

UNITED STATES FOOD & DRUG ADMINISTRATION

Biological Products –  
General Records and Postmarket Adverse Experience Requirements

OMB Control No. 0910-0308 - EXTENSION

SUPPORTING STATEMENT

**Part A: Justification**

1. Circumstances Making the Collection of Information Necessary

This information collection helps support implementation of statutory and regulatory authorities that govern adverse experience reporting for biological products. Under the Public Health Service Act (PHS Act) (42 U.S.C. 262), the Food and Drug Administration (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 applicable to biological products are codified in part 600 (21 CFR part 600). Postmarketing safety reporting for combination products are found in 21 CFR part 4 (Regulation of Combination Products), subpart B, and apply to a biological product that is part of a combination product (defined in 21 CFR 4.2 as a “*constituent part*”). The collections of information are intended to 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.

To assist respondents with the reporting provisions, we have created both paper-based and electronic forms. Information may be submitted electronically through FDA’s Adverse Event Reporting System, including MEDWATCH, or the Vaccine Adverse Experience Reporting System (VAERS), co-monitored with the Centers for Disease Control. AER reports filed using MEDWATCH utilize Form FDA-3500A (approved in OMB control no. 0910-0291) or the VAERS-2. Both versions of the forms and instructions are available from the internet:

- <https://www.fda.gov/safety/report-problem-fda>
- [Vaccine Adverse Event Reporting System \(VAERS\) \(hhs.gov\)](https://www.hhs.gov/vaers/)

Forms may also be downloaded, completed, and submitted by mail or facsimile.

We are therefore requesting extension of OMB approval for the information collections found in the referenced regulation and associated forms, 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 (FAERS) and VAERS in CBER are to identify safety problems with licensed biological products, focusing especially on newly licensed products. Although premarket studies disclose a general safety profile of a new biological product, the larger and more diverse patient populations exposed to the licensed biological product provides the opportunity to collect information on rare, latent, long-term and other adverse events potentially causally associated with biological products that may not have been identified from pre-market use. FAERS and VAERS reports are obtained from a variety of sources, including manufacturers, patients, physicians, foreign regulatory agencies, and clinical investigators. New and unexpected safety issues or new aspects of known safety issues identified through the analysis of the data in FAERS and VAERS 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), requirements or commitment that the application holder conduct additional study of the potential safety issue, coordination with application holders to ensure adequate corrective action is taken, and removal of a biological product from the market where necessary.

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.

## 4. Efforts to Identify Duplication and Use of Similar Information

We are unaware of any duplicative information collection.

## 5. Impact on Small Businesses or Other Small Entities

We believe there is no undue burden on small entities as defined by the small business administration. 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

The information collection schedule is consistent with applicable statutory and regulatory requirements.

#### 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), we published a 60-day notice soliciting public comment in the *Federal Register* of September 28, 2023 (88 FR 66856). One comment was received. The commenter suggested our estimate of 28 hours per response for periodic adverse experience might be high. At the same time, no alternative figure was proffered, nor a basis for making a reduction. While we will continue to explore ways to reduce burden associated with mandatory product reporting, we did not adjust our estimate based on this comment.

#### 9. Explanation of Any Payment or Gift to Respondents

There are no incentives, payments or gifts associated with this information collection.

#### 10. Assurance of Confidentiality Provided to Respondents

**Consistent with 5 CFR 1320.5(d)(2)(vii) and agency regulations in 21 CFR § 20.20, data will be kept private to the extent allowed by law:**

*The Privacy Act of 1974*

In preparing this supporting statement, we consulted our Privacy Office to ensure appropriate identification and handling of information collected. Although the ICR collects personally identifiable information (PII), it is collected in the context of the subject individuals' professional capacity and the FDA-related performed for their employer (e.g., point of contact at a regulated entity), as well as the subject individual's capacity as a member of the public. The PII is submitted via Form FDA 3500 (MedWatch, The FDA Safety Information and Adverse Event Reporting Program – approved in OMB control no. 0910-0291), Form FDA 3500A (MedWatch,

The FDA Safety Information and Adverse Event Reporting Program, For Use by User-Facilities, Importers, and Manufacturers – Mandatory Reporting), and Form FDA 3500B (MedWatch Consumer Voluntary Reporting). PII submitted via Form FDA 3500 is patient identifier, date of birth, age, gender, ethnicity, race, first name, last name, address, phone number, email address, and country. PII submitted via Form FDA 3500A is patient identifier, age, sex, date of birth, ethnicity, race, first name, last name, address, phone number, and email address. PII submitted via Form FDA 3500B is first name, last name, address, country, telephone number, and email address. This information collection supports regulations implementing adverse experience reporting (AER) requirements as codified in 21 CFR Part 600 and enables 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). Through appropriate form and webpage design, FDA limited submission fields and minimized the PII collected to protect the privacy of the individuals.

### *The Freedom of Information Act (FOIA)*

Under FOIA (5 U.S.C. 552), the public has broad access to government documents. However, FOIA provides certain exemptions from mandatory public disclosure of government records (5 U.S.C. 552(b)(1-9)). FDA will make the fullest possible disclosure of records to the public, consistent with the rights of individuals to privacy, the property rights of persons in trade and confidential commercial or financial information.

#### 11. Justification for Sensitive Questions

The collection of information does not involve sensitive questions.

#### 12. Estimates of Annualized Burden Hours and Costs

*Respondents* to the collection of information are manufacturers of biological products (including blood and blood components) 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) 2022. Based on information obtained from the FDA's database system, there were **109** 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).

12a. Annualized Hour Burden Estimate

Table 1 – Estimated Annual Reporting Burden—Biological Products<sup>1</sup>

21 CFR Section; Activity	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Average Burden per Response (in hours)	Total Hours
600.80(c)(1), 600.80(d), and 600.80(e); postmarketing 15- day Alert Reports	109	3,806.95	414,958	1	414,958
600.82; Notification of discontinuance or interruption in manufacturing	23	1.435	33	2	66
600.80(c)(2); periodic adverse experience reports	109	3,697	402,973	28	11,283,244
600.81; distribution reports	172	5.727	985	1	985
600.80(h)(2), 600.81(b)(2), and 600.90; waiver requests	35	1.886	66	1	66
TOTAL	---		0		0

<sup>1</sup> There are no capital or operating and maintenance costs associated with the information collection.

The total annual responses are based on the number of submissions received in FY 2022. There were an estimated 414,958 15-day Alert reports, 402,973 periodic reports, and 985 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. We received 66 requests from 35 manufacturers for waivers under § 600.90 (including §§ 600.80(h)(2) and 600.81(b)(2)), of which 49 were granted. The hours per response are based on FDA experience. The burden hours required to complete the MEDWATCH Form (Form FDA3500A) for § 600.80(c)(1), (e), and (f) are account for in OMB control no. 0910-0291.

Table 2 – Estimated Annual Recordkeeping Burden—Biological Products<sup>1</sup>

21 CFR Section; Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping (in hours)	Total Hours
600.12 <sup>2</sup> ; maintenance of records	131	40.145	5,259	32	168,288
600.12(b)(2); recall records	216	3.4028	735	24	17,640
600.80(c)(1) and 600.80(k); AER Records	109	7,503.95	817,931	1	817,931
TOTAL	---		0		0

<sup>1</sup> There are no capital or operating and maintenance costs associated with the information collection.

<sup>2</sup> The recordkeeping requirements in § 610.18(b) are included in the estimate for § 600.12.

Based on information obtained from FDA’s database system, there were 216 licensed manufacturers of biological products in FY 2022. However, the number of recordkeepers listed for § 600.12(a) through (e), excluding (b)(2), is estimated to be **109**. This number excludes manufacturers of blood and blood components because their burden hours for recordkeeping are counted under § 606.160, covered in OMB control no. 0910-0116. The total annual records is based on the annual average of lots released in FY 2022 (6,670), number of recalls made (735), and total number of adverse experience reports received (305,951) in FY 2022. The estimated average time per record is based on our experience with the information collection.

Table 3 - Estimated Annual Reporting Burden--Combination Products<sup>1</sup>

21 CFR 4, subpart B: Postmarketing Safety Reporting for Combination Products	Number of Respondents	Number of Disclosures per Respondents	Total Annual Disclosures	Average Burden per Disclosure (in hours)	Total Hours
4.102, 4.103, 4.104, 4.105; reports and sharing information with other constituent part applicants (biological products)	11	18	198	0.35 (21 mins.)	69

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

For operational efficiency, on March 20, 2023, we requested, and OMB approved, the addition of burden attributable to provisions set forth in part 4, subpart B, previously included in OMB control number 0910–0834. When information regarding an event that involves a death or serious injury, or an adverse event, associated with the use of the combination product is received by the product sponsor, the information must be provided to the other constituent part applicant(s) no later than 5 calendar days after receipt under § 4.103. Relatedly, § 4.104 explains how and where to submit reports.

*12b. Annualized Cost Burden Estimate*

The estimated annualized cost to the respondents is \$993,171,003.

Cost to Respondents			
Activity	Total Burden Hours	Hourly Wage Rate	Total Respondent Cost
Reporting	11,699,388	\$80	\$935,951,040
Recordkeeping	1,003,859	\$57	\$57,219,963
TOTAL			\$993,171,003

This cost is based on an average pay rate of \$80.00 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 \$57 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/Recordkeepers or 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 total annual cost to FDA is \$21,707,968.

Annual Cost to FDA				
Activity	Number of Reports	Hours per Report	Cost per Hour	Total Cost
Report Distribution	819,213	0.1	\$37	\$3,031,088
Report Review	819,213	0.33	\$68	\$18,383,120
TOTAL				\$21,414,208

The cost is based on two Regulatory Information Specialists, (GS-9/11), who are responsible for reviewing 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	108	40	\$68	\$293,760

There are 216 licensed manufacturers of biological products that will be inspected on a biennial basis. Therefore, we assume one-half (108 establishments) will be inspected annually. The cost estimate is based on an 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 adjustment. As communicated in Q-12 above, on March 20, 2023, we requested, and OMB approved, the addition of burden attributable to provisions set forth in part 4, subpart B, previously included in OMB control number 0910-0834. Upon this submission, however, we noted an inadvertent recording overage (+20hrs) and have corrected it with this submission. We have also made adjustments to the reporting and recordkeeping estimates associated with biological product AERS based on recent submissions. Cumulatively these adjustments result in annual increases of 927,450 responses and 6,788,803 hours. We attribute this fluctuation to increased reporting during the recent PHE and the inclusion of postmarketing safety reporting for combination biological products.

16. Plans for Tabulation and Publication and Project Time Schedule

This information collected will not be published or tabulated.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

The OMB expiration date will be displayed as required by 5 CFR 1320.5(b).

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.