U.S. Food and Drug Administration
Adverse Experience Reporting for
Licensed Biological Products and General Records

OMB Control No. 0910-0308

SUPPORTING STATEMENT **Part A: Justification**

1. Circumstances Making the Collection of Information Necessary

This information collection supports Food and Drug Administration (FDA) regulations. 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. Regulations implementing adverse experience reporting (AER) requirements are codified in 21 CFR Part 600 and enable FDA to take actions necessary for the protection of the public health in response to reports of adverse experiences related to biologics licensed under any provision of section 351 of the PHS Act (42 U.S.C 262). Reporting and recordkeeping provisions found in the regulations include the following:

Reporting:

21 CFR 600.80(c)(1) and 600.80(d)	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. Also includes a 15-day Alert report based on information in the scientific literature which must be accompanied by a copy of the published article.
21 CFR 600.82	Requires licensed manufacturers to report each permanent discontinuance of manufacturing or each interruption in manufacturing of a biological product that is likely to lead to a meaningful disruption in supply of that biological product.
21 CFR 600.80(c)(2)	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)	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	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, 600.80(h)(2), and 600.81(b)(2)	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.

Recordkeeping:

21 CFR 600.12(a), (b)(1), (c), (d) & (e)	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 that 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)	Requires manufacturers to maintain complete records pertaining to the recall from distribution of any product.
21 CFR 600.80(k)	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)	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.

To assist respondents with the reporting provisions of the information collection, FDA has created both paper-based and electronic forms. Information may be submitted electronically through *MEDWATCH* or the *Vaccine Adverse Experience Reporting System* (VAERS). AER reports are filed using the MEDWATCH Form FDA-3500A (approved under OMB Control No.0910-0291) or the VAERS-1. Both versions of the forms and instructions are available on the internet. 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.

We therefore request extension of OMB approval for the information collection found in the regulations at 21 CFR Part 600 as discussed in this supporting statement, and the associated collection instruments.

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.

The 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.

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

The regulations prescribe no particular use of information technology, however we believe nearly all respondents will use electronic means to satisfy the reporting elements of the information collection. In addition, section 321 of the *National Childhood Vaccine Injury Act* (NCVIA, Public Law 99-660) specifically provides for 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.

4. Efforts to Identify Duplication and Use of Similar Information

We are unaware of duplicative information collection. While FDA has received OMB approval for other collections that support product experience reporting (e.g., OMB Control Nos., 0910-0284, 0910-0290, 0910-0291), adverse experience reports under this information collection are exclusively

relicensed biological products refers to biologics licensed under any provision of section 351 of the PHS Act (42 U.S.C 262).

5. Impact on Small Businesses or Other Small Entities

Because of the public health protection provisions, there are no exceptions to the information collection requirements. At the same time, FDA aids small businesses in complying with its requirements through the agency's Regional Small Business Representatives and through the scientific and administrative staffs within the agency. FDA has provided a Small Business Guide on the agency's website at http://www.fda.gov/ForIndustry/SmallBusinessAssistance/default.htm.

6. Consequences of Collecting the Information Less Frequently

Information collection is consistent with statutory requirements under the PHS and the FFDCA, and with existing agency regulations.

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 July 18, 2017 (82 FR 32836). 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 (FOIA) 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

We estimate the burden of the information collection as follows:

12a. Annualized Hour Burden Estimate

Table 1 – Estimated Annual Reporting Burden[1]

21 CFR Section; Activity	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
600.80(c)(1) 600.80(d) and 600.80(e); Postmarketing 15-day alert reports	93	1,348.07	125,371	1	125,371
600.82; Notification of discontinuance or interruption in Manufacturing	18	1.61	29	2	58
600.80(c)(2) Periodic adverse experience reports	93	1,941.72	180,580	28	5,056,240
600.81; Distribution reports	93	7.28	677	1	677
600.80(h)(2), 600.81(b)(2), and 600.90; Waiver requests	40	2.02	81	1	81
Total					5,182,427

[1] There are no capital or operating and maintenance costs associated with the information collection.

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) 2016. Based on information obtained from the FDA's database system, there were 93 manufacturers of licensed biologics. 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(m).

The total annual responses are based on the number of submissions received annually by FDA in FY 2016. There were an estimated 125,371 15-day Alert reports, 180,580 periodic reports, and 677 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 81 requests from 40 manufacturers for waivers under § 600.90 (including §§ 600.80(h)(2) and 600.81(b)(2)), of which 79 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.

Table 2 – Estimated Annual Recordkeeping Burden[1]

21 CFR Section; Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Avg. Burden per Recordkeeping	Total Hours
600.12[2]; Maintenance of records	114	63.14	7,198	32	230,336
600.12(b)(2); Recall records	263	2.19	575	24	13,800
600.80(k); Recordkeeping requirements	93	3,289.80	305,951	1	305,951
TOTAL					550,087

[1] There are no capital or operating and maintenance costs associated with the information collection.
[2] The recordkeeping requirements in § 610.18(b) are included in the estimate for § 600.12.

In table 2 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 263 licensed manufacturers of biological products in FY 2016. However, the number of recordkeepers listed for § 600.12(a) through (e), excluding (b)(2), is estimated to be 114. 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 2016 (7,198), number of recalls made (575), and total number of adverse experience reports received (305,951) in FY 2016. The hours per record are based on FDA experience.

12b. Annualized Cost Burden Estimate

The estimated annualized cost to the respondents is $367,894,271.

Cost to Respondents			
Activity	Total Burden Hours	Hourly Wage Rate	Total Respondent Cost
Reporting	5,182,427	$66	$342,040,182
Recordkeeping	550,087	$47	$25,854,089
TOTAL			$367,894,271

This cost is based on an average pay rate of $66.00 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 $47 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 costs, operating and maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

The estimated annual cost to FDA is $117,797,140.

Annual Cost to FDA				
Activity	Number of Reports	Hours per Report	Cost per Hour	Total Cost
Report Distribution	5,182,427	0.1	$32	$16,583,766
Report Review	5,182,427	0.33	$59	$100,901,854
TOTAL				$117,485,620

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	132	40	$59	$311,520

There are 263 licensed manufacturers of biological products that will be inspected on a biennial basis. Therefore, it is estimated that approximately one-half (132 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 information collection reflects agency adjustments by +1,439,133 burden hours and +161,233 annual responses for an overall increase. We attribute this to an increase in the number of submissions received by the agency, as well as a greater number of biological products entering the marketplace for which the underlying regulatory requirements apply. We also note that burden for provisions under 21 CFR Part 600 established by our final rule of June 10, 2014 (79 FR 33072), entitled, "*Postmarketing Safety Reports for Human Drug and Biological Products: Electronic Submission Requirements*" and previously included under OMB Control No. 0910-0770 (21 CFR 600.80(h)(2) and 600.81(b)(2)), have now been consolidated into this collection request.

Finally, we have we have revised the IC list appearing at www.reginfo.gov by consolidating the previously itemized regulatory provisions. We believe this will assist the reader by more easily identifying the summary of cumulative fluctuations for the collection. At the same time, readers may still view estimated burden associated with individual provisions by referring to the agency's 60-day and 30-day notices and in the burden tables found in Q.12: *Estimates of Annualized Burden Hours and Costs* of this supporting statement.

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.