 2,200,000) is due to the normal variation in the submission of AER reports depending on various factors (e.g., new biological products on the market).

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 display of the expiration date for OMB approval.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.