Biological Products: Reporting of Biological Product Deviations and Human Cells, Tissues, and Cellular and Tissue-Based Product Deviations; Form FDA 3486 and Addendum 3486A

OMB# 0910-0458

SUPPORTING STATEMENT

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. 0910-0458 and OMB approval for the information collection for provisions including Forms FDA 3486 and FDA 3486A. A summary of the information collection provisions in 21 CFR Parts 600, 606, and 1271 are listed below:

Section (§) 600.14 (Reporting) -
In brief, requires the licensed manufacturer who holds the biological product license, for other than human blood and blood components, and who had control over a distributed product when the deviation occurred, to report to the Center for Biologics Evaluation and Research (CBER) or to the Center for Drugs Evaluation and Research (CDER) as soon as possible but at a date not to exceed 45 calendar days after acquiring information reasonably suggesting that a reportable event has occurred.

Section (§) 606.171 (Reporting) -
In brief, requires licensed manufacturers of human blood and blood components, including Source Plasma; unlicensed registered blood establishments; or transfusion services who had control over the product when the deviation occurred, to report to CBER as soon as possible but at a date not to exceed 45 calendar days after acquiring information reasonably suggesting that a reportable event has occurred.

Section (§) 1271.350(b) (Reporting) -
In brief, requires human cells, tissues, and cellular and tissue-based product (HCT/P) establishments that manufacture non-reproductive HCT/Ps described in § 1271.10 to investigate and report to CBER all HCT/P deviations relating to a distributed HCT/P that relates to the core current good tissue practice (CGTP) requirements, if the deviation occurred in the establishment's facility or in a facility that performed a manufacturing step for the establishment under contact, agreement, or other arrangement; and to report such HCT/P deviations within 45 days of the discovery of the event.

Form FDA 3486 is used to submit biological product deviation (BPD) and HCT/P deviation reports. CBER also developed an addendum to Form FDA 3486 to provide additional information when a BPD report submitted under § 606.171 has been reviewed by FDA and evaluated as a possible recall.

Under section 351 of the Public Health Service Act (PHS Act)(42 U.S.C. 262), all biological products, including human blood and blood components, offered for sale in interstate commerce

must be licensed and meet standards, including those prescribed in the FDA regulations, designed to ensure the continued safety, purity, and potency of such products. In addition under section 361 of the PHS Act (42 U.S.C. 264), FDA may issue and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between the States or possessions or from foreign countries into the States or possessions. Further, the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 351) provides that drugs and devices (including human 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 FD&C Act. Establishments manufacturing biological products including human blood and blood components must comply with the applicable CGMP regulations Parts 211, 606, and 820 (21 CFR Parts 211, 606, and 820) and CGTP regulations (21 CFR Part 1271) as appropriate. FDA regards biological product deviation (BPD) reporting and HCT/P deviation reporting to be 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 Collection

The objectives of the BPD reporting and HCT/P deviation reporting requirements are to: (1) Enable FDA to respond when public health may be at risk; (2) expedite reporting of BPD and HCT/P 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 that licensed manufacturers and unlicensed blood establishments as well as manufacturers of HCT/Ps are taking appropriate actions to investigate and correct biological product deviations. The reporting system is not intended to overlap quality assurance (QA) programs, but instead builds on those QA programs to assure better protection of the public health. Reporting of BPDs and HCT/P deviations will also enable FDA to identify areas in which further regulation or guidance is needed to assist licensed manufacturers and unlicensed blood establishments as well as non-reproductive HCT/P establishments in decreasing the occurrence of these events.

3. Use of Improved Information Technology and Burden Reduction

FDA has prepared a standardized form for reporting deviations in the manufacturing of a biological product (BPDR, Form FDA 3486) that may be downloaded from CBER's website. After completion, the form is sent as provided under §§ 600.14(e), 606.171(e), or 1271.350(b)(3). In an effort to expedite and simplify reporting, FDA also provides industry the opportunity to complete and submit the Form FDA 3486 electronically. The establishment may create a user account and insert the requested information into the appropriate fields on-line and submit the report through CBER's website. The addendum to Form FDA 3486 (Form FDA 3486A) is also web-based and can be submitted electronically. FDA is not aware of any other improved technology to reduce the burden.

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 some programs that may be misconstrued as being duplicative, but are not duplicative because of their difference in orientation. These programs are: (1) Adverse Experience Reporting for licensed biological products (AER, 21 CFR 600.80), which excludes blood, blood components, and in vitro diagnostic kits: (2) Medical Device Reporting (MDR, 21 CFR Part 803): and (3) Adverse Reaction Reports for HCT/Ps (ARR, 21 CFR 1271.350). BPD reporting and HCT/P 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, MDR, and ARR reports are focused on the adverse effect of the product on the patient or user.

5. Impact on Small Businesses or Other Small Entities

This collection of information applies to small as well as large establishments. Although FDA must apply the statutory and regulatory requirements equally to all enterprises, the agency does provide special help to small businesses. CBER's Office of Communication, Outreach, and Development, Division of Manufacturers Assistance and Training, provides assistance to small businesses subject to FDA's regulatory requirements. CDER's Office of Communication, Division of Drug Information, also provides assistance to small businesses.

6. Consequences of Collecting the Information Less Frequently

Less frequent information collection would not provide the information necessary for FDA to monitor the safety, purity, and potency of distributed biological products. BPD reports and HCT/P 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 FDA more frequently than quarterly based on the frequency of BPD reports and HCT/P deviation reports that may occur during manufacturing.

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 June 5, 2013 (78 FR 33846). FDA received one letter of 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 would be consistent with the Freedom of Information Act (FOIA) and the FDA's published regulations of "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 Annualized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

The total annual estimated burden imposed by this collection of information is 112,485 hours.

Estimated Annual Reporting Burden[1]

21 CFR Section	FDA Form Number	Number. of Respondents	Number of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
600.14	3486	91	7.71	702	2.0	1,404
606.171	3486	1,679	32.73	54,947	2.0	109,894
1271.350(b)	3486	94	2.66	250	2.0	500
	3486A[1]	84	32.70	2,747	0.25	687
Total						112,485

[1]Five percent of the number of respondents (1,679 x 0.05 = 84) and total annual responses to CBER (54,947 x 0.05 = 2,747).

Respondents to this collection of information are the licensed manufacturers of biological products other than human blood and blood components, licensed manufacturers of blood and blood components including Source Plasma, unlicensed registered blood establishments, transfusion services, and establishments that manufacturer non-reproductive HCT/Ps regulated solely under section 361 of the PHS Act as described in § 1271.10. The number of respondents and total annual responses are based on the BPD reports and HCT/P deviation reports FDA received in fiscal year (FY) 2012. The number of licensed manufacturers and total annual responses under § 600.14 include the estimates for both CBER and CDER. Based on information from industry, the estimated average time to complete and submit a deviation report is 2 hours, which includes a minimal one-time burden to create a user account for those reports submitted electronically. The

availability of the standardized report Form FDA 3486, and the ability to submit this report electronically to CBER (CDER does not currently accept electronic filings) further streamlines the report submission process.

CBER has developed an addendum to Form FDA 3486. The Web-based addendum (Form FDA 3486A) provides additional information when a BPD report has been reviewed by FDA and evaluated as a possible recall. The additional information requested includes information not contained in the Form FDA 3486 such as: (1) Distribution pattern; (2) method of consignee notification; (3) consignee(s) of products for further manufacture; (4) additional product information; (5) updated product disposition; and (6) industry recall contacts. This information is requested by CBER through e-mail notification to the submitter of the BPD report. This information is used by CBER for recall classification purposes. At this time, Form FDA 3486A is used only for those BPD reports submitted under § 606.171. Form FDA 3486A is not used for the biological products regulated by CDER because they receive very few BPD reports and do not accept electronic filings. CBER estimates that 5 percent of the total BPD reports submitted to CBER under § 606.171 would need additional information submitted in the addendum. CBER estimates that it would take between 10 to 20 minutes to complete the addendum. For calculation purposes, CBER is using 15 minutes.

Activities such as investigating, changing standard operating procedures (SOPs) or processes, and follow-up are currently required under 21 CFR Part 211, (approved under OMB control number 0910-0139), Part 606 (approved under OMB control number 0910-0116), Part 820 (approved under OMB control number 0910-0073), and Part 1271 (approved under OMB control number 0910-0543) and, therefore, are not included in the burden calculation for the separate requirement of submitting a deviation report to FDA.

12b. Annualized Cost Burden Estimate

The estimated annualized cost to the respondents is $4,499,400.

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting	112,485	$40	$4,499,400

This estimated cost is based on a pay rate of $40 per hour for a mid-level professional who has the training and skills to handle the various reporting requirements. This salary estimate includes benefits but no overhead costs. There should not be any additional costs of investigating BPDs and HCT/P deviations or keeping records of them, since these activities are already required under other sections in 21 CFR Parts 211, 606, 820, and 1271.

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

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

14. Annualized Cost to the Federal Government

The estimated annualized cost to FDA is $1,016,531.

Activity	No. of Reports	Hours per Report	Average Cost per Hour	Total Cost
Report Review	58,646	1/3 (20 min.)	$52	$1,016,531

This estimate is based on a CBER reviewer, at an average pay rate of $52 per hour (GS 13-5), who performs a review and assessment of the report for possible regulatory action. This 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.

15. Explanation for Program Changes or Adjustments

The previous burden estimate in 2010 was 90,029.5 hours. The current overall increase (~22,455 hours) in burden to 112,485 hours is mostly attributed to the increase in the number of respondents and number of annual responses under § 606.171(21,644 burden hours). This increase is mostly due to the normal variation in submissions of BPDs to FDA.

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 the display of the expiration date of the OMB approval.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.