Decoquinate in grams per ton	Combination in grams per ton	Indications for use	Limitations	Sponsor
*	*	* *	* *	*
	Chlortetracycline approximately 400, varying with body weight and feed consumption to provide 10 mg/lb of body weight per day.	Calves, beef and nonlactating dairy cattle: prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii*, for treatment of bacterial enteritis caused by *Escherichia coli*, and for treatment of bacterial pneumonia caused by *Pasteurella multocida* organisms susceptible to chlortetracycline.	Feed Type C feed to provide 22.7 mg decoquinate and 1 g chlortetracycline/100 lb body weight (0.5 mg/kg)/day for not more than 5 days. Type C feed may be prepared from Type B feed containing 535.8 to 5,440 g/ton decoquinate and 6,700 to 80,000 g/ton chlortetracycline. When consumed, feed 22.7 mg decoquinate/100 lb body weight/day for a total of 28 days to prevent coccidiosis. Withdraw 24 hours prior to slaughter. Do not feed to calves to be processed for veal. Do not feed to animals producing milk for food.	046573
*	*	* *	* *	*

Dated: October 26, 2000.

Stephen F. Sundlof,

Director, Center for Veterinary Medicine.

[FR Doc. 00–28524 Filed 11–6–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 558

New Animal Drugs for Use in Animal Feeds; Pyrantel Tartrate

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of an abbreviated new animal drug application (ANADA) filed by Farnam Companies, Inc. The ANADA provides for use of pyrantel tartrate in horse feed for the prevention and control of various species of internal parasites.

DATES: This rule is effective November 7, 2000.

FOR FURTHER INFORMATION CONTACT: Lonnie W. Luther, Center for Veterinary Medicine (HFV–102), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–0209.

SUPPLEMENTARY INFORMATION: Farnam Companies, Inc., 301 West Osborn, Phoenix, AZ 85013–3928, is sponsor of ANADA 200–282 that provides for use of CONTINUEX™ (pyrantel tartrate) Daily Dewormer. The ANADA provides for use of pyrantel tartrate in horse feed for the prevention and control of various species of internal parasites. The ANADA is approved as a generic copy of Pfizer Inc.'s NADA 140–819 for STRONGID® 48. ANADA 200–282 is approved as of September 26, 2000, and the regulations are amended in 21 CFR 558.485 to reflect the approval. The basis for approval is discussed in the freedom of information summary.

In accordance with the freedom of information provisions of 21 CFR part 20 and 514.11(e)(2)(ii), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, between 9 a.m. and 4 p.m., Monday through Friday.

The agency has determined under 21 CFR 25.33(a)(1) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

This rule does not meet the definition of ''rule'' in 5 U.S.C. 804(3)(A) because it is a rule of ''particular applicability.'' Therefore, it is not subject to the congressional review requirements in 5 U.S.C. 801–808.

List of Subjects in 21 CFR Part 558

Animal drugs, Animal feeds.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR part 558 is amended as follows:

PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

1. The authority citation for 21 CFR part 558 continues to read as follows:

Authority: 21 U.S.C. 360b, 371.

2. Section 558.485 is amended by adding paragraph (a)(29) to read as follows:

§ 558.485 Pyrantel tartrate.

(a) * * *

(29) To 017135: 48 grams per pound, paragraph (e)(2) of this section.

* * * * *

Dated: October 26, 2000.

Stephen F. Sundlof,

Director, Center for Veterinary Medicine.

[FR Doc. 00–28523 Filed 11–6–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 600 and 606

[Docket No. 97N–0242]

Biological Products: Reporting of Biological Product Deviations in Manufacturing

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the regulation requiring licensed

manufacturers of biological products to report errors and accidents in manufacturing that may affect the safety, purity, or potency of a product. FDA also is amending the current good manufacturing practice (CGMP) regulations for blood and blood components to require establishments involved in the manufacture of blood and blood components, including licensed manufacturers, unlicensed registered establishments and transfusion services, to report biological product deviations in manufacturing. The final rule requires licensed manufacturers, unlicensed registered blood establishments, and transfusion services who had control over the product when a deviation occurred to report to FDA the biological product deviation if the product has been distributed. The final rule also establishes a 45-day reporting period. FDA is issuing the final rule as part of a retrospective review under Executive Order 12866 of significant FDA regulations to improve the effectiveness of FDA's regulatory program.

DATES: This rule is effective May 7, 2000.

FOR FURTHER INFORMATION CONTACT: Paula S. McKeever, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of September 23, 1997 (62 FR 49642), FDA published a proposed rule to amend the requirements for reporting errors and accidents in manufacturing biological products in § 600.14 (21 CFR 600.14). The proposed rule would also have added § 606.171 and expanded the requirement for reporting of errors and accidents in the manufacturing of biological products to include unlicensed registered blood establishments and transfusion services. FDA provided 90 days for comments on the proposed rule.

FDA is extending a reporting requirement to establishments defined in 21 CFR 607.3(c) that manufacture blood and blood components. Such establishments include unlicensed registered blood establishments and transfusion services (hereinafter referred to as ''unlicensed blood establishments''). FDA believes this action is necessary because it has observed an increase in the number of product recalls initiated by unlicensed blood establishments due to biological product deviations in manufacturing that were not reported voluntarily to the agency. FDA is also narrowing the scope of the reporting requirement as discussed in section II of this document to those reports that are necessary to protect the public health, while relieving industry of some reporting burden. FDA also believes the reporting requirement will address concerns, identified by the Office of Inspector General of the Department of Health and Human Services, that: (1) Error and accident reports required under § 600.14 were not being submitted in a timely manner; and (2) unlicensed blood establishments were not obligated to submit such reports.

II. Highlights of the Final Rule

In response to comments received on the proposed rule, FDA has revised several substantive provisions of the proposed rule. FDA has replaced the term ''error and accident''with the term ''biological product deviation.'' In §§ 600.14(b) and 606.171(b), the final rule more clearly describes the types of events, now termed ''biological product deviations,'' that must be reported to FDA. These are events which may affect the safety, purity, or potency of a distributed biological product and which represent either a deviation from CGMP, applicable regulations, applicable standards, or established specifications, or are unforeseen or unexpected.

In an effort to reduce the reporting burden on both industry and the agency, while protecting the public health, FDA has changed the threshold for when a deviation must be reported. As proposed, a licensed manufacturer or unlicensed blood establishment would have reported deviations related to products ''made available for distribution.'' The final rule focuses on deviations involving distributed products only, because such deviations may involve products administered to patients, and therefore present the greatest risk to public health.

FDA defines the terms ''distributed'' and ''control'' to make clear that the reporting requirement applies only to distributed product. The final rule defines ''distributed'' as meaning the biological product has left the control of the licensed manufacturer or unlicensed blood establishment; or the licensed manufacturer has provided Source Plasma or any other blood component for use in the manufacture of a licensed product. ''Control'' is defined as having responsibility for maintaining a product's continued safety, purity, and potency, and compliance with applicable product and establishment standards and CGMP requirements.

If the product never leaves the control of the licensed manufacturer or unlicensed blood establishment, no biological product deviation report (BPDR) should be filed. However, the licensed manufacturer or unlicensed blood establishment who discovers a biological product deviation before the product has left its control must investigate the deviation. Such an obligation exists independent of this rule. For example, under CGMP, a licensed manufacturer must thoroughly investigate unexplained discrepancies and batch failures, including the failure of a product to meet specifications, and must document the discovery, investigation, and followup taken (parts 211 and 820 (21 CFR parts 211 and 820)). Manufacturers of in vitro products licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) must investigate the cause of nonconformities related to product, processes, and the quality system, and identify the action needed to correct and prevent recurrence of nonconforming product and other quality problems (§ 820.100). The CGMP regulations applicable to licensed and unlicensed blood establishments provide, ''A thorough investigation, including the conclusions and follow-up, of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications shall be made and recorded'' (§ 606.100(c) (21 CFR 606.100(c))). FDA will monitor internal quality assurance (QA) procedures through routine inspections.

In § 600.14(a)(2)(i), FDA has limited the exception to the reporting requirement for manufacturers of in vitro diagnostic products to manufacturers who only manufacture in vitro diagnostic products that are not licensed under section 351 of the PHS Act. Manufacturers of such products continue to have reporting obligations under 21 CFR part 803. Establishments that manufacture both in vitro diagnostic products licensed under section 351 of the PHS Act and unlicensed medical devices will be required to report under § 600.14 only those events which may affect the safety, purity, or potency of the licensed product.

In § 600.14(a)(2)(iii), FDA is clarifying the reporting requirement for licensed manufacturers of biological products when the manufacturer, as part of its license application, is approved to manufacture Source Plasma or any other blood component for further manufacture of other biological products. When a biological product deviation occurs during the manufacture of the Source Plasma or

any other blood component, the BPDR must be submitted under § 606.171. When a biological product deviation occurs after the manufacture of that Source Plasma or any other blood component and during the manufacture of another biological product, the BPDR is submitted under § 600.14. When a licensed manufacturer provides Source Plasma or any other blood component for use in the manufacture of another licensed biological product, such Source Plasma or any other blood component has been distributed under § 606.3(k).

FDA also is clarifying the reporting responsibilities of licensed manufacturers and unlicensed blood establishments who contract out certain manufacturing steps. A manufacturer who contracts with another person to perform any manufacturing step but who retains control over the product is still responsible for reporting under the rule even if the deviation occurred or was discovered at the contract establishment. Sections 600.14(a)(1) and 606.171(a)(1) make explicit that licensed manufacturers and unlicensed blood establishments must establish, maintain, and follow a procedure for receiving from their contractors the information necessary to fulfill their reporting requirements.

FDA is retaining the proposed 45-day reporting time in the final rule but is clarifying that the 45-day time period runs from the date that the manufacturer, its agent, or another person performing a manufacturing, holding, or distribution step under the manufacturer's control, first discovers information reasonably suggesting a reportable event has occurred. FDA is also adding a requirement in §§ 600.14(d) and 606.171(d) that licensed manufacturers and unlicensed blood establishments use Form FDA–3486 to report biological product deviations. This form is available in paper form and also on the Internet. Sections 600.14(e) and 606.171(e) indicate where and how the BPDR form should be submitted.

Finally, FDA has written the final rule using plain language in accordance with the presidential memorandum on plain language in government writing, dated June 1, 1998. FDA has adopted the plain language approach to make its written communications with the public more accessible and understandable. As a result, FDA is expanding § 600.14 and 606.171 in the final rule to address the following: (1) Who must report, (2) What must be reported, (3) When must the report be submitted, (4) How must the report be submitted, and (5) Where must the report be sent?

III. Comments on the Proposed Rule and FDA Responses

FDA received 98 comments on the proposed rule. The comments were submitted by manufacturers, blood establishments, trade associations, professional associations, Department of Defense, and individuals. In addition, the Office of Management and Budget (OMB) forwarded to FDA a number of comments it received on the proposed rule. Thirty-two comments supported FDA's goal of creating a standardized reporting system to identify biological product deviations in manufacturing and recognized the importance to blood safety of requiring prompt reporting of biological product deviations in the manufacture of blood and blood components. Fifteen comments objected to the proposed rule. Several comments, mostly those from transfusion services and pharmaceutical entities, objected to a mandatory reporting requirement being applied to them. Several expressed concerns that the reporting burden would be overwhelming.

In general, the comments expressed specific concerns about the scope and content of the proposed rule and requested clarification of certain definitions. FDA summarizes and responds to each of the received comments in the following sections.

A. General Comments

(Comment 1) Twenty-one comments questioned the public health benefit of the proposed rule and asked FDA to further define its public health and safety objective. Many of the comments suggested that the reporting system overlapped existing QA programs and was, therefore, unnecessary.

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 noncomplying entities, and (5) help ensure licensed manufacturers and unlicensed blood establishments are taking appropriate actions to investigate and correct biological product deviations.

The reporting system will enable the agency to evaluate and monitor blood establishments in response to detected deviations, and regularly alert field staff and blood establishments with trend analysis of the types of deviations reported. Under the existing rule, there were two impediments to the success of the reporting process: (1) Error and accident reports were not being submitted in a timely manner by establishments, and (2) there was no assurance that unlicensed blood establishments were submitting reports.

The reporting system is not intended to overlap QA programs. Instead, it provides FDA with information that an individual establishment's QA program may not detect. For example, if an event occurs once a year in every establishment, it may not appear significant to any single establishment. The reporting system will allow FDA to recognize the significance of that event in a timely fashion and to take appropriate action to protect 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.

(Comment 2) Fifty comments wanted to know how FDA will use or analyze the information and what procedure FDA will use to respond to reports received under the rule. Two comments stated that the reports should not be used as a basis for issuing a Form FDA–483.

A BPDR alone will not be a basis for issuing a Form FDA–483. Form FDA–483 is a list a list of observations noted during an FDA inspection and issued to the firm at the conclusion of the inspection. The firm is expected to respond to the observations and make the necessary corrections. First, this information will aid FDA, licensed manufacturers, and unlicensed blood establishments in appropriately targeting QA efforts to improve product quality and reduce manufacturing problems. In addition to reviewing reports upon receipt at FDA, FDA will review all reports during routine inspections and examine all manufacturing deviations, not merely reportable deviations, to ensure that the establishment has followed all established standard operating procedures (SOP's) related to investigation, followup, and reporting of deviations. Secondly, the BPDR's will inform FDA about specific problems licensed manufacturers and unlicensed blood establishments encounter in the manufacture of biological products. FDA intends to provide this data to industry, in accordance with its responsibility to safeguard trade secrets and confidential commercial information. FDA already provides this kind of data in fiscal quarter summaries, available to the public by mail, facsimile, and Internet. Thirdly, these

reports will identify areas needing future guidance from the agency. FDA will issue such guidance in accordance with its good guidance practices (GGP's).

A BPDR alone will not be a basis for issuing a Form FDA–483. However, a documented failure to follow CGMP or other regulatory compliance problem connected to a deviation may become an observation on a Form FDA–483. For example, an investigator may include an observation under one of the following conditions: (1) The deviation reoccurs because of inadequate corrective action, (2) investigation of the deviation is inadequate, or (3) the deviation represents an underlying systemic problem in the operation. Significant CGMP deficiencies related to a BPDR may also become the subject of a Form FDA–483 observation. Of course, an investigator may include the failure to file a BPDR as an observation on a Form FDA–483.

(Comment 3) Several comments expressed concern that FDA would not have the resources to handle the reports submitted under the proposed rule.

After reviewing the comments to the proposed rule, FDA has worked actively to reduce the burden of reporting on licensed manufacturers, unlicensed blood establishments, and the agency under the final rule. FDA has refocused the final rule to require reports only for distributed products. FDA is also developing a standardized format for reporting, which will not only streamline the process for the reporter, but also allow FDA to process the reports more efficiently. FDA believes that the reporting requirement under the final rule will not present an undue burden on licensed manufacturers, unlicensed blood establishments, or the agency.

(Comment 4) Three comments asked how FDA would enforce the proposed rule.

In 1983, through a memorandum of understanding (MOU), the Healthcare Financing Administration (HCFA) and FDA coordinated all federally authorized inspections of unlicensed blood establishments in order to minimize duplication of effort and to reduce the burden on affected facilities. HCFA and FDA will use their usual enforcement tools available under the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 *et seq.*) and the PHS Act (42 U.S.C. 201 *et seq.*). The agencies will review compliance with the reporting requirements during inspections. If upon inspection of a licensed manufacturer or unlicensed blood establishment, the inspecting agency discovers the establishment is not complying with the biological product deviation reporting requirement, or the requirements for investigation and followup, the inspecting agency may take further enforcement action, as warranted.

(Comment 5) One comment questioned whether biological product deviation reports would be subject to the Freedom of Information Act (FOIA) and, accordingly, available to the media or public and whether reporting could cause disclosure of confidential information.

BPDR's would be subject to disclosure under the provisions of the FOIA and the implementing regulations in 21 CFR part 20. FDA will appropriately purge all nondisclosable information prior to the release of the reports.

(Comment 6) Seven comments requested that FDA obtain additional data and hold a public meeting before implementing a final rule. One comment suggested proceeding with a demonstration project first.

In addition to following the normal rulemaking process, FDA has discussed the rule in various public forums. FDA believes interested parties have been given ample opportunity to express their views on the proposed rule. A ''demonstration program'' is unnecessary because this is not a new program, but a revision and updating of an existing program with which most licensed manufacturers have experience. However, FDA may engage in further public discussion to provide guidance to industry concerning what constitutes a reportable deviation within the parameters of the final rule.

(Comment 7) Three comments requested that FDA develop guidance for the proposed rule.

FDA agrees that guidance to industry would be helpful. FDA has developed draft guidance regarding those events it would expect to be reported under this rule. The draft guidance recognizes that licensed manufacturers and unlicensed blood establishments may shoulder a wide range of responsibilities in manufacturing. A manufacturer of licensed biological products would be in control of the product for more steps in manufacturing than a small hospital transfusion service. Accordingly, the draft guidance describes specific guidance for each type of licensed manufacturer and unlicensed blood establishment. The notice of availability for the draft guidances specific for licensed manufacturers of products other than blood and blood components, and licensed and unlicensed blood establishments will issue in the **Federal Register** in the near future.

(Comment 8) FDA received several comments from industry that extending the reporting requirement to unlicensed entities in proposed § 606.171 imposed an unnecessary burden on these entities.

FDA indicated in proposing this regulation that one of its primary objectives was to make the biological product deviation reporting requirement applicable to all blood establishments, whether licensed manufacturers, unlicensed registered blood establishments, or transfusion services. In the proposed rule, FDA stated that reports from the full spectrum of establishments engaged in manufacturing and distribution of blood and blood components were necessary to effectively evaluate and monitor the blood industry. FDA continues to believe that a mandatory reporting requirement is necessary for all establishments involved in blood and blood product manufacturing and is establishing the biological deviation reporting requirement as part of the CGMP regulations, which these establishments must follow.

B. Scope

(Comment 9) One comment recommended FDA adopt a single mechanism for reporting all errors and accidents, adverse events, etc., for all blood products, medical devices and all drugs, and eliminate all other reporting programs, voluntary or mandatory.

FDA recognizes that the reporting programs for biological products, human drugs, and medical devices have varying requirements. What is reported, and how it is reported, are different under the different systems. These differences are intentional. For example, the adverse event reporting (AER) and medical device reporting systems focus on patient impact. The starting point for reporting, therefore, is often patient reaction to a product. In contrast, biological product deviation reporting focuses on the manufacturing process as it may affect the safety, purity, and potency of the product. FDA anticipates that information submitted in BPDR's will improve product quality and may help reduce the incidence of adverse patient outcomes without undue burden on licensed manufacturers and unlicensed blood establishments.

(Comment 10) Five comments stated that the proposed rule should apply only to blood and blood products and should not extend to biotechnology products. These comments argued that the need to revise error and accident regulations for biotechnology products is not clear because there does not exist a pattern of recalls for these products. The comments stated that the recall

guidelines in part 7 (21 CFR part 7) and the AER system (21 CFR 600.80) are adequate to ensure the safety and quality of biotechnology products.

The regulatory scheme for biotechnology products has always included recall guidelines (part 7), AER, and error and accident reporting (§ 600.14). These three programs, each designed to serve different objectives, have worked together to ensure the safety and quality of biotechnology products. Adverse experience reporting focuses on patient outcomes. Consequently, the type and specificity of the information reported as adverse experiences differs substantially from that required in biological product deviation reports. Under the recall provisions of part 7, manufacturers notify FDA when they voluntarily remove products from the marketplace that are in violation of the laws administered by FDA. The biological product deviation regulations are designed to gather information about the events that give rise to defective or potentially defective products and provide FDA with an essential tool to monitor potential risks to public health and to facilitate a response when necessary.

Section 600.14, in its current form, requires error and accident reporting by all licensed biological product manufacturers, including manufacturers of biotechnology products. This rule would not impose new requirements on such manufacturers. In fact, by limiting reporting to biological product deviations involving distributed products, the new rule would decrease the preexisting burden on such manufacturers. FDA believes the revised reporting requirement is necessary to ensure that all manufacturers understand their reporting requirements, to expedite biological product deviation reporting, and to enable FDA to monitor accurately the safety of biological products.

(Comment 11) Ten comments requested that transfusion centers not be regulated to the same extent as blood collection centers and the pharmaceutical industry under the proposed rule. Of these, five comments proposed that the reporting guidelines themselves be specific to each type of establishment. Six comments called for definitions or examples specific to transfusion service practice and two comments called for separate data collection forms.

FDA believes that in order to achieve an accurate overview of the industry, it is most useful to impose the same reporting requirement on all blood establishments, including transfusion centers. However, FDA recognizes that different regulated entities may need specific guidance on how the biological deviation reporting requirement will apply to them. FDA is issuing guidance to support the final rule that will include examples specific to blood and source plasma collection centers, pharmaceutical and biological device manufacturers, and transfusion services. FDA also developed a biological product deviation reporting form. FDA believes one form for all the entities covered under the rule will facilitate processing of the reports and will aid reporters in providing the necessary information. The agency will provide separate instructions on completing and submitting the biological product deviation reporting form.

(Comment 12) Eight comments asked how the biological product deviation reporting requirement will affect the new drug application (NDA) Field Alert Report regulations under 21 CFR 314.81(b)(1) and several comments recommended harmonizing these regulations.

The BPDR's will have little, if any affect on the NDA Field Alert regulations. The NDA Field Alert regulations are applicable only to those products that are approved for marketing under the provisions of part 314 (21 CFR part 314), and not to drug products subject to licensing under the PHS Act. FDA has harmonized a number of regulations for certain biotechnology products where products regulated as biological products subject to licensure are similar to products subject to regulation as new drugs. See § 601.2(c) (21 CFR 601.2(c)) for a list of such biotechnology products and § 314.70(g), 601.2(c)(1) and (c)(2), and 601.12 (21 CFR 601.12) for examples of harmonization.

For these biotechnology products, a total of 13 error and accident reports were submitted under § 600.14 in the fiscal year (FY) 1999. Because FDA believes this is a very small burden to industry, FDA has determined that reports for such biotechnology products should continue to be submitted consistent with the requirements for other biological products under § 600.14 of the final rule. This will allow the Center for Biologics Evaluation and Research (CBER) to keep all reports in a single data base and will facilitate the overall assessment of its biological product deviation reporting program. If the level of reporting or the needs of the agency change, FDA will reconsider whether to harmonize its reporting requirements for biotechnology products.

(Comment 13) Twenty-two comments recommended developing a tiered system of reporting based on the severity of the deviation in which serious errors or accidents would be reported and all other errors and accidents would be handled through internal QA programs.

FDA considers any biological product deviation that may affect the safety, purity, and potency of a product to be ''serious.'' However, deviations that are discovered before distribution pose less of a threat to the public health because no patient would receive the product, and because the licensed manufacturer or unlicensed blood establishment's QA procedures worked to prevent the distribution of product subject to that biological product deviation. Accordingly, FDA has established an approach to reporting biological product deviations that limits reporting to events that involve distributed products and that may affect the safety, purity, or potency of the product.

(Comment 14) Eighteen comments recommended adopting an alternative reporting system such as the medical event reporting system for transfusion medicine (MERS–TM).

MERS–TM, a voluntary reporting system, was designed as a standard method for collection and analysis of event reports for blood establishments to implement as part of their QA system. The MERS–TM is designed to capture all manufacturing errors and accidents, including those ''near miss'' events that may be discovered by the blood establishment prior to distribution of the product. While FDA believes that the MERS–TM system is useful in reporting ''near miss'' events on a voluntary basis, FDA is limiting the requirement for reporting to biological product deviations affecting distributed products.

C. Definitions

(Comment 15) Forty-five comments requested clarification of the definition of the terms ''errors and accidents'' in proposed §§ 600.3(hh) and 606.3(k). Several of these comments suggested alternative language.

FDA is clarifying the regulations by eliminating the terms ''error and accident.'' The classification of events as an ''error'' or ''accident'' is immaterial to the purposes underlying the rule and appears to have caused confusion. Consequently, FDA has revised the rule to focus the reporting requirement on events that represent a deviation from CGMP, applicable regulations, applicable standards or established specifications, or represent unexpected or unforeseeable events,

which may affect the safety, purity, or potency of a distributed product. Such events are reportable regardless of whether or not they are considered ''errors'' or ''accidents.'' In the final rule, FDA has termed such events ''biological product deviations'' and described what constitutes a biological product deviation in §§ 600.14(b) and 606.171(b).

(Comment 16) Three comments suggested that the reporting requirement in proposed §§ 600.3(hh)(1) and 606.3(k)(1) should be limited to deviations from CGMP and that extending it to ''applicable standards'' or ''established specifications'' was beyond the FDA's jurisdiction.

FDA disagrees with the suggestion that such matters are beyond FDA's jurisdiction. As set out in §§ 600.14(b) and 606.171(b), licensed manufacturers and unlicensed blood establishments must submit a BPDR only if the deviation ''may affect the safety, purity, or potency'' of a product, and if other reporting criteria are met. Events affecting the safety, purity, and potency of biological products fall squarely within FDA's jurisdiction. Moreover, the PHS Act requires FDA to consider ''standards designed to assure that the biological product continues to be safe, pure, and potent'' (42 U.S.C. 262(a)(2)(B)(i)(II)).

(Comment 17) Thirty-two comments requested clarification of the definition of ''made available for distribution'' in proposed §§ 600.3(ii) and 606.3(l). Thirty-seven comments requested that the definition be amended to limit the scope of the proposed rule to reporting of deviations which occur after a product has been distributed, and six comments asked that ''made available for distribution'' be defined by each facility based on their established process controls.

FDA agrees with the comments that suggested that the scope be limited to those products that have been distributed and has written the final rule to reflect this. FDA considers all events that may affect the safety, purity, or potency of a biological product to be significant, whether prior to or after distribution. Limiting the reporting requirement to distributed products will reduce the burden of reporting on licensed manufacturers, unlicensed blood establishments, and on FDA, while not sacrificing public safety.

Licensed manufacturers and unlicensed blood establishments remain obligated to document, investigate and followup any event that may affect the safety, purity, or potency of a biological product under CGMP regulations, whether the event is reportable under this rule or not. FDA will continue to monitor both reportable and nonreportable events and corrective actions through inspections.

(Comment 18) One comment stated the term ''made available for distribution'' in proposed §§ 600.3(ii) and 606.3(l) is ambiguous in relation to intermediates since at each intermediate state the product may be released for further processing.

FDA has clarified the final rule by limiting reporting of biological product deviations to distributed products, i.e., they have left the licensed manufacturer or unlicensed blood establishment who controlled the product at the time the deviation occurred; or the licensed manufacturer has provided Source Plasma or any other blood component for use in the manufacture of a licensed product.

D. Who Must Report?

(Comment 19) One comment asked for clarification on how FDA will apply this regulation to cooperative manufacturing arrangements, including shared and contract manufacturers.

Under § 600.14, it is the licensed manufacturer who must report biological product deviations. That is because, up until the time the product is distributed, it is the license holder who is responsible for maintaining the continued safety, purity, and potency of the biological product, for compliance with applicable product and establishment standards, and for compliance with CGMP. If the license holder arranges for another manufacturer to perform a manufacturing step, that manufacturing step is performed under the license holder's control, and the license holder must report biological product deviations that occur during that manufacturing step. In shared manufacturing situations, where two or more manufacturers operate under their own license, each manufacturer would report a biological product deviation that occurred when the product was in its control; i.e., when the first shared manufacturer completes his manufacturing step and sends the product to the second shared manufacturer for additional manufacturing, the product is considered distributed by the first shared manufacturer.

Section 606.171 applies to all blood establishments, including licensed establishments, unlicensed registered blood establishments, and transfusion services. The rule requires the blood establishment that has control over a product when a blood product deviation occurs to report to FDA. If a blood establishment contracts a manufacturing step to another facility, or enters into a shared manufacturing agreement, the establishment responsible for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with CGMP, must submit a BPDR for any deviation occurring while the biological product is under its control.

(Comment 20) One comment suggested FDA require both the blood bank or transfusion service who receives a defective product from a licensed manufacturer and the licensed manufacturer to report biological product deviations to ensure the effectiveness of the reporting process.

In the final rule, FDA has attempted to eliminate duplicate reporting by regulated entities. The licensed manufacturer or unlicensed blood establishment who had control over the product when the deviation occurred is in the best position to provide the necessary information to FDA. Therefore, under the final rule, the licensed manufacturer or unlicensed blood establishment who had control over the product when the deviation occurred is responsible for reporting. Consignees should report product deficiencies to the licensed manufacturer or unlicensed blood establishment and assist in the investigation of the product's deficiencies, if necessary.

Example 1: An unlicensed blood establishment pools 10 units of cryoprecipitate and affixed an incorrect, extended expiration date. The unlicensed blood establishment issues the pooled cryoprecipitate to a patient. The unlicensed blood establishment would be required to submit a BPDR to FDA because: (1) The product did not meet CGMP; (2) the unlicensed blood establishment had control of the product when the deviation occurred; (3) the deviation may have affected the safety, purity, and potency of the product for the patient; and (4) the product was distributed.

Example 2: An unlicensed blood establishment receives a unit of irradiated red blood cells from a licensed manufacturer and issues the product to a patient requiring irradiated red blood cells. The licensed manufacturer of the blood product subsequently notifies the unlicensed blood establishment that the unit was improperly irradiated. The licensed manufacturer, not the unlicensed blood establishment, is required to submit a BPDR to FDA because: (1) The product did not meet CGMP; (2) the deviation

occurred under the control of the licensed manufacturer; (3) the deviation may affect the safety, purity, and potency of the product; and (4) the licensed manufacturer distributed the product to the unlicensed blood establishment.

E. What Kind of Events Are Reportable?

(Comment 21) Forty-two comments stated that FDA provided insufficient information about what events must be reported in proposed §§ 600.14 and 606.171. Numerous comments also expressed concern regarding the examples of what events to report that FDA provided in the preamble to the proposed rule. Ten comments asked for information on what not to report. Seven comments asked FDA to provide specific examples of events to be reported by hospital-based transfusion services.

In response to these comments, FDA has changed the final rule to limit reportable events to those involving distributed products. As discussed in comment seven of this document, FDA developed guidance that will provide specific examples of reportable events as those events relate to the various regulated entities. FDA considered these comments in developing its guidance.

(Comment 22) Two comments asked whether the proposed rule was limited to manufacturing activities or whether it included nonmanufacturing events such as testing, storage, labeling, and recordkeeping.

FDA disagrees with the interpretation that testing, storage, labeling, and recordkeeping are not manufacturing activities. The term ''manufacture'' is defined in 21 CFR 600.3(u) as ''all steps in propagation or manufacture and preparation'' and includes, for example, filling, testing, labeling, packaging, and storage.

The final rule further states in §§ 600.14(b) and 606.171(b) that any event, and information relevant to the event, associated with manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding, or distribution, must be reported if they meet the other criteria. If a recordkeeping error may have affected the safety, purity, and potency of the product and meets the other criteria in §§ 600.14(b) and 606.171(b), it is reportable under the regulations.

(Comment 23) One comment asked how a licensed manufacturer or unlicensed blood establishment would distinguish between an error and accident that would be reportable from any unexplained discrepancies or in-process or final specification investigations conducted under § 211.192 or other regulation, which would not have to be reported.

The requirements to investigate discrepancies under § 211.192 and to report product deviations under §§ 600.14 and 606.171 are not mutually exclusive. Under § 211.192, manufacturers are required to investigate any unexplained discrepancies or failure to meet in-process or final product specifications. The CGMP regulations applicable to blood establishments provide, ''A thorough investigation, including the conclusions and follow-up, of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications shall be made and recorded'' (§ 606.100(c)). If during the investigation the criteria described in §§ 600.14(b) and 606.171(b) are met, a BPDR is required.

(Comment 24) One comment asked whether the biological product deviation reporting requirement applied to validation batches submitted in support of a biologics license application (BLA), or to materials submitted under an investigative new drug application (IND).

Under §§ 600.14 and 606.171, biological product deviations related to products under an IND would not be reportable unless the product was licensed for another intended use. However, information related to the deviation may be required to be reported under the IND regulations in 21 CFR part 312. Biological product deviations related to validation batches would not be reportable unless the products were distributed after receipt of a biologics license.

(Comment 25) One comment asked if the submission of a supplement for reprocessing would preclude the submission of a BPDR.

The submission of a supplement for reprocessing would not preclude the submission of a BPDR. If a product has been distributed and a licensed manufacturer or unlicensed blood establishment determines that a biological product deviation has occurred, then the licensed manufacturer or unlicensed blood establishment must submit a BPDR whether or not it subsequently reprocesses the product. If the licensed manufacturer or unlicensed blood establishment discovers a biological product deviation before it distributes the product, and subsequently reprocesses and distributes the affected product, no BPDR would be required as long as the reprocessed product was unaffected by the original deviation.

F. What Type of Information Do Licensed Manufacturers and Unlicensed Blood Establishments Report?

(Comment 26) Two comments requested that FDA delete any reference to ''disposition of the product'' from the information that is to be reported under the rule because this information would not be available within the 45-day time requirement.

FDA believes licensed manufacturers and unlicensed blood establishments will usually know the disposition of the product within the 45-day reporting period. Licensed manufacturers and unlicensed blood establishments should know if the product was shipped to another facility, destroyed, quarantined, designated for reprocessing, disposed of in some other manner, or, in many cases, administered to a patient.

(Comment 27) Seventeen comments recommended that if the product has been subject to recall, then the recall should be the instrument for reporting the disposition of the product.

FDA disagrees. FDA believes information on the disposition of the product and retrieval efforts are important in analyzing the impact of reported deviations on the public and should be submitted in BPDR's. The information required for the BPDR is not as extensive as the recall information voluntarily provided to the district. The information regarding final disposition does not need to be complete by the time the BPDR is submitted. By obtaining as much information as possible on the disposition of a product at the time the report is submitted, FDA will be able to perform appropriate followup action. The draft guidance document will further describe the required information to be reported in the BPDR.

(Comment 28) One comment asked if FDA would require licensed manufacturers and unlicensed blood establishments to consider previous and subsequent lots in investigating any lot that instigated a BPDR.

The regulations in this final rule do not affect the manner in which a biological product deviation is investigated. The obligation to investigate a biological product deviation is part of the CGMP regulations for biological drug products and biological devices, including blood and blood components. The CGMP requirements for blood establishments, whether licensed or unlicensed, require blood establishments to thoroughly investigate discrepancies (§ 606.100(c)) and to maintain and make available to FDA appropriate records of such investigation, conclusions, and

followup (§§ 606.100(c) and 606.160(b)(7)(iii) (21 CFR 606.160(b)(7)(iii))). Licensed manufacturers subject to drug CGMP (§§ 211.192 and 211.198) and medical device manufacturers (see § 820.100) are similarly obligated to investigate, correct, and record findings related to biological product deviations. Under these existing regulations FDA expects the licensed manufacturer or unlicensed blood establishment to determine what impact the deviation may have had on other product lots and take appropriate corrective action. These regulations do not mandate the manner of investigation by a licensed manufacturer or unlicensed blood establishment but require that the investigation be complete.

G. When to Report

(Comment 29) Twenty-three comments stated that 45-calendar days to report a biological product deviation as proposed in §§ 600.14(a) and 606.171 is not enough time since licensed manufacturers and unlicensed blood establishments must analyze and correct the deviation prior to reporting. One comment suggested that fewer than 45 days to report would be better.

In adopting a 45-day time requirement, FDA looked at the history of reporting under the prior regulations and determined that 45 days was a reasonable period given the importance of timely reporting. The agency reviewed the reports submitted during FY 1997 through 1999 and an average of 73 percent of the reports was received within 45 days.

Licensed manufacturers and unlicensed blood establishments should not wait to report biological product deviations until after completing their corrective actions. Rather, licensed manufacturers and unlicensed blood establishments should submit BPDR's as soon as possible but no later than 45 days after the date that the licensed manufacturer or unlicensed blood establishment, its agent, or another person performing a manufacturing, holding, or distribution step under the manufacturer's or establishment's control, first discovers information reasonably suggesting a reportable event has occurred. The reports should include information on the intended followup to be taken if followup is not completed prior to submission of the report. To facilitate timely reporting by licensed manufacturers and unlicensed blood establishments, FDA is providing guidance on how to report as well as a standardized form for reporting.

(Comment 30) Fourteen comments requested clarification as to when the 45-day reporting time limit begins. Several of these comments offered various possible starting dates.

In response to these comments, FDA has clarified the 45-day time requirement in the final rule. The 45 days commence on ''the date (the licensed manufacturer or unlicensed blood establishment, its agent, or another person who performs a manufacturing, holding, or distribution step under the control of the licensed manufacturer or unlicensed establishment) acquire(s) information reasonably suggesting that a reportable event has occurred.'' For example, if a manufacturer contracted with a third party to receive and process its customer complaints, that third party would be the manufacturer's agent for purposes of this rule, and the 45 days would begin to run upon the agent's receipt of information reasonably suggesting a reportable event has occurred.

(Comment 31) Four comments recommended adopting a hierarchy for when to report based on the potential risk of the deviation. For example, one comment suggested errors with substantial risk be reported within 45 days, errors with moderate risk be reported when the internal investigation is complete and errors with minimal risk be reported in an annual report.

FDA has adopted a simpler approach based on the potential public health risk of the event. Biological product deviations involving distributed products must be reported within 45 days. Biological product deviations that are discovered before the product leaves the control of the licensed manufacturer or unlicensed blood establishments are nonreportable, but reviewable during routine inspections, because such events present significantly less public health risk.

H. How to Report

(Comment 32) Forty-seven comments requested a standardized format for reporting biological product deviations and several of these submitted a proposed form. Fourteen comments requested one form for hospital-based transfusion centers and a separate form for blood collection centers and pharmaceutical manufacturers. Seventeen comments requested FDA to develop means for electronic reporting. One comment suggested FDA supply forms to blood suppliers.

FDA recognizes the need for a standardized method for reporting biological product deviations. FDA has developed a form for licensed manufacturers and unlicensed blood establishments to use to report under the final rule and is issuing guidance including instructions for completing the biological product deviation reporting form. FDA also has developed an electronic format for reporting. The agency has taken into consideration the comments and sample forms submitted in devising the biological product deviation reporting form. The agency also is requesting comments to the docket from the public on the report form and the instructions for preparing the report in accordance with the Paperwork Reduction Act of 1995. The agency is making the form available in various ways, including the FDA website at http://www.fda.gov/cber and the CBER FAX information system at 1–888–CBER–FAX.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104094). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to analyze whether a rule may have a significant impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation) in any one year.

The agency has determined that the final rule is a significant action as defined in section 3, paragraph (f)(4) of Executive Order 12866. We have also determined that this rule will not result in aggregate expenditures for State, local, and tribal governments, or the private sector of $100 million in any one year. Based on FDA's analysis using available data, the agency does not anticipate that the rule will result in a significant impact on a substantial number of small entities.

A. Estimated Economic Impact

The rule will have an impact on licensed manufacturers and unlicensed blood establishments as described in table 1 of this document. All of these types of establishments will experience both a one-time cost impact to make changes to their recordkeeping systems and reporting procedures, as well as an annual cost impact associated with the ongoing reporting of product deviations that are encountered. Table 1 below summarizes these two components of cost impact. The rule is estimated to have an aggregate one-time cost impact of $8,131,648 and an annual cost impact of $340,319. These estimates are detailed in the discussion that follows.

TABLE 1.—SUMMARY OF ESTIMATED COST IMPACT OF THE RULE

Industry Affected	Total One-Time Cost	Total Annual Cost
Licensed Manufacturers (Other than Blood and Blood Components)		
111 Manufacturers of biologics	$348,096	($1,803)[1]
Subtotal for manufacturers of biologics	$348,096	($1,803)[1]
Blood Establishments		
Licensed blood establishments	$727,552	($286,395)[1]
2,800 Registered blood establishment	$4,390,400	$95,397
3,400 Transfusion services	$2,665,600	$533,120
Subtotal for blood establishments	$7,783,552	$342,122
Total Cost Impact	$8,131,648	$340,319

[1]Use of parenthesis indicates savings.

Based on the agency's registration data base, there are an estimated 111 licensed biologics manufacturers, 232 licensed blood establishments, and 2,800 unlicensed registered blood establishments. Based on data from the HCFA, there are estimated to be 3,400 transfusion services currently in operation. Such manufacturers and establishments currently conduct some QA activities. The impact of the final rule reflects the change in these ongoing activities that would be required by the rule.

B. One-Time Costs for Affected Establishments

Licensed biologics manufacturers must comply with part 211 or part 820; and licensed and unlicensed blood establishments must comply with parts 211 and 606 (21 CFR part 606), which encompasses a variety of QA activities embodied in CGMP's, to include investigating problems, performing followup, and recordkeeping.

The proposed rule stated that FDA had no precise estimates of the one-time cost for preparation and/or revision of the SOP, staff training, and time spent making the report. The agency expected that such activities would require an average of 2 hours to create an SOP for submitting error and accident reports, and approximately 1 hour to review and update existing SOP's at the establishments that have been reporting. The majority of the comments from industry stated that the estimates were underestimated. However, only a couple of comments, based on their experience, suggested a range of timeframes from 20 hours to a few days to develop and implement a new SOP. FDA has reassessed the time for staff review of the requirements of the rule, establishing or making adjustments to current systems and procedures, and for staff training. These estimates are discussed below.

Licensed biologics manufacturers currently have recordkeeping systems and QA systems in place. These establishments are estimated to incur a one-time cost for staff review of the requirements of the rule, and accompanying modifications to current systems and procedures, and for staff training in the use of modified procedures. FDA estimates that these activities may require a total of 80 hours of staff time. Using an estimated hourly wage rate of $39.20,[1] the total one-time cost for these manufacturers is estimated to be $348,096 ($39.20 × 80 × 111).

For blood establishments, the changes made in response to the rule are expected to vary according to whether the establishment is currently licensed. The 232 licensed blood establishments are currently required to report the product deviations under § 606.14. These facilities are likely to have systems in place for keeping record of product deviations, and will not be expected to have to establish a new reporting system. However, the licensed blood establishments are also likely to handle the majority of product deviation reports, because these facilities account for an estimated 90 percent of the total volume of U.S. blood collections. The licensed blood establishments will need to allocate staff time for a one-time review of the rule and some modifications to their current recordkeeping system and reporting procedures. In addition, these facilities will allocate a few hours of training time to review the reporting changes with staff who will be involved in the reporting of product deviations to FDA. FDA estimates that these activities may require a total of 80 hours of staff time. Using an estimated hourly wage rate of $39.20, the total one-time cost for these manufacturers is estimated to be $727,552 ($39.20 x 80 x 232).

The 2,800 registered blood establishments that are not licensed are estimated to account for about 10 percent of total U.S. blood collections, and currently perform product deviation reporting on a voluntary but less consistent basis. It is anticipated that the registered blood establishments will allocate staff time to establish a recordkeeping system for reportable product deviations involving products. In addition, the registered blood establishments will allocate staff time to modify current SOP's to comply with the biological product deviation reporting required by the rule, and to review the SOP changes with the staff who will be involved in reporting these deviations to FDA. FDA estimates that these activities will require an average of 40 hours of staff time per facility. Using an estimated hourly wage rate of $39.20, the total one-time cost for these establishments is estimated to be $4,390,400 ($39.20 x 40 x 2,800).

[1]This estimated wage rate is based on the rate of $37.98 used in the proposed rule published in 1997, inflation-adjusted to 1999.

Transfusion services currently perform a variety of QA activities, but report product deviations to FDA on a voluntary and very limited basis. Transfusion services currently must comply with 42 CFR 493.1273(a). This regulation requires transfusion services to comply with parts 606 and 640 (21 CFR part 640) provisions, which includes keeping records of errors and accidents, transfusion reaction reports and complaints, with a record of investigation and followup. These establishments are expected to allocate staff time to review the requirements of the rule, modify current SOP's to comply with the biological product deviation reporting requirements, and train appropriate staff in using the modified procedures. This one-time effort is estimated to involve approximately 20 hours of staff time per facility, yielding an estimated cost of $2,665,600 ($39.20 x 20 x 3,400) for transfusion services. Based on the estimates for licensed and unlicensed blood establishments, the total one-time cost for blood and blood component manufacturers is $7,783,552 ($727,552 + $4,390,400 + $2,665,600).

C. Annual Costs for Affected Establishments

In addition to the cost of establishing modified systems and procedures, unlicensed blood establishments will experience some annual costs associated with ongoing reporting of product deviations that fit the criteria specified in the rule. Those costs are estimated below.

Licensed manufacturers and unlicensed blood establishments will be required to report to FDA product deviations when: (1) The event is associated with the manufacturing, to include testing, processing, packing, labeling, and storage, or with the holding or distribution of a licensed biological product, or a licensed or unlicensed blood or blood component; (2) the deviation occurs in the licensed manufacturer or unlicensed blood establishment's facility or in another facility while the product remains in the control of the licensed manufacturer or unlicensed blood establishment; (3) the deviation may affect the safety, purity, or potency of that product, and either represents a deviation from CGMP, applicable regulations, applicable standards, or established specifications; or represents an unexpected or unforeseeable event; and (4) the deviation involves a distributed product.

When a manufacturer becomes aware of a reportable product deviation, the manufacturer investigates the deviation, records the deviation, and performs followup. FDA estimates that the establishment will allocate an additional 2 hours of staff time to prepare and submit a report to FDA. In the comments on the proposed rule, FDA received one comment that suggested the agency's estimate of 30 minutes to file a report was reasonable for the filing task itself, but would not cover the time needed to prepare the report. Other comments stated that their establishments average 4, 6, or 8 hours to prepare a report, but some comments also explained that these hours included investigations, followup, and SOP revision. FDA agrees that 30 minutes would not reflect the anticipated time for preparing, in addition to filing, the report. The reporting to FDA required in this rule does not introduce additional requirements for recordkeeping, investigation, and followup of manufacturing problems and deviations beyond what is required under CGMP requirements. Therefore, the estimated time for complying with this final rule does not include recordkeeping, investigation, and followup of a biological product deviation.

Licensed manufacturers already report a broad range of product deviations to FDA. This range includes all deviations in products made available for distribution, and has not previously been limited to those products actually distributed. Under the existing regulation, a total of 93 biologics manufacturing deviations were reported to FDA in 1999. Since the new rule limits the criteria for reporting, FDA estimates that reporting will be 25 percent reduced, yielding an estimated total of 70 reports (93 x (1090.25)) rather than the current 93 reports. Based on the estimate of 2 hours to complete and file a report, FDA estimates a total savings of $1,803 ((93–70) × 2 × $39.20).

Under the current rule, a total of 14,611 blood and blood component errors and accidents were reported by licensed blood establishments to FDA in FY 1999. These facilities are also estimated to account for approximately 90 percent of all blood and plasma collections, totaling approximately 26 million units, or 23,400,000 (0.90 x 26,000,000) units processed by licensed blood establishments. The current rate of reporting per unit of blood collected and processed is thus 6.24 ((14,611/23,400,000) x 10,000) per 10,000 units. Under the final rule, FDA estimates that reporting for these facilities will be reduced by 25 percent, reducing the total reports to 10,958 ((1090.25) x 14,611) or a rate of 4.68 (10,958/23,400,000 x 10,000) per 10,000 units of collection. This translates to a projected savings of $286,395 ((14,611–10,958) × 2 × $39.20)).

Assuming a deviation reporting rate of 4.68 per 10,000 units for those unlicensed registered blood establishments that account for approximately 10 percent of the total blood collections of 26 million units, the agency estimates that unlicensed registered blood establishments will incur new annual costs of $95,397 (0.10 x 26,000,000 x (4.68/10,000) x 2 x $39.20) to make an estimated 1,217 reports. This translates to an increased annual cost of approximately $34.07 ($95,397/2,800) per unlicensed registered blood establishment.

Transfusion services will be newly required to report product deviations that meet the criteria specified in the rule. The annual cost to transfusion services for this reporting requirement is based on the voluntary annual reporting rate of transfusion services for FY 99, i.e., two reports per transfusion service. This reporting rate is supported by the estimate of BPDR's per hospital per year by bedsize calculated in table 2 of this document. The reporting by the transfusion service is estimated to involve approximately 2 hours of staff time at the transfusion facility. As noted earlier, this rule does not require new investigations of such reports. Records of investigations and followup to address problems with the manufacturing process are already required as part of the CGMP for blood and blood components. FDA therefore estimates the total cost of annual reporting by transfusion services to be $533,120 (3,400 x 2 x 2 x $39.20). This translates to an increased annual cost of approximately $156.80 per transfusion service.

In summary, the annual cost impact of the rule is estimated to be $342,122 (($95,397 + $533,120)—$286,395) for licensed and unlicensed blood establishments, and a net savings of $1,803 for licensed manufacturers of biological products other than blood and blood components.

D. Impact on Small Entities

The agency does not anticipate that the final rule will have a significant impact on a substantial number of small business establishments. However, because of the limits of available data, the agency is uncertain about the number of small entities affected and the actual extent of current product deviations at these facilities that would trigger reporting and determine the cost impact. Since the agency received no comments supported by data regarding the estimated impact on small entities in the proposed rule, the following

analysis is based on the limited data available.

The licensed manufacturers and unlicensed blood establishments affected by the final rule are included under the major Standard Industrial Code (SIC) group 80 for providers of health services. According to section 601 of the Regulatory Flexibility Act of 1980, the term ''small entity'' encompasses the terms ''small business,'' ''small organization,'' and ''small governmental jurisdiction.'' According to the Small Business Administration (SBA), a small business within the blood industry is an enterprise with less than $5 million in annual receipts. A small organization is a not-for-profit enterprise which is independently owned and operated and is not dominant in its field. A ''small governmental jurisdiction'' generally means governments of cities, counties, towns, townships, villages, school districts, or special districts, with a population of less than 50,000. Because the rule would reduce reporting requirements for currently licensed facilities, FDA has focused the following small business analysis on those blood collection facilities and transfusion services that will be newly required to report these product deviations, and are therefore expected to incur new costs.

E. Impact on Small Blood and Blood Component Manufacturers

The FDA registry of blood establishments does not provide an indication of the size of the registered entities. Although uncertain, it is likely that some smaller facilities may experience significant costs as a result of compliance with the final rule. According to the 1996 directory of the American Association of Blood Banks (AABB), only 34 regional and community blood centers have annual revenues of less than $5 million and each collect no more than 30,000 donations per year. With an estimated rate of 4.68 product deviation reports per 10,000 units collected [see annual cost estimates in section IV.C of this document], this would imply an estimated 14 product deviation reports (4.68 x 3) per smaller blood center per year, and associated cost of $1,098 ($39.20 x 2 x 14 reports). The one-time cost for these facilities is expected to be similar to the unlicensed registered blood establishments estimate involving 40 hours of staff time, thus $1,568 ($39.20 x 40) per facility.

F. Impact on Small Transfusion Service Facilities

Hospital transfusion services are expected to be the primary entity affected by the requirements, but the extent of the small business impact is uncertain. Although the details of manufacturing activities at transfusion services are not available, FDA examined other data to develop a preliminary assessment of small business impact. The size of U.S. hospitals varies substantially. The 1998 American Hospital Association (AHA) survey data indicate a total of 5,134 U.S. registered community hospitals grouped into 8-bedsize categories. The average annual revenues for facilities in these bedsize categories range from approximately $5.5 million to $513 million. However, since many hospitals are not-for-profit or are operated by State and local governments, the SBA annual receipt criteria for small businesses would not apply to these facilities. Of the 5,134 U.S. community hospitals included in the AHA report 1,330 are under the control of State and local government, 3,045 are nonprofit institutions and the remaining 759 are reported to be investor-owned.

The number of hospitals that would meet at least one of the various SBA definitions for small entities is uncertain. According to the AHA statistics for 1998, the smallest reported hospital size category includes 262 hospitals with 6 to 24 beds, and total gross revenues of $1.43 billion, yielding average revenues of $5.46 million. FDA assumes that the 11 facilities reported to be investor-owned within this bedsize category could qualify as small entities. Although it is possible that all nonprofit hospitals may qualify as small entities, it appears that a number of facilities might be excluded from that definition because they are reported to be hospitals in a system. According to the AHA survey definition, ''hospitals in a system'' refer to those ''hospitals belonging to a corporate body that owns and/or manages health provider facilities or health-related subsidiaries; the system may also own non-health-related facilities.'' The AHA currently has record of 1,592 hospitals that are nonfederal and nonprofit (including State and local government controlled) that are hospitals in a system. If these facilities were excluded, FDA estimates that 2,783 [1,330 State & local + 3,045 nonprofit—1,592 in-a-system] nonfederal, nonprofit hospitals may qualify as small entities. Thus, a total of 2,794 [2,783 + 11] hospitals might qualify as small entities.

The following analysis of potential impact by size of hospital suggests that, regardless of hospital size, the cost impact of product deviation reporting will be limited if the number of deviation reports per facility is proportionate to the utilization of blood transfusions implied by relative number of inpatient surgeries performed by hospitals in different size categories. Table 2 of this document estimates the percentage of all inpatient hospital surgeries, based on the number of inpatient surgeries reported to AHA as performed by hospitals in different bedsize categories. This percentage is used to estimate a share of the total reports that would be made by hospitals in each category. The estimated number of product deviation reports per hospital within a bedsize category is based on the total projected number of reports and the percentage of inpatient surgeries reported for hospitals within each size category.

TABLE 2.—ESTIMATES OF BPDR'S PER HOSPITAL PER YEAR BY BEDSIZE CATEGORY

Bedsize Category	Nonfederal Hospitals	Estimated Percent Inpatient Surgeries	Estimated Share of 1,217 Product Deviation Reports	Estimated Reports per Hospital[1]
6 to 24	262	0.21	2.6	0
25 to 49	906	2.02	24.6	0
150 to 99	1,128	6.03	73.3	0
100 to 199	1,338	19.38	235.9	0
200 to 299	692	20.99	255.4	0
300 to 399	361	16.24	197.6	1
400 to 499	196	12.17	148.1	1
500 +	251	22.97	279.5	1

[1]Rounded to the nearest whole number.

The cost impact of product deviation reporting is based on the table 2 estimates of reports per hospital and the earlier estimate of one-time cost of $784 (20 hours x $39.20) per hospital to modify systems and SOP's for recordkeeping and reporting. Based on the low expected volume of reports per hospital, the agency found that the estimated annual reporting cost, as a percentage of average annual facility revenues, approached zero for hospitals in every bedsize category. This suggests that the relative cost impact may be quite limited, across hospitals of different sizes, if the number of BPDR's required per hospital is proportionate to the number of inpatient surgeries performed by hospitals in different size categories.

G. Expected Benefits of the Rule

As described in the preamble, the benefits of the rule relate to the safety of biological products and protection of the public health. The final rule focuses on the subset of risk events in which the product is actually distributed and the cause of the problem is related to steps in the manufacturing process, that may affect the safety, purity, and potency of the product. FDA needs to receive timely reports of such events in order to quickly address problems, and provide updated industry guidance to assure continued product safety and good manufacturing practice. The requirements provide FDA with the ability to detect broader risks that extend beyond the reach of a single manufacturer or hospital's QA systems and staff resources.

In addition to these public health benefits, the final rule benefits licensed manufacturers in terms of a reduced level of reporting and streamlining the reporting process by providing a standardized report form that may be submitted electronically. Reporting requirements are now focused more narrowly on product deviations that represent more immediate risks.

V. The Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by OMB under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Biological Products: Reporting of Biological Product Deviations in Manufacturing.

Description: FDA is amending the current regulations that require licensed manufacturers of biological products to report to FDA errors and accidents in manufacturing; and adding regulations requiring unlicensed blood establishments to report certain biological product deviations in the manufacture of blood and blood components. Under this final rule, a licensed manufacturer or unlicensed blood establishment must submit a report to FDA based on the following criteria: (1) The event is associated with the manufacturing, to include testing, processing, packing, labeling, and storage, or with the holding or distribution, of a licensed biological product, or a licensed or unlicensed blood or blood component; (2) the deviation occurs in the licensed manufacturer or unlicensed blood establishment's facility or in another facility while the product remains in the control of the licensed manufacturer or unlicensed blood establishment; (3) the deviation may affect the safety, purity, or potency of that product and either represents deviation from CGMP, applicable regulations, applicable standards, or established specifications; or represents an unexpected or unforeseeable event; and (4) the deviation involves a distributed product. The agency is requiring a 45-calendar day reporting timeframe and is making available to industry a standardized format for reporting biological deviations in manufacturing that may be submitted either by hard copy or electronically.

Authority is given to the agency to issue regulations for the efficient enforcement of the act under section 701 of the act (21 U.S.C. 371) and to inspect all establishments responsible for manufacturing biological products (section 704 of the act (21 U.S.C. 374) and 42 U.S.C. 262). FDA regards biological product 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.

Description of Respondents: Licensed manufacturers of biological products, unlicensed registered blood establishments, and transfusion services.

As required by section 3506(c)(2)(B) of the PRA, FDA provided an opportunity for public comment on the information collection requirements of the proposed rule (62 FR 49642). 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 this document. Responses to additional comments in the letters received by OMB that were not addressed in section III of this document are addressed in the following paragraphs.

(Comment 33) One comment to OMB and 24 comments submitted to the docket state that the estimated time of 0.5 hours to complete a deviation report is underestimated. Several of these comments further state that their establishments currently average about 4 to 6, or 6 to 8 hours for preparing a deviation report under § 600.14. One comment states that ''[A] single investigation in our institution may take four hours per incident as we thoroughly investigate, report, change SOP's or processes if indicated, and follow-up to ensure that changes were implemented and work as intended.''

FDA agrees that the burden is underestimated and is adjusting the ''hours per response'' estimate in table 3 from 0.5 hours to 2 hours based on: (1) Information from industry representatives about typical reporting procedures, (2) the issuance of guidance that will assist industry in identifying reportable events, and (3) the availability of a standardized report form. The standardized report form, and the ability to submit a report electronically, should streamline the process and improve the quality of time. Activities such as investigating, changing SOP's or processes, and followup are currently required under parts 211, 606, and 820 and, therefore, are not included in the burden calculation for the separate requirement of submitting to FDA a deviation report.

(Comment 34) Two comments state that in determining the estimated time for completing and submitting a deviation report, FDA may not have met its statutory obligations under the PRA because it used anecdotal evidence, that is not representative of current practices.

When FDA seeks information from industry to estimate burden for a proposed rule, the agency ordinarily contacts fewer than 10 representatives. If FDA requested information from 10 or more industry representatives, the agency would be required to prepare a separate burden analysis and seek OMB approval before it could ask for such information. Although less than 10

persons usually do not represent the majority of the industry, the comment period for the proposed rule provides the opportunity for all interested persons to comment on the estimated burden. For this final rule, FDA considered all of the comments received regarding the estimated burden numbers and, in response, adjusted the estimates.

(Comment 35) Another comment states that the added hourly burden of generating these reports may compromise the ability of hospitals to provide optimal technical support for blood transfusion activities.

The requirement for reporting has not changed for licensed manufacturers. Licensed manufacturers are currently required to report errors and accidents under § 600.14, and the agency recommended reporting of errors and accidents by unlicensed blood establishments in a memorandum to registered blood establishments dated March 20, 1991. Unlicensed registered blood establishments and transfusion services are required under 42 CFR 493.1273(a) to comply with CGMP regulations set forth at parts 606 and 640, and specifically with § 606.100(c) for the investigation and followup of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications, and with § 606.160(b)(7)(iii) for recordkeeping requirements for errors and accidents. The only additional requirement under this final rule is that the unlicensed registered blood establishment or transfusion service submit a report based on this recordkeeping of deviations. FDA estimates that preparing and submitting one report would involve only 2 hours, and that only two reports would be submitted per year by an unlicensed registered blood establishment or transfusion service. The estimated total burden per year is only 4 hours per establishment. Therefore, FDA concludes that the final rule should not affect a hospital's ability to provide optimal technical support for blood transfusion activities.

(Comment 36) One comment notes that the paper-based reporting system that is now being used by FDA does not provide a format from which reported information can be entered into a usable data base without a great deal of difficulty and expense.

FDA agrees with the comment and has prepared a standardized form for reporting deviations in manufacturing a biological product (BPDR, Form FDA–3486) that may be downloaded from CBER's website or received by facsimile. After completion, the form is sent to the identified address 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 online and submit the report through the Internet.

(Comment 37) One comment notes that FDA estimates that there are no capital costs or operation and maintenance costs associated with the proposed rule. The comment noted that these terms are undefined.

The agency considers capital costs or operation and maintenance costs to be costs other than those needed for usual and customary business practice. FDA believes there are no capital costs or operation and maintenance costs associated with the maintenance of files and records because respondents should have the facilities and the infrastructure for recordkeeping and retention as part of their usual and customary practice. The final rule provides for the use of a standardized reporting form, which will be available for convenience on CBER's website. For those establishments that do not have access to the Internet, the form may also be accessed and submitted by facsimile or mail. Therefore, the purchase of computer equipment and Internet access would not be necessary in order to comply with this rule.

A. Estimated Annual Reporting Burden

The 54,208 total hours estimated in table 3 of this document are based on information from FDA's data bases and CBER's annual summary on error and accident reporting for 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 the 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 establishment is expected to submit no more than 2 reports annually, totaling 12,400 reports annually.

Licensed manufacturers of blood and blood components collect 90 percent 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.

In the proposed rule, the agency estimated that industry would expend 58,393.5 hours to submit approximately 116,787 total annual responses. In the final rule, FDA estimates that it will take 54,208 hours to submit 27,104 total annual responses. The decrease in total reports submitted annually is due to the more narrow scope in the final rule, which requires BPDR's only for distributed products.

B. Estimated One-Time Burden for Implementation of Rule

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 SOP's, and staff training. As previously discussed in section IV.B of this document, 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 3.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
600.14[2]	111	0.8	93	2	186

TABLE 3.—ESTIMATED ANNUAL REPORTING BURDEN[1]—Continued

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
606.171[3]	232	62.9	14,611	2	29,222
606.171[4]	6,200	2	12,400	2	24,800
Total	6,543		27,104		54,208
One-Time Burden[5]					
Licensed manufacturers[2]	111	1	111	80	8,880
Licensed manufacturers[3]	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]1ALicensed 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 SOP's, and staff training

The information collection requirements of the final rule have been submitted to OMB for review. Prior to the effective date of the final rule, FDA will publish a document in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection requirements in the final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VI. Environmental Impact

The agency has determined under 21 CFR 25.30(j) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

List of Subjects

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 600 and 606 are amended as follows:

PART 600—BIOLOGICAL PRODUCTS: GENERAL

1. The authority citation for 21 CFR part 600 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25.

2. Amend § 600.3 by adding paragraphs (hh) and (ii) to read as follows:

§ 600.3 Definitions.

* * * * *

(hh) *Distributed* means the biological product has left the control of the licensed manufacturer.

(ii) *Control* means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

3. Revise § 600.14 to read as follows:

§ 600.14 Reporting of biological product deviations by licensed manufacturers.

(a) *Who must report under this section*? (1) You, the manufacturer who holds the biological product license and who had control over the product when the deviation occurred, must report under this section. If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

(2) Exceptions:

(i) Persons who manufacture only in vitro diagnostic products that are not subject to licensing under section 351 of the Public Health Service Act do not report biological product deviations for those products under this section but must report in accordance with part 803 of this chapter;

(ii) Persons who manufacture blood and blood components, including licensed manufacturers, unlicensed registered blood establishments, and transfusion services, do not report biological product deviations for those products under this section but must report under § 606.171 of this chapter;

(iii) Persons who manufacture Source Plasma or any other blood component and use that Source Plasma or any other blood component in the further manufacture of another licensed biological product must report:

(A) Under § 606.171 of this chapter, if a biological product deviation occurs during the manufacture of that Source Plasma or any other blood component; or

(B) Under this section, if a biological product deviation occurs after the manufacture of that Source Plasma or

any other blood component, and during manufacture of the licensed biological product.

(b) *What do I report under this section*? You must report any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of a licensed biological product, if that event meets all the following criteria:

(1) Either:

(i) Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or

(ii) Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and

(2) Occurs in your facility or another facility under contract with you; and

(3) Involves a distributed biological product.

(c) *When do I report under this section*? You should report a biological product deviation as soon as possible but you must report at a date not to exceed 45-calendar days from the date you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, acquire information reasonably suggesting that a reportable event has occurred.

(d) *How do I report under this section*? You must report on Form FDA–3486.

(e) *Where do I report under this section*? You must send the completed Form FDA–3486 to the Director, Office of Compliance and Biologics Quality (HFM–600), Center for Biologics Evaluation and Research, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, by either a paper or an electronic filing:

(1) If you make a paper filing, you should identify on the envelope that a BPDR (biological product deviation report) is enclosed; or

(2) If you make an electronic filing, you may submit the completed Form FDA–3486 electronically through CBER's website at www.fda.gov/cber.

(f) *How does this regulation affect other FDA regulations*? This part supplements and does not supersede other provisions of the regulations in this chapter. All biological product deviations, whether or not they are required to be reported under this section, should be investigated in accordance with the applicable provisions of parts 211 and 820 of this chapter.

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

4. The authority citation for 21 CFR part 606 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

5. Amend § 606.3 by adding paragraphs (k) and (l) to read as follows:

§ 606.3 Definitions.

* * * * *

(k) *Distributed* means:

(1) The blood or blood components have left the control of the licensed manufacturer, unlicensed registered blood establishment, or transfusion service; or

(2) The licensed manufacturer has provided Source Plasma or any other blood component for use in the manufacture of a licensed biological product.

(l) *Control* means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

6. Amend § 606.160 by revising paragraph (b)(7)(iii) to read as follows:

§ 606.160 Records.

* * * * *

(b) * * *

(7) * * *

(iii) Biological product deviations.

* * * * *

7. Add § 606.171 to subpart I to read as follows:

§ 606.171 Reporting of product deviations by licensed manufacturers, unlicensed registered blood establishments, and transfusion services.

(a) *Who must report under this section*? You, 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 product when the deviation occurred, must report under this section. If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

(b) *What do I report under this section*? You must report any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of both licensed and unlicensed blood or blood components, including Source Plasma, if that event meets all the following criteria:

(1) Either:

(i) Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or

(ii) Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and

(2) Occurs in your facility or another facility under contract with you; and

(3) Involves distributed blood or blood components.

(c) *When do I report under this section*? You should report a biological product deviation as soon as possible but you must report at a date not to exceed 45-calendar days from the date you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, acquire information reasonably suggesting that a reportable event has occurred.

(d) *How do I report under this section*? You must report on Form FDA–3486.

(e) *Where do I report under this section*? You must send the completed Form FDA–3486 to the Director, Office of Compliance and Biologics Quality (HFM–600), 1401 Rockville Pike, suite 200N, Rockville MD, 20852–1448 by either a paper or electronic filing:

(1) If you make a paper filing, you should identify on the envelope that a BPDR (biological product deviation report) is enclosed; or

(2) If you make an electronic filing, you may submit the completed Form FDA–3486 electronically through CBER's website at www.fda.gov/cber.

(f) *How does this regulation affect other FDA regulations*? This part supplements and does not supersede other provisions of the regulations in this chapter. All biological product deviations, whether or not they are required to be reported under this section, should be investigated in accordance with the applicable provisions of parts 211, 606, and 820 of this chapter.

Dated: June 8, 2000.

Margaret M. Dotzel

Associate Commissioner for Policy

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