VII. Request for Comments

Interested persons may, on or before December 22, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 200

Drugs, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 200 be amended as follows:

PART 200—GENERAL

1. The authority citation for 21 CFR part 200 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 515, 701, 704, 705 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360e, 371, 374, 375).

2. New § 200.51 is added to subpart C to read as follows:

§ 200.51 Sterility requirements for inhalation solution drug products.

(a) All inhalation solutions for nebulization shall be manufactured to be sterile.

(b) Manufacturers shall also comply with the recordkeeping requirements in § 211.113(b) of this chapter.

Dated: September 12, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–25130 Filed 9–22–97; 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 Errors and Accidents in Manufacturing

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the regulations 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 is proposing to establish a reporting period for licensed biological products; require that error and accident reports be submitted for products that have been made available for distribution, and amend the current good manufacturing practice (CGMP) regulations for blood and blood components to require error and accident reporting by unlicensed registered blood establishments and transfusion services which are currently reporting on a voluntary basis. The proposed reporting requirements are intended to expedite reporting of errors and accidents in manufacturing of biological products; provide FDA with a more accurate surveillance of the nation's blood supply, thereby enabling FDA to monitor actions taken in response to the errors and accidents detected for all establishments involved in manufacturing of blood and blood components; and facilitate a rapid response where the public health may be at risk.

DATES: Submit written comments on the proposed rule by December 22, 1997. Submit written comments on the information collection provisions by October 23, 1997. The agency is proposing that any final rule that may issue based upon this proposed rule become effective March 23, 1998.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503. ATTN: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Paula S. McKeever, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION:

I. Introduction

Establishments that engage in the manufacture, preparation, propagation, compounding, or processing of drug and device products, including biological products, must register with the FDA under section 510 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360), unless specifically exempted by regulation.

Establishments propagating or manufacturing and preparing biological products for interstate commerce are subject to licensing under the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)). These licenses are issued by FDA only upon a showing that the establishment and the product for which a license is desired meet applicable standards designed to ensure the continued safety, purity, and potency of such products prescribed in the regulations (42 U.S.C. 262(d)(1)).

Blood and blood products are regulated as drugs under section 201(g) of the act (21 U.S.C. 321(g)) and biologicals are regulated under 42 U.S.C. 262 of the PHS Act. Establishments manufacturing blood and blood components are required to register with FDA and to comply with the CGMP (parts 211 and 606 (21 CFR parts 211 and 606)). Transfusion services which do not routinely collect or process blood and blood components are exempted from registering as blood establishments (§ 607.65(f) (21 CFR 607.65(f))), but are required under 42 CFR 493.1273(a) to comply with parts 606 and 640 (21 CFR part 640) as they pertain to the performance of manufacturing activities, such as compatibility testing, storage, labeling, and recordkeeping, or any other process involving manufacturing.

A product is considered adulterated under the act when the methods used in its manufacture, processing, packing, or holding do not conform to the CGMP (section 501(a)(1) of the act (21 U.S.C. 351(a)(1))). By applying the CGMP, firms assure that the products meet the requirements for safety, have the identity and strength, and meet the quality and purity characteristics which they purport or are represented to possess (section 501(a)(2)(B) of the act). A product is also adulterated if its strength differs from, or purity or quality falls below what it is purported or represented to possess (section 501(c) of the act). A product is considered misbranded if its labeling is false or misleading in any particular (section 502(a) of the act (21 U.S.C. 352(a))) or if the product is dangerous to health when used as labeled under section 502(j) of the act. The introduction or delivery for introduction of adulterated and/or misbranded biological products into interstate commerce is prohibited under section 301(a) of the act (21 U.S.C. 331(a)). It is also a prohibited act to adulterate and/or misbrand biological products while held for sale after receipt of shipment in interstate commerce (section 301(k) of the act). These prohibited acts are punishable by prescribed penalties under the act.

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 the proposal to amend the error and accident reporting regulations to be an essential tool in its directive to protect public health by establishing and maintaining surveillance programs that provide timely and useful information.

II. Background

Section 600.14 (21 CFR 600.14) requires that licensed manufacturers of biological products notify the Director, Office of Compliance, Center for Biologics Evaluation and Research (CBER), promptly of errors or accidents in manufacturing that may affect the safety, purity, or potency of any product. In addition, all blood establishments, whether licensed or unlicensed, are required by the CGMP to thoroughly investigate and make adequate corrections to their manufacturing processes concerning errors and accidents (§ 606.100(c)) and to maintain and make available to FDA appropriate records of such investigations and corrections (§§ 606.100(c) and 606.160(b)(7)(iii)). CBER has recommended to blood and blood component establishments that error and accident reports be submitted to CBER when the error or accident is associated with blood or blood components that have been made available for distribution, whether or not actual release or shipment has occurred. FDA believes this reporting standard is appropriate for ensuring the safety of the nations blood supply and proposes to codify it in the regulations.

In a memorandum to all registered blood establishments dated March 20, 1991, entitled ''Responsibilities of Blood Establishments Related to Errors and Accidents in the Manufacture of Blood and Blood Components,'' CBER recommended that unlicensed registered blood establishments and transfusion services voluntarily report to CBER errors and accidents that may affect product quality. The memorandum was issued, in part, because of an increase in the number of product recalls initiated by blood establishments due to errors and accidents in manufacturing which were not reflected in error and accident reports to CBER.

In May of 1995, the Office of Inspector General (OIG) of the Department of Health and Human Services issued a report on the ''Reporting Process for Blood Establishments to Notify the Food and Drug Administration of Errors and Accidents Affecting Blood.'' The report states that the error and accident reporting process enables the agency to evaluate and monitor blood establishments in response to detected errors and accidents, and regularly alert field staff and blood establishments with trend analysis of the types of errors and accidents reported. However, OIG placed emphasis on two existing conditions that were impeding the success of the reporting process: (1) Error and accident reports were not being submitted in a timely manner by blood establishments and (2) there was no assurance that unlicensed establishments were submitting reports. This proposed rule is intended as a step in addressing conditions identified in the OIG report.

On July 14, 1995, FDA published a notice of availability of a ''Guideline for Quality Assurance in Blood Establishments'' (60 FR 36290) initiating a blood quality assurance program aimed at ensuring the continued safety of the nation's blood supply and maintaining the operational quality of blood establishments. The goals of the quality assurance (QA) program are to significantly decrease errors, ensure the credibility of test results, implement effective manufacturing process and system controls, and ensure continued product safety, purity, and potency. The QA program includes measures to prevent, detect, investigate, assess, and correct errors. The emphasis is on preventing errors rather than detecting them retrospectively. This guidance is intended to assist manufacturers of blood and blood components, i.e., blood banks, blood centers, transfusion services, and plasmapheresis centers, in developing QA programs that are consistent with recognized principles of QA and the CGMP. One component of this guidance focuses on the blood industry's self audit, including analysis and trending of errors and accidents that may affect the safety, purity, and potency of blood and blood components.

In the **Federal Register** of January 20, 1994 (59 FR 3043), FDA announced its plan to review significant regulations under Executive Order 12866, which requires all Federal agencies to develop a program for periodically reviewing existing significant regulations. The purpose of the review is to determine whether existing significant regulations should be modified or eliminated to reduce their regulatory burden or to make the agency's regulatory program more effective. This proposed rule is considered part of the retrospective regulation review and is intended to improve the effectiveness of FDA's regulatory program.

III. Summary of the Proposed Rule

FDA is proposing to amend the regulations that require licensed manufacturers of biological products to report errors and accidents in manufacturing and to amend the CGMP regulations for blood and blood components to require error and accident reporting by all manufacturers of blood and blood components. The proposed amendments would provide definitions for the terms ''error and accident'' and ''made available for distribution'' in part 600 (21 CFR part 600) at §§ 600.3 and 606.3; require a specific timeframe for reporting at §§ 600.14 and 606.171; require reports for products that have been made available for distribution, at §§ 600.14 and 606.171; and extend the reporting requirements to unlicensed registered blood establishments and transfusion services, at § 606.171.

A. Definitions (§§ 600.3 and 606.3)

Although the terms ''error'' and ''accident'' are generally used conjunctively, FDA has listed distinguished events affecting the purported safety, purity, and potency of the product into two categories.

''Made available for distribution'' is being defined because of the numerous release and distribution patterns unique to some biological products, and to avoid the potential for misinterpretation of the term.

1. Error and Accident

In proposed §§ 600.3(ff) and 606.3(k), the first category of events is defined as an incident that represents a deviation from the CGMP, applicable standards or established specifications that may affect the safety, purity, or potency of the biological product, or otherwise cause the biological product to be in violation of the act or the PHS Act. These events are within the realm of control of the manufacturer. Examples of this category of reportable events in the manufacturing of blood and blood components which may affect product safety, purity, or potency include, but are not limited to: (1) Arm preparation not performed or performed incorrectly; (2) components prepared more than 8 hours after collection; (3) testing for ABO/Rh or infectious diseases not performed according to the package insert; (4) incorrect crossmatch label or tag; (5) shipment of a unit with a repeatedly reactive viral marker test result; and (6) shipment of a unit prior

to completion of all testing. Examples of reportable events for biological products other than blood and blood components include, but are not limited to: (1) Route of administration labeling error; (2) shipment of a product at an inappropriate temperature; (3) mold contamination of a vaccine; (4) missing product labels; (5) incorrect package insert; and (6) missing lot number.

The second category of events to be reported is defined as an unexpected or unforeseeable event that may affect the safety, purity, or potency of the biological product, or otherwise cause the biological product to be in violation of the Act or the PHS Act. These events generally are beyond the control of the manufacturer. Examples of this category of reportable events in the manufacture of blood and blood components which may affect product safety, purity, or potency include, but are not limited to: (1) Certain post donation information; (2) a collection device defect that affects the product; (3) contaminated solutions used to prepare components; (4) an autologous unit labeled with incorrect information provided by the donor; or (5) a unit of blood or blood components which becomes broken/damaged during shipment. Examples of reportable events in the manufacture of biological products other than blood and blood components which may affect product safety, purity, or potency include, but are not limited to: (1) Sterility compromised and beyond the control of the manufacturer; (2) notification from a supplier of source materials concerning a quality problem with the product shipped for use in further manufacturing; and (3) inadvertent contamination of cell lines or replication competent viruses.

2. Made Available for Distribution

In proposed §§ 600.3(ii) and 606.3(l), ''made available for distribution'' is defined as a biological product that has been determined to meet all release criteria and to be suitable for distribution, whether or not actual distribution has occurred. Thus, error and accident reports would be submitted to FDA for products that the manufacturer or blood establishment has determined are suitable for distribution.

B. Biological Product Reporting (§ 600.14)

FDA has the responsibility for protecting the public health by reviewing the safety and efficacy of biological products. FDA believes that error and accident reports help ensure that industry identifies instances where additional corrective action is needed, such as additional training and revisions of standard operating procedures (SOP's). Error and accident reports, in conjunction with inspections and other surveillance activities, give FDA a continuing overview of the biological product industry. While FDA provides guidance to help industry determine how to comply with regulations, manufacturers of biological products have the primary responsibility for ensuring the safety, purity, and potency of their products.

Section 600.14 applies to all licensed manufacturers of biological products. It requires manufacturers to report errors and accidents in manufacturing promptly to the Director, Office of Compliance, CBER. FDA agrees with the OIG's recommendations and has identified two changes that are needed to make the error and accident reporting program more meaningful and useful, i.e., timeliness in reporting for all biological products and reporting by unlicensed blood establishments and transfusion services.

1. Reporting Period

FDA is proposing to amend § 600.14(a) to replace the term ''promptly'' with a reporting period of ''as soon as possible but not to exceed 45 calendar days.''

FDA has found that licensed manufacturers of biological products were not always submitting the error and accident reports in a consistent and timely manner after detecting the error or accident. FDA has found that by not previously specifying a definitive time period for reporting errors and accidents, a liberal interpretation of the timeframe had been taken. When reports are not submitted in a timely manner, FDA is unable to adequately evaluate the public health significance of an error or accident, or assess a firm's proposed actions including activities to prevent recurrence and to address the status of the affected products. While the agency is proposing a maximum of 45 calendar days to report errors and accidents, FDA encourages manufacturers to implement SOP's to submit these reports sooner, including prior to the implementation of any corrective actions.

2. Applicability to Unlicensed Blood Establishments

FDA is proposing the addition of § § 600.14(c) and 606.171 in order to encompass all blood establishments in the reporting of errors and accidents, not just licensed manufacturers. Registered blood establishments and transfusion services are required to comply with the CGMP and additional standards for blood and blood components, set forth in parts 606 and 640, including recordkeeping requirements relating to errors and accidents. By including error and accident reporting in part 606, the regulations would make clear that all licensed blood manufacturers, unlicensed registered blood establishments, and transfusion services would submit error and accident reports as a part of their compliance with the CGMP for blood and blood components. With full reporting, the public can be further assured that expeditious and appropriate actions are being taken to protect all of the nation's blood supply.

3. Reporting for Biological Products Made Available for Distribution

FDA proposes to require manufacturers to submit error and accident reports for biological products that have been made available for distribution. FDA believes that this reporting requirement will permit it to conduct appropriate oversight of biological products manufactured for distribution to the public (including blood and blood components) and of actions taken by manufacturers to correct errors and accidents without hindering a firm's ability to expeditiously manufacture biological products. By requiring reports of errors and accidents after the manufacturer has determined that a biological product is suitable for distribution, the firm is able to investigate and correct errors and accidents during the manufacturing process and before distribution, and FDA is able to receive information necessary to adequately review and monitor the quality and safety of products released for distribution to the public, as well a firm's investigative and corrective efforts relating to the errors and accidents. FDA is also able to review and monitor a manufacturer's procedures for correcting and preventing errors and accidents during manufacture by the requirement that manufacturers investigate all such errors and accidents (§§ 211.192, 606.100(c), and 21 CFR 820.162), and maintain complete records of the investigation and promptly make them available to FDA for review during inspections (§§ 211.198(b)(2), 606.160(b)(7)(iii), and 21 CFR 820.180).

C. Error and Accident Reporting, Blood and Blood Components (§ 606.171)

FDA is proposing the addition of a new § 606.171 *Reporting errors and accidents in manufacturing* to subpart I, Records and Reports of part 606. A primary objective of this proposed rule is to make the error and accident reporting requirement applicable to all

blood establishments, i.e., licensed manufacturers, unlicensed registered manufacturers, and transfusion services. Including error and accident reporting requirements for blood and blood component manufacturing in part 606 will assure that these reporting requirements will become part of the CGMP and apply to any establishment that participates in the collection, processing, compatibility testing, storage, or distribution of blood and blood components. In order for FDA to more effectively evaluate and monitor the blood industry, it needs reports from the full spectrum of establishments engaged in manufacturing and distribution of blood and blood components. Because unlicensed registered blood establishments and transfusion services represent a large sector of the blood processing community, FDA believes these establishments must also be required to submit reports of those errors or accidents that may affect the safety, purity, or potency of distributed blood and blood components.

1. Scope

a. Establishments. FDA is proposing in the new § 606.171 to require the reporting of errors and accidents by all blood establishments including licensed manufacturers of blood and blood components, unlicensed registered blood establishments, and transfusion services. All of these establishments are required to follow the CGMP (parts 211 and 606) in their daily operation. Although certain transfusion services are exempt from registration under § 607.65(f), all transfusion services are required under 42 CFR 493.1273(a) to comply with the CGMP if performing compatibility testing, storage, labeling, and recordkeeping, or any other process involving manufacturing.

Transfusion services may receive blood or blood components from outside sources. When transfusion services discover errors and accidents made by an outside manufacturer in relation to such products they should report these errors and accidents to the manufacturer. The manufacturer, i.e., the collecting facility, would then be responsible for notifying CBER of the errors and accidents. However, errors and accidents in manufacturing which are made by the transfusion service, such as incorrect identification of samples used in compatibility testing, or incorrect tag/crossmatch label, or storing product at the incorrect temperature should be reported to CBER directly by the transfusion service if the product was made available for distribution.

b. *Blood and blood components.* FDA is proposing in new § 606.171 that all blood establishments be required, as part of their CGMP programs, to report errors and accidents for blood and blood components made available for distribution. FDA believes this reporting mechanism will help assure the quality and safety of the nation's blood supply.

2. Format for Reporting

FDA is not at this time proposing the use of a specific report form. FDA has recommended to manufacturers of blood or blood components certain essential information that should be submitted in the report. This information should include, but not be limited to: The name of the blood establishment, registration or CLIA (Clinical Laboratories Improvement Act) numbers if applicable, the unit number(s), the type of blood product(s), the nature of the error or accident, the final disposition of the blood product, and the notification of consignee(s), if any. The information submitted by manufacturers of biological products other than blood or blood components should include, but not be limited to: The name of the manufacturer, the registration/license number of the manufacturer, the location, the type of product, the lot number(s), the nature of the error or accident, the final disposition of the product, and the notification of consignee(s), if any. The report for any biological product, including blood and blood components, should also describe contributing factors causing the error or accident and the actions or proposed corrective actions taken by the manufacturer of the biological product to prevent recurrence.

At this time, the agency is requesting that any establishment or other organization submit to the docket for review any proposed format for the reporting of errors and accidents in manufacturing to be used by industry, and any comments on the issue. FDA is also soliciting comments on development of a program for electronic submission of error and accident reports.

IV. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (Pub. L. 104–4). 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; and 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 that impact. The Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local and tribal governments, in the aggregate, or by the private sector, of $100,000,000 (adjusted annually for inflation). The agency has determined that the proposed rule is not an economically significant rule as described in the Executive Order, nor a significant action as defined in the Unfunded Mandates Reform Act. Aggregate impacts of the rule, and aggregate expenditures caused by the rule, will not approach $100 million for either the public or the private sector.

Available information suggests that costs to the entities most affected by this rule, including small entities, are not expected to increase by more than approximately 0.04 percent per year, as described in the analysis in section IV.C of this document. Therefore, the agency certifies that this rule will not have a significant economic impact on a substantial number of small entities.

A. Objective and Basis of the Proposed Action

As discussed previously, FDA is considering the proposed action in response to concerns regarding the accuracy, timeliness, and completeness of error and accident reporting associated with the manufacturing of blood and other biological products. The proposed reporting requirements will expedite reporting of errors and accidents in the manufacture of such products, enhance FDA's ability to identify potential quality assurance problems, and facilitate a rapid response where public health may be at risk. This action is taken under the authority of sections 351 and 361 of the PHS Act and sections 501 and 502 of the act. FDA has reviewed related Federal rules and has not identified any rules that duplicate, overlap, or conflict with the proposed rule.

B. Small Entities Affected

This proposal affects both entities that currently submit mandatory error and accident reports and those entities currently subject only to voluntary reporting. However, the magnitude of

the impact is expected to be greater for the latter group than for the former.

Entities currently subject to mandatory error and accident reporting comprise approximately 102 licensed manufacturers of biological products (excluding blood and blood components) with 280 locations, and approximately 294 licensed manufacturers of blood and plasma with 725 locations. Entities currently subject only to voluntary reporting of such incidents include approximately 2,560 unlicensed registered blood establishments and an estimated 4,500 transfusion services inspected by the Health Care Financing Administration. FDA believes many of these entities to be small entities as defined by the Regulatory Flexibility Act. For example, most of the transfusion services are located in hospitals, and nearly three-fourths of community hospitals are either not-for-profit or have fewer than 50 beds.

C. Nature of the Impact

All of the entities described in section IV.B of this document would be affected by the proposed rule. The main cost involved in implementing the rule would be the time required to review current SOP's and to ensure that the appropriate staff understand the types of errors and accidents that must be reported and the importance of timely reporting. The new time limit for reporting is expected to increase the timeliness of report submissions, but because the reporting activity itself is unchanged by this provision the costs of this increased compliance should be limited to the preparation/revision of the SOP and staff training activities. FDA has no precise estimate of this one-time cost, but the agency expects that it should require an average of 2 hours per establishment to prepare the 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 provision of the proposed rule that extends mandatory error and accident reporting to all unlicensed registered blood establishments and transfusion services will affect nearly all such entities. At present, these entities are requested to submit such reports voluntarily, but FDA estimates that only about 1 percent are doing so, and even these entities may not be submitting all the reports that would be required under this rule. Thus, this requirement would involve a new routine activity for the great majority of unlicensed blood establishments and transfusion services.

FDA has no precise estimates of the cost of submitting error and accident reports. Anecdotal evidence suggests that such reports can take an average of 30 minutes per report to complete, and that some blood establishments may be reporting up to 8 errors and accidents per 10,000 units of blood collected annually. It is not known whether these anecdotal data are representative of current practice. Nor is it known whether these figures represent unusually high (or low) levels of quality assurance, or unusually high (or low) compliance with current reporting requirements.

Nonetheless, these figures tentatively suggest that a small entity that handles 10,000 units of blood annually and that is newly subject to the requirements presented in this proposed rule might incur new costs of 6 hours per year of staff time, 2 hours for the preparation of the SOP, and 4 hours preparing and submitting error and accident reports. At an estimated $37.98 per hour value of staff time, this would lead to an annual cost of $227.88, or roughly $.028 per unit. Based on an average cost of producing a unit of blood of $65 to $75, this requirement would increase the average entity's per unit cost of producing a unit of blood by approximately 0.04 percent. Entities with above average numbers of errors and accidents would incur higher costs. (There should not be any additional costs of investigating errors and accidents or keeping records of them, since these activities are already required under other sections in 21 CFR parts 200, 600, and 800).

There are no specific educational or technical skills required to complete and submit error accident reports. These reports are generally completed by trained and qualified employees of an establishment. Updating SOP's and training staff regarding the new requirements of this proposed rule would require a person knowledgeable and experienced in medical laboratory practice.

D. Minimizing the Impact on Small Entities

A number of different possibilities for formatting and submitting the reports are possible. FDA is soliciting comments on the following topics and reporting alternatives: (1) Examples of simple, user-friendly reporting formats that would minimize the time required to submit a report but that would contain the requisite information; (2) whether a specified, uniform format is less burdensome than permitting entities to create their own formats or select from a range of possible formats; and (3) whether electronic reporting is less burdensome than paper reporting and, if so, which electronic formats are best suited to this requirement.

V. The Paperwork Reduction Act of 1995

This proposed rule contains information collection requirements which are subject to public comment and review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection requirements are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing the instructions, gathering necessary information, and completing and reviewing the report.

With respect to the following collection of information, FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Biological Product Reporting of Errors and Accidents in Manufacturing.

Description: FDA is proposing to amend the regulations that require licensed manufacturers of biological products to report errors and accidents in manufacturing that may affect the safety, purity, or potency of a product. FDA proposes to define certain terms, i.e., ''error and accident'', and ''made available for distribution;'' replace ''promptly'' with ''as soon as possible but not to exceed 45 calendar days'' with regard to the timeframe for reporting; limit the error and accident reporting requirements to biological products that have been made available for distribution; and amend the CGMP regulations to require all manufacturers of blood and blood components, including unlicensed registered blood establishments and transfusion services, to submit error and accident reports. FDA is proposing this action in response to concerns regarding the accuracy, timeliness, and completeness of error and accident reporting associated with the manufacturing of blood and other biological products, and as an essential tool in FDA's directive to

protect public health by establishing and maintaining surveillance programs that provide timely and useful information. FDA is not at this time proposing to require the use of a specific form for error and accident reports, but is requesting that establishments submit to the docket for review any proposed format for these reports. FDA is also soliciting comments on development of a program for electronic reporting of errors and accidents.

Description of Respondents: Manufacturers of blood and blood components; manufacturers of other biological products.

There are approximately 102 licensed manufacturers of biological products other than blood and blood components with 280 locations, and 294 licensed blood and plasma establishments with 725 locations. In fiscal year 1996, these manufacturers submitted a total of 10,793 error and accident reports. Of this total, 10,781 reports were submitted by licensed blood and plasma establishments. Although approximately 7,060 unlicensed registered blood establishment and transfusion service locations are currently submitting reports on a voluntary basis, FDA received only 159 error and accident reports for fiscal year 1996 from such entities. Based on the substantially larger number of reports received from licensed blood and plasma establishments, FDA believes that the number of reports currently received from unlicensed establishments is not an accurate indicator of the number of reports that will be submitted once the unlicensed establishments are required to submit error and accident reports for products made available for distribution.

The following reporting burden for proposed § 600.14 was estimated by using 1996 reporting figures for licensed manufacturers of biological products other than blood and blood components. The reporting burden for proposed § 606.171 was estimated by using the 1996 reporting frequency average for all licensed blood and plasma establishment locations of 15 reports per year; the number of respondents was estimated by adding the number of unlicensed registered blood establishment and transfusion service locations (7,060 according to FDA's records) to the number of licensed blood and plasma establishment locations that are already reporting. An average time of 0.5 hours (according to several respondents contacted by FDA) is used in the preparation of each report.

ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
600.14	280	0.04	12	0.5	6.0
606.171	7,785	15	116,775	0.5	58,387.5
Total					58,393.5

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

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted a copy of this proposed rule to OMB for review of the information collection provisions. Interested persons are requested to submit written comments regarding information collection by October 23, 1997 to the Office of Information and Regulatory Affairs, OMB (address above), ATTN: Desk Officer for FDA.

VI. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(10) 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. Request for Comments

Interested persons may, on or before December 22, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal, except that comments regarding information collection provisions should be submitted in accordance with the instructions in section V of this document. Two copies of any comments on issues other than information collection are to be submitted, of this document except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

21 CFR Part 606

Blood, Labeling, Laboratories, and 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, it is proposed that 21 CFR parts 600 and 606 be amended as follows:

PART 600––BIOLOGICAL PRODUCTS: GENERAL

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

Authority: Secs. 201, 501, 502, 503, 505, 510, 519, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374); secs. 215, 351, 352, 353, 361, 2125 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25).

2. Section 600.3 is amended by adding new paragraphs (hh) and (ii) to read as follows:

§ 600.3 Definitions.

* * * * *

(hh) *Error and accident* means:

(1) An event that represents a deviation from current good manufacturing practice (CGMP), applicable standards, or established specifications that may affect the safety, purity, or potency of a biological product, or otherwise cause the product to be in violation of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, or

(2) An unexpected or unforeseeable event that may affect the safety, purity, or potency of a biological product, or otherwise cause the product to be in violation of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act.

(ii) *Made available for distribution* means that the biological product has been determined to meet all release

criteria and to be suitable for distribution.

3. Section 600.14 is amended by revising the section heading and paragraph (a) and by adding new paragraph (c) to read as follows:

§ 600.14 Reporting of errors and accidents.

(a) Except as provided in paragraph (c) of this section, the Director, Office of Compliance (HFM–650), Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852–1448, shall be notified as soon as possible but not to exceed 45 calendar days, of errors or accidents in the manufacture of products that may affect the safety, purity, or potency of any biological product made available for distribution.

* * * * *

(c) In lieu of the requirements of paragraph (a) of this section, all manufacturers of blood and blood components shall submit reports to FDA in accordance with § 606.171 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: Secs. 201, 301, 501, 502, 505, 510, 520, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374); secs. 215, 351, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263a, 264).

5. Section 606.3 is amended by adding new paragraphs (k) and (l) to read as follows:

§ 606.3 Definitions.

* * * * *

(k) *Error and accident* means:

(1) An event that represents a deviation from current good manufacturing practice (CGMP), applicable standards, or established specifications that may affect the safety, purity, or potency of blood or blood components, including source plasma, or otherwise cause the product to be in violation of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, or

(2) An unexpected or unforeseeable event that may affect the safety, purity, or potency of blood or blood components, including source plasma, or otherwise cause the product to be in violation of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act.

(l) *Made available for distribution* means that the blood or blood component, including source plasma, has been determined to meet all release criteria and to be suitable for distribution.

6. Section 606.171 is added to subpart I to read as follows:

§ 606.171 Error and accident reporting, blood and blood components.

All establishments as defined in § 607.3(c) of this chapter shall notify the Director, Office of Compliance (HFM–600), Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852–1448, as soon as possible but not to exceed 45 calendar days, of errors or accidents in the manufacture of blood or blood components, including source plasma, that may affect the safety, purity, or potency of any blood or blood component made available for distribution.

Dated: June 25, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97–25129 Filed 9–22–97; 8:45 am]

BILLING CODE 4160–01–F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[ME–046–6996b; A–1–FRL–5894–7]

Approval and Promulgation of Air Quality Implementation Plans; Maine; (General Conformity Rule)

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is proposing to approve a State Implementation Plan (SIP) revision submitted by the State of Maine for the purpose of implementing General Conformity (Section 176(c)(4)(C) of the Clean Air Act (CAA) and its regulations 40 CFR part 51, Subpart W). The Maine SIP incorporates by reference the criteria and procedures set forth at 40 CFR part 51, Subpart W. This SIP revision establishes and requires federal actions to conform to all applicable implementation plans developed pursuant to Section 110 and Part D of the CAA. In the Final Rules Section of this **Federal Register**, EPA is approving the State's SIP revision as a direct final rule without prior proposal because the Agency views this as a noncontroversial revision amendment and anticipates no adverse comments. A detailed rationale for the approval is set forth in the direct final rule. If no adverse comments are received in response to that direct final rule, no further activity is contemplated in relation to this proposed rule. If EPA receives adverse comments, the direct final rule will be withdrawn and all public comments received will be addressed in a subsequent final rule based on this proposed rule. EPA will not institute a second comment period on this proposal. Any parties interested in commenting on this proposal should do so at this time.

DATES: Comments must be received on or before October 23, 1997.

ADDRESSES: Comments may be mailed to Susan Studlien, Deputy Director, Office of Ecosystem Protection (mail code CAA), U.S. Environmental Protection Agency, Region I, JFK Federal Bldg., Boston, MA 02203. Copies of the State submittal are available for public inspection during normal business hours, by appointment at the Office of Ecosystem Protection, U.S. Environmental Protection Agency, Region I, One Congress Street, 11th floor, Boston, MA and the Bureau of Air Quality Control, Department of Environmental Protection, 71 Hospital Street, Augusta, ME 04333.

FOR FURTHER INFORMATION CONTACT: Donald O. Cooke, (617) 565–3508, at the EPA Region I address above.

SUPPLEMENTARY INFORMATION: For additional information, see the direct final rule which is located in the Rules Section of this **Federal Register**.

Authority: 42 U.S.C. 7401—7671q.

Dated: September 9, 1997.

John P. DeVillars,

Regional Administrator, Region I.

[FR Doc. 97–25229 Filed 9–22–97; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[PA58–4039; AD–FRL–5897–2]

Approval and Promulgation of Air Quality Implementation Plans; Pennsylvania; Pennsylvania Power—New Castle NO_X RACT Proposal; Extension of Comment Period

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule; extension of the comment period.

SUMMARY: EPA is reopening the comment period for a proposed rule published on August 18, 1997 (62 FR 43959). In the August 18 document, EPA proposed to disapprove the April 19, 1995 Pennsylvania Department of