

## SUPPORTING STATEMENT

### Biological Products: Reporting of Biological Product Deviations in Manufacturing OMB No. 0910-0458

#### A. JUSTIFICATION

##### 1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) is requesting Office of Management and Budget (OMB) approval of the information collection requirements contained in 21 CFR Parts 600 and 606 (Attachment A). These requirements are listed below:

§600.14 (Reporting): The manufacturer who holds the biological product license and who had control over the distributed product when the deviation occurred, must report to the Director, Office of Compliance and Biologics Quality as soon as possible but not to exceed 45 calendar days after acquiring information reasonably suggesting that a reportable event has occurred.

§606.17 (Reporting): A licensed manufacturer of blood and blood components, including Source Plasma; an unlicensed registered blood establishment; or a transfusion service who had control over the distributed product when the deviation occurred, must report to the Director, Office of Compliance and Biologics Quality as soon as possible but not to exceed 45 calendar days after acquiring information reasonably suggesting that a reportable event has occurred.

The reporting requirements for §600.14 (Attachment B) have not been previously submitted for approval by OMB. However, the current requirement for reporting in §600.14 and the new regulation in §606.171 will be addressed in this supporting statement. The supporting statement for the proposed rule was submitted to OMB under the title “Biological Product Reporting of Errors and Accidents in Manufacturing - Proposed Rule.”

The current regulations in §600.14 require licensed manufacturers of all biological products to report to the agency any error or accident that occurs during manufacturing that may affect the safety, purity, or potency of a product. In May of 1995, the Office of Inspector General (OIG) issued a report on the “Reporting Process for Blood Establishments to Notify the Food and Drug Administration of Errors and Accidents Affecting Blood” (Attachment C). The report states that the error and accident reporting process enables the agency to evaluate and monitor blood establishments in response to detected errors and accidents, and regularly alert field staff and blood establishments with trend analysis of the types of errors and accidents reported. However, OIG placed emphasis on two existing conditions that were impeding the success of the reporting process: 1) error and accident reports were not being submitted in a timely manner; and 2) there was no assurance that unlicensed establishments were submitting reports even after reporting had been recommended on a voluntary basis.

In January of 1997, the United States General Accounting Office issued a report entitled “Blood Supply: FDA Oversight and Remaining Issues of Safety” (Attachment D). The report stated that

only 1 percent of all errors and accidents in the manufacture of blood and blood components are reported by unlicensed facilities (i.e., registered unlicensed blood establishments and transfusion services) although they collect 10 percent of the nation's blood supply. Without reporting by the full spectrum of establishments that engage in the manufacture of blood and blood establishments, FDA is unable to effectively monitor and evaluate the blood industry. GAO found that more than half of all observations of problems by FDA inspectors were issued to unlicensed facilities. The discrepancy between the proportions of problems observed and the voluntary reported errors and accidents by unlicensed facilities underscores the need for better FDA oversight. Therefore, GAO recommends that FDA require unlicensed facilities to report all error and accidents.

Under section 351 of the Public Health Service Act (42 U.S.C. 262) (Attachment E), all biological products, including blood and blood components, offered for sale in interstate commerce must be licensed and meet standards designed to ensure the continued safety, purity, and potency of such products. In addition, the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 351) (Attachment F) provides that drugs and devices (including blood and blood components) are adulterated if they do not conform with current Good Manufacturing Practice (cGMP) assuring that they meet the requirements of the Act. All establishments manufacturing blood and blood components are required to register with FDA, and comply with the current Good Manufacturing Practice (cGMP) regulations for blood and blood components (21 CFR Parts 211 and 606). Transfusion services are required under 42 CFR 493.1273(a) to comply with 21 CFR Parts 606 and 640 as they pertain to the performance of manufacturing activities.

FDA regards the final rule requirement for reporting biological product deviations in manufacturing as an important step in helping to minimize medical errors, and an essential tool in its directive to protect public health by establishing and maintaining surveillance programs that provide timely and useful information.

## 2. Purpose and Use of the Information

The objectives of the biological product deviation reporting requirement are to: (1) enable FDA to respond when public health may be at risk; (2) expedite reporting of biological product deviations in manufacturing; (3) provide FDA with uniform data to track trends that may indicate broader threats to the public health; (4) create a uniform reporting requirement that can be enforced against non-complying entities; and (5) help ensure licensed manufacturers and unlicensed blood establishments are taking appropriate actions to investigate and correct biological product. The reporting system is not intended to overlap quality assurance programs (QA), but instead builds on those QA programs to assure better protection of the public health. Reporting of biological product deviations will enable FDA to identify areas in which further regulation or guidance is needed to assist licensed manufacturers and unlicensed blood establishments in decreasing the occurrence of these events.

## 3. Use of Information Technology and Burden Reduction

FDA has prepared a standardized form for reporting deviations in manufacturing a biological product (Biological Product Deviation Report (BPDR, Form FDA-3486) (Attachment G) that may be downloaded from the Center for Biologics Evaluation and Research (CBER)'s web site or received by FAX. After completion, the form is sent to the address identified in §600.14(e). In an effort to expedite and simplify reporting, FDA also is providing to industry the opportunity to complete and submit a Form FDA-3486 electronically. The establishment may insert the requested information into the appropriate fields on-line and submit the report through the web.

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

In an effort to reduce duplicative reporting, FDA has reviewed other reporting programs. There are two programs that may be misconstrued as being duplicative, but are not duplicative because of their difference in orientation. They are adverse experience reporting for licensed biological products (AER, 21 CFR 600.80) (Attachment H) which excludes blood, blood components, and in vitro diagnostic kits, and medical device reporting (MDR, 21 CFR Part 803) (Attachment I). Biological product deviation reporting by a firm focuses on the impact deviations in manufacturing have or may have on the safety, purity, and potency of the final product, whereas, AER and MDR reports are focused on the adverse effect of the product on the patient or user.

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

FDA believes its duty requires the equal application of the regulations to both small and large establishments to adequately protect the nation's health. While FDA does not believe it can apply different standards with respect to statutory requirements, FDA's Center for Biologics Evaluation and Research, Division of Manufacturers Assistance and Training, provides guidance to small businesses concerning regulatory requirements.

#### 6. Consequences of Less Frequent Information Collection

Less frequent information collection would not provide the information necessary for FDA to monitor the safety, purity, and potency of distributed biological products. Biological product deviation reports, in conjunction with inspections and other surveillance activities, give FDA a continuing overview of the biological product industry. Less frequent collection of information would inhibit FDA's oversight. There are no technical or legal obstacles to reducing the burden.

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

The information may be reported to the agency more frequently than quarterly based on the frequency of biological product deviations that may occur during manufacturing.

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

A 30-day notice requesting comments from the public on the information collection provisions was provided in the proposed rule published in the **Federal Register** (62 FR 49642, September 23, 1997). Nine letters of comment on the information collection requirements were submitted to OMB. Most of the comments submitted to OMB were the same as those submitted directly to FDA in response to the proposed rule. FDA's responses to these comments are found in section III of the preamble to the final rule. Responses to additional comments in the letters received by OMB that were not addressed in section III are addressed in section V., The Paperwork Reduction Act of 1995.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift was provided to respondents.

10. Assurance of Confidentiality Provided to Respondent

The confidentiality of information received by FDA is determined consistent with the Freedom of Information Act and the agency's published regulations on "Public Information" under 21 CFR Part 20.

11. Justification for Sensitive Questions

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

12. Estimates of Hour Burden Including Annualized Hourly Costs

The total estimated annual reporting burden for this information collection is 261,648 hours. A one-time burden for preparation of SOPs is 207,440 hours, and the on-going annual burden is 54,208 hours.

The 54,208 Total Hours estimated in table 1 are based on information from FDA's databases and CBER's annual summary on error and accident reporting in FY 1999. In calculating the reporting burden for the revised §600.14 in this final rule, FDA found that approximately 111 licensed manufacturers of biological products other than blood and blood components submitted 93 error and accident reports in FY 1999 under current §600.14. In calculating the reporting burden for §606.171 under this final rule, FDA found that approximately 232 licensed manufacturers of blood and blood components, including Source Plasma, submitted 14,611 error and accident reports.

In calculating the burden for unlicensed registered blood establishments and transfusion services under the new §606.171, FDA found that 48 establishments of the estimated 2,800 unlicensed registered blood establishments voluntarily submitted 94 error and accident reports; and 15 of the estimated 3,400 transfusion services voluntarily submitted 28 error and accident reports. Based on this voluntary reporting rate, each of the 6,200 unlicensed blood

establishments is expected to submit no more than two reports annually, totaling 12,400 reports annually.

Licensed manufacturers of blood and blood components collect 90% of the nation's blood supply. Accordingly, the estimated total number of reports submitted annually by each licensed blood establishment is greater than the total number of reports submitted by each unlicensed blood establishment.

FDA has estimated a total of 207,440 hours as a one-time burden for performing the following activities: staff review of the requirements of the rule, establishing or making adjustments to current systems and SOPs, and staff training. The estimated one-time burden to perform these activities would be 80 hours for each licensed manufacturer of biological products and licensed manufacturer of blood and blood components, 40 hours for each unlicensed registered blood establishment, and 20 hours for each transfusion service.

**Table 1--Estimated Annual Reporting Burden<sup>1</sup>**

21 CFR Section	No. Of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
600.14 <sup>2</sup> FDA Form-3486	111	0.8	93	2	186
606.171 <sup>3</sup> FDA Form-3486	232	62.9	14,611	2	29,222
606.171 <sup>4</sup> FDA Form-3486	6,200	2	12,400	2	24,800
Total	6,543		27,104		54,208
<b>One-Time Burden<sup>5</sup></b>					
Licensed <sup>2</sup> manufacturers	111	1	111	80	8,880
Licensed <sup>3</sup> manufacturers	232	1	232	80	18,560
Unlicensed registered blood establishments	2,800	1	2,800	40	112,000

Transfusion services	3,400	1	3,400	20	68,000
Total					207,440

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

2 Licensed manufacturers of biological products other than blood and blood components.

3 Licensed manufacturers of blood and blood components, including Source Plasma.

4 Unlicensed registered blood establishments and transfusion services.

5 one-time burden activities; staff review of the requirements of the rule, establishing or making adjustments to current systems and SOPs, and staff training.

### Estimate of Other Total Annual Cost Burden to Respondents

The estimated total cost to the respondents is \$6,541,200; \$5,186,000 for a one-time burden of preparing SOPs, and an on-going reporting burden cost of \$1,355,200. This cost is based on an estimated \$25.00 per hour value of staff time to prepare the SOPs, review the records, and prepare the report. There should not be any additional costs of investigating biological product deviations or keeping records of them, since these activities are already required under other sections in 21 CFR Parts 200, 600, and 800.

There are no specific educational or technical skills required to complete and submit biological product deviation reports. These reports are generally completed by trained and qualified employees of an establishment.

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting			
One-Time Burden	207,440	\$25	\$5,186,000
On-going Burden	54,208	\$25	\$1,355,200
Total	261,648		\$6,541,200

### 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 \$360,280. This estimate is based on a GS-12 Consumer Safety Officer, at a pay rate of \$33.23 per hour, who performs a review and assessment of the report for possible regulatory action. The estimate includes the estimated

additional time required to input the data into the database for statistical purposes. The salary estimate includes benefits but no overhead costs.

Activity	Number of Responses	Hours per Response	Cost per Hour	Total Cost
Report Review	54,208	0.2	\$33.23	\$360,280

15. Explanation for Program Changes or Adjustments

Changes in burden are not applicable at this time, as this is the first submission for 21 CFR 600.14 and 21 CFR 606.171.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no tabulated results to publish for this information collection.

17. Reason Display of OMB Expiration Date is Inappropriate

We are 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 Item 19 of OMB Form 83-I.