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Adverse Experience Reporting Requirements For Licensed Biological Products; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 600

[Docket No. 85N–0506]

RIN 0905–AB53

Adverse Experience Reporting Requirements for Licensed Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the regulations to require manufacturers of licensed biological products (hereinafter referred to as licensed manufacturers) to report to FDA within 15 working days all adverse experiences associated with the use of a biological product that are both serious and unexpected; any significant increase in the frequency of a serious, but expected adverse experience; periodically, all other adverse experiences; and product distribution and disposition data. FDA is taking this action to provide a mechanism under which licensed manufacturers would inform the agency, on a timely basis, of any unanticipated safety problems with marketed biological products.

EFFECTIVE DATE: This regulation is effective December 27, 1994.

ADDRESSES: Copies of Form FDA–3500A may be obtained from the Center for Biologics Evaluation and Research (HFM–210), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. Additional copies of the form may be obtained from the Consolidated Forms and Publications Distribution Center, 3222 Hubbard Rd., Landover, MD 20785. Copies of the VAERS form may be obtained from the Vaccine Adverse Event Reporting System (VAERS) by calling 1–800–822–7967.

All reports required by this regulation pertaining to nonvaccine biological products should be sent to the Center for Biologics Evaluation and Research (address above). All reports required by this regulation pertaining to vaccines should be sent to VAERS, P.O. Box 1100, Rockville, MD 20849–1100.

FOR FURTHER INFORMATION CONTACT: Paula S. McKeever, Center for Biologics Evaluation and Research (HFM–635), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of April 24, 1979 (44 FR 24233), FDA made available for public comment a draft proposed regulation that would require the maintenance of records and submission of reports of adverse experiences involving licensed biological products. After evaluating the comments received and analyzing other information, FDA issued a proposed regulation (hereinafter referred to as the 1990 proposal) and notice of availability of a draft guideline in the **Federal Register** of March 29, 1990 (55 FR 11611 and 11655, respectively). The 1990 proposal was to require all manufacturers of licensed biological products to submit the following reports to FDA: (1) Alert reports within 15 working days of receipt of adverse experiences associated with the use of a licensed biological product that are both "serious and unexpected," and of any "significant increase in frequency" of an adverse experience that is both "serious and unexpected;" and (2) periodic reports of all adverse experiences, including both serious and nonserious adverse experiences, that are not included in a 15-day Alert report. The statutory authority for promulgating these regulations was described in detail in the preamble to the 1990 proposal (55 FR 11611 at 11613). The agency provided 60 days for interested persons to submit written comments on the 1990 proposal.

Prior to promulgation of this final rule, only adverse experiences associated with certain childhood vaccines (see 53 FR 10565, April 1, 1988) and fatalities resulting from blood collection or transfusion (§ 606.170 (21 CFR 606.170)) were required to be reported to FDA for biological products. Although many manufacturers of other types of biological products voluntarily submit adverse experience reports to FDA, there has not necessarily been consistent or complete reporting from all licensed manufacturers.

In the **Federal Register** of June 3, 1993 (58 FR 31596), FDA issued a notice announcing the availability of a new form for reporting adverse events and product problems with human drug products, biologic products, medical devices, special nutritional products, and other products regulated by FDA. One version of the form (FDA Form 3500) was made available for use by health professionals for voluntary reporting; the other version of the form (FDA Form 3500A) was made available for use by user facilities, distributors, and manufacturers for reporting that is required by statute or by FDA regulation. The new form is part of an FDA MEDWATCH program which is intended to consolidate and simplify reporting of adverse events and product problems for all FDA-regulated products.

Many of the comments received in response to the 1990 proposal, while having merit, if implemented would require changes to the regulations governing the reporting of adverse experiences for biologic products which would cause these requirements to diverge significantly from the requirements and reporting program for drugs as provided in §§ 310.305 and 314.80 (21 CFR 310.305 and 314.80)). Such a divergence would be contrary to the MEDWATCH program which is intended, in part, to enhance consistency in the reporting and collection of information on adverse experiences related to FDA-regulated products. Rather than making such significant changes in this final rule, FDA is issuing a notice of proposed rulemaking elsewhere in this issue of the **Federal Register** which would appropriately amend the requirements in §§ 310.305, 312.32 (21 CFR 312.32), and 314.80 for reporting of adverse experiences related to human drugs and the requirements in this final rule (§§ 600.80 and 600.81) for reporting adverse experiences related to biological products. Later in this preamble, in response to a number of public comments which request significant changes to the regulations, FDA refers to the proposed rule which provides a more substantial discussion of the issues involved.

Elsewhere in this issue of the **Federal Register**, FDA is also announcing the availability of a guideline entitled "The Guideline for Adverse Experience Reporting for Licensed Biological Products" (referred to as "guideline" in this final rule). The guideline discusses in detail the reports required by this rule, and provides guidance concerning some appropriate means of meeting the reporting requirements.

II. Highlights of the Final Rule

This final rule establishes procedures under §§ 600.80 and 600.81 for licensed manufacturers to inform FDA about adverse experiences that are associated with the use of a licensed biological product and about biological product distribution. These procedures are intended to support the agency's efforts to protect the public safety by providing the agency with the information necessary for effective postmarket surveillance of biological products. This final rule requires licensed manufacturers of biological products to

submit various reports to the agency and specifies the timeframes for submission of these reports. The reports are: (1) Fifteen-day Alert reports, (2) increased frequency alert reports, (3) periodic adverse experience reports and (4) distribution reports. The timeframes and contents of these adverse experience reports were the subject of numerous comments, which are discussed below. In addition to the reporting requirements, the final rule specifies record-keeping requirements, provides for exemptions of two categories of biological products, provides a disclaimer regarding causality, and provides for license revocation if licensed manufacturers fail to establish and maintain records and submit the required reports. In addition, this final rule provides procedures, under § 600.90, for applying for waivers from any of the reporting requirements.

The requirements in this final rule are consistent with existing requirements in §§ 314.80 and 314.81 (21 CFR 314.81) regarding approved new drug products, except when differences are necessary to accommodate laws, terminology, procedures, and characteristics unique for biological products.

A. Scope

The new procedures apply to all licensed manufacturers of biological products and any person, other than the licensed manufacturer of a biological product, whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or a participant in divided manufacturing.

B. Format

The format of § 600.80 has been revised from what was proposed to be consistent with § 314.80. FDA believes that the revised format will reduce the burden for manufacturers following the regulations for both drug and biological products.

III. Comments on the Proposed Rule and FDA Responses

FDA received 15 letters of comment on the proposed rule. Most letters contained numerous comments on various areas of the proposed rule. Four of these comments supported codification of the reporting requirements for adverse experiences associated with biological products. Other comments either addressed particular paragraphs in the proposed regulation or dealt with the effect of the regulation on a particular type of biological product. In addition to the amendments discussed below, editorial changes were made throughout the rule. A summary of these comments and the agency's responses follow:

A. General Comments

1. Consistency With Section 314.80

Two comments on § 600.80 recognized the reporting issues unique to biological products and were supportive of both the 1990 proposal and the draft guideline for recognizing the differences between drugs and biological products. In contrast, four comments requested that FDA not deviate from the rules and guidelines applicable to drugs and requested that the regulations for reporting adverse experiences for biological products mirror the regulations for drugs.

FDA intends these rules to be consistent with other agency initiatives and requirements regarding adverse experience reporting for drugs and medical devices wherever practical. This is demonstrated by the new adverse experience reporting Form FDA–3500A, which, with the exception of adverse experience reports associated with vaccines, is to be used for reporting of adverse events associated with drugs, biologics, and certain other products regulated by FDA. The final rule contains requirements unique to biological products only when necessary to accommodate the laws applicable only to biological products, such as vaccines, or to accommodate special characteristics of biological products.

2. Agency Review of Adverse Experience Reports

One comment requested that the unit of FDA responsible for receiving adverse experience reports for drugs continue to be responsible for the adverse experiences for biologics to assure consistency of interpretation of the regulations and dissemination of information within FDA.

The agency intends to maintain consistency between the Center for Biologics Evaluation and Research (CBER) and the Center for Drugs Evaluation and Research (CDER) in the interpretation of the regulations, especially with respect to terminology. A separate unit was created with the responsibilities related to postmarketing surveillance of licensed biological products because the agency recognizes that these products can present different safety concerns due to inherent differences in the products. In addition, the National Childhood Vaccine Injury Act of 1986 (NCVIA) mandated specific reporting requirements for manufacturers of certain vaccines and for health care providers administering those vaccines. VAERS was established to receive these required reports, as well as reports on other vaccines. The VAERS program is administered jointly by FDA and by the Centers for Disease Control and Prevention (CDC) and replaces previous vaccine reporting systems within both agencies. Section 600.80(c) has been amended in the final rule to reflect the change of address for submitting reports due to the reorganization and relocation of CBER.

3. Clarification of Overlap Between the Vaccine Adverse Event Reporting System and § 600.80

Comments were received requesting clarification of overlap between the requirements of NCVIA and the regulations.

NCVIA created a new Title XXI of the Public Health Service Act (the PHS Act). Section 2125 of the PHS Act (42 U.S.C. 300aa-25) requires health care providers who administer certain vaccines and manufacturers of the vaccines to report specified adverse experiences, occurring within specified time intervals after administration of the vaccines. These adverse experience reports are submitted to VAERS, which is jointly managed by FDA and CDC and became operational on November 1, 1990. A form VAERS–1 was developed for these reports. When the requirements set forth in both § 600.80 and NCVIA necessitate reporting of an adverse event, licensed manufacturers of vaccines are not required to submit duplicate reports to VAERS and FDA. Submission of the report to VAERS is sufficient. However, licensed manufacturers of vaccines must comply with the regulations in § 600.80. Therefore, any requirements in these regulations that are in addition to those specified in the NCVIA must be satisfied. For example, although NCVIA does not specify the time periods for submission of adverse experience reports, the time periods set forth in § 600.80 apply to reports being submitted to VAERS.

4. Requests for Waivers

Six comments requested waivers from the reporting requirements for specific types of adverse experiences or for certain categories of biological products. These requests for waivers were with respect to parts or all of the requirements of proposed § 600.80. In addition, one comment requested that the final rule specify the provisions for requesting a waiver.

The agency agrees that the provisions for a waiver should be specified in the final rule and has added a new § 600.90 describing the procedures for requesting

a waiver. Section 600.90 is similar to § 314.90 (21 CFR 314.90), the provision for waivers for drugs or antibiotics. Manufacturers and other interested persons should submit requests for waivers as provided in § 600.90 of the final rule.

5. Economic Assessment

One comment requested clarification of FDA's estimate of the cost of complying with the reporting requirements of the proposed rule of approximately $255,490. The company estimates that its cost in labor and overhead would be approximately $40,000. In contrast, another comment stated that the company did not anticipate that this reporting requirement would significantly alter the manner in which companies would share their postmarketing information with FDA.

The agency's assessment of cost was made over 4 years ago when both the number of approved biological products was fewer and costs somewhat less. In addition, the agency's figures did not take into account overhead and other costs associated with basic manufacturing practices. Every responsible manufacturer and distributor, regardless of the type of product manufactured, implements a means to receive inquiries about the quality and adverse effects of its products as good manufacturing practices and as an accepted part of doing business. Therefore, this cost has not been included in assessing the cost of this regulation. The costs assessed for this regulation only related to the specific costs incurred by the requirements in the regulation which are in addition to customary business practice. The costs of the regulation are for preparation of the specific reports and analyses required by the regulation and do not include the normal operating and overhead costs of doing business. The revised economic assessment is discussed at the end of this preamble.

B. Definitions Section 600.80(a)

1. Adverse Experience

Four comments requested clarification of the definition of "adverse experience" in proposed § 600.80(a), particularly the phrase "significant failure of expected pharmacological action * * * whether or not considered product related." One comment stated that the word "significant" has one meaning in the definition of "adverse experience" and another statistical meaning in the usage of the term "increased frequency" in proposed § 600.80(c)(1)(ii) and requested that the word be used consistently with the same meaning throughout the regulation. Another comment requested a definition of "significant failure" as used in the definition of adverse experience. One comment requested that the definition be amended to require reporting of changes in failure rates instead of any significant failure. One comment gave the following examples of incidents that would be considered an adverse experience with any significant failure: a patient who dies of acute myocardial infarction in spite of thrombolytic therapy; or a patient who dies of congestive heart failure despite diuretic therapy, i.e., deaths from progression of the indicated disease. One comment stated that it concurs with the agency's definition of "adverse experience" because it does not include "loss of response" as an adverse experience. The comment goes on to state that loss of immunity over time from a vaccine is not logically an adverse event.

The agency agrees that the word "significant" when used in this context is a source of confusion and ambiguity. To eliminate this source of confusion and to encourage the reporting of all adverse experiences, FDA revised § 314.80 to delete the word "significant" from the definition of "adverse experience" in the reporting requirements for drugs (see 57 FR 17950, April 28, 1992) and is revising the definition of "adverse experience" in this final rule by deleting the word "significant."

The agency is retaining the proposed language in the definition of "adverse experience" instead of adopting the suggestion to require reporting only of changes in failure rate because a "change in failure rate" can only be determined retrospectively. A change in failure rate is to be reported in an increased frequency report; however, a failure of expected pharmacological action that causes a serious and unexpected adverse experience in humans should be reported within 15 days regardless of the rate of such reports.

The agency believes that the examples given may or may not indicate a "failure of expected pharmacological action." For example, patients with congestive heart failure often have irreparable kidney damage which even the most potent diuretics cannot overcome. In such a situation congestive heart failure would not be a failure of expected pharmacologic action. However, the extent of pre-existing kidney damage and the degree to which kidney failure may be expected would be demonstrable through kidney function tests prior to medication. Therefore, FDA is not amending the definition of adverse experience as requested.

The agency agrees partially with the comment regarding "loss of response." If loss of immunity over time is the expected pharmacologic action of the vaccine, then it is not an adverse experience. If loss of immunity is due to a patient's compromised immune system, this also would not be considered an adverse experience. However, loss of immunity due to an unexpected failure of the pharmacologic action of the vaccine, thereby leaving recipients susceptible to a communicable disease, is an adverse experience and should be reported. The guideline points out that for purposes of adverse events reporting, "lack of effect" is generally synonymous with "failure to produce the expected pharmacologic action." Certain products are indicated for immunization through a recommended course of several doses to achieve a specified level of antibody titer to provide seroprotection. In this case, "lack of effect" is synonymous with "failure to produce the expected pharmacologic action" only when adequate seroconversion is not achieved following the final dose.

2. Blood Components

One comment noted that the language in the proposed § 600.80(l)(1) and preamble refers to blood components yet the section of the CFR upon which the exemption is predicated (§ 606.170) refers to blood products. The comment specifically asked whether albumin and immunoglobulin are exempt from the rule and requested clarification of the meaning of blood component in § 600.80(a).

FDA is clarifying the regulations by adding in § 600.80(a) of the final rule a reference to 21 CFR 606.3(c), which defines a "Blood Component" as "that part of a single-donor unit of blood separated by physical or mechanical means." The exemption in § 600.80(l), for reporting adverse experiences associated with blood components, does not include products derived from pooled blood such as albumin or immunoglobulin. Therefore, albumin and immunoglobulin are biological products subject to this rule.

In a future issue of the Federal Register FDA intends to propose revisions to § 606.170, concerning reports related to blood collection or transfusion.

3. Disability

Two comments requested that a definition for "disability" be included in § 600.80(a) as the phrase

"permanently disabling" is used in the definition of "serious."

The agency agrees that the term "disability" should be defined and is proposing a definition in the notice of proposed rulemaking found elsewhere in this issue of the **Federal Register**.

4. Increased Frequency

Four comments on proposed § 600.80(a) requested clarification of the definition for "increased frequency." Two comments stated that the proposed definition of "increased frequency," as an increase in the rate of occurrence, is misleading inasmuch as the rate of occurrence cannot be determined by a spontaneous reporting system. Two comments requested that the definition of increased frequency take into account an adjustment for product exposure.

The agency agrees with these comments and is revising the definition in § 600.80(a) as follows: "Increased frequency means an increase in the rate of occurrence of a particular adverse biological product experience, after appropriate adjustment for exposure to the biological product."

5. Life Threatening

One comment requested that a definition for "life threatening" be included, similar to that found in 21 CFR 312.32.

The agency agrees and is proposing a definition of "life threatening" in the notice of proposed rulemaking found elsewhere in this issue of the **Federal Register**.

6. Serious

Three comments noted discrepancies between the preamble, § 600.80(a) of the proposed rule, reporting form FDA–1639, and the draft guideline regarding the meaning of the term "serious." The discrepancies consisted of differences in scope regarding the reportability of overdose, prolonged hospitalization, and severe disability.

To clarify the discrepancies concerning "overdose," the agency reevaluated the definition of "serious" to determine whether all overdoses should be included in the definition and determined that not all overdoses are serious.

In resolving the discrepancies in the definition of "serious" regarding inpatient hospitalization, the agency determined that prolonged inpatient hospitalization should be included as a serious adverse event. FDA is proposing a revision of the definition of "serious" to exclude the term "overdose" and to include "requires or prolongs inpatient hospitalization" in the notice of proposed rulemaking found elsewhere in this issue of the **Federal Register**.

The term "disability" is discussed in section III.B.3 of this preamble.

7. Significant

One comment requested that a definition for the word "significant" which compensates for changes in use patterns be included in § 600.80(a). The comment is in reference to the use of the term "significant" in the increased frequency alert reports.

The agency agrees in part with this comment. The agency considers "significant" in this context to mean a noticeable or measurable increase in frequency after adjustment for documented changes in use patterns. However, the agency is not codifying this definition in § 600.80(a) because "significant" may have a different meaning in a different context within adverse experience reporting. The guideline provides clarifying examples utilizing a formula and table to determine if there is a significant increase in frequency of an adverse experience.

8. Clarification Between Product Defects and Adverse Experiences

One comment requested clarification regarding the definitions in § 600.80(a) for adverse experiences and the reporting of product defects.

The definition of "adverse experience" in § 600.80(a) specifies that the adverse experience must be "associated with the use of a biological product in humans * * *." Therefore, product defects either discovered in the manufacturing process or not associated with an adverse experience in humans are not subject to this regulation. These defects may be reportable under good manufacturing practice regulations covered in 21 CFR 600.14. However, product defects which result in an adverse experience in a human are subject to reporting under § 600.80.

C. Review of Adverse Experiences Section 600.8(b)

1. Reported by Scientific Papers or Competitors

One comment on proposed § 600.80(b) stated that to place responsibility on the licensed manufacturer for review of all adverse experience information pertaining to its product from any source, including published and unpublished scientific papers, is both time consuming and possibly open to abuse by competitors. The comment went on to state that if an unsubstantiated mailing from a competitor alleged "adverse or unexpected experiences," the licensed manufacturer becomes subject to the entire 15-day alert procedures, including the need to conduct, if not actually report to FDA, the followup investigation. One comment asked the agency to specify the degree of vigor that licensed manufacturers should use to pursue reports of adverse experiences in the scientific literature.

Section 600.80(b) is not intended to require licensed manufacturers to discover every published and unpublished report on its product. However, once a report of an adverse experience is made known to the licensed manufacturer, it is the licensed manufacturer's responsibility to comply with the requirements in § 600.80 regardless of the source of the adverse experience report. It is acceptable for the licensed manufacturer to come to the conclusion that the mailing or publication alleging an adverse experience is false or misleading and report this conclusion to the agency. In some cases the agency may take appropriate regulatory action against persons preparing a false or misleading report of an adverse experience.

2. Lack of Response Reports

One comment on proposed § 600.80(b) stated that "lack of response" complaints from consumers do not have sufficient validity to aid in decisionmaking and therefore should not be submitted to FDA. Another comment requested that "lack of response" should not be submitted for single patient incidents but limited to studies.

The agency believes that all reports of "lack of response" for single patient incidents should be reviewed and submitted by the licensed manufacturer. Complaints from consumers should be verified with the patient's health-care provider, if possible, prior to being submitted to FDA.

D. Clarification of Reporting Requirements Section 600.80(c)

1. Terminology

Two comments on proposed § 600.80(c) requested clarification of terminology between the term "applicant" used in § 314.80 and the term "manufacturer" used in proposed § 600.80. One comment preferred the term "licensee" for this regulation regarding biological products.

The agency uses the term "licensed manufacturer" in these rules because it presents a more accurate representation of those required to comply with these regulations. These rules are being promulgated for the purpose of

gathering postmarketing surveillance information, which will occur after product licensing.

2. Responsibilities

Two comments requested clarification of responsibilities for joint manufacturers, shared manufacturers, divided manufacturers, and contractual manufacturers so that duplicate adverse experience reports are not submitted. One comment requested that, in order to avoid duplicate reporting or failures to report adverse experiences, the agency should add language similar to § 314.80(c)(1)(iii). Another comment requested that the agency specify the reporting requirements of a nonapplicant.

FDA recognizes that manufacturing of a biological product can be shared or divided among a number of business establishments. In the **Federal Register** of November 25, 1992 (57 FR 55544), FDA published a notice that discussed cooperative manufacturing arrangements for licensed biological products. In addition, 21 CFR 600.12(e) requires that "each participating manufacturer shall furnish to the manufacturer who prepares the product in final form for sale, barter or exchange, a copy of all records relating to the manufacturing operations performed by such participating manufacturer insofar as they concern the safety, purity and potency of the lots of the product involved, * * *." Other requirements regarding divided manufacturing are contained in 21 CFR 610.63, which requires that "If two or more establishments participate in the manufacture of a product, the name, address, and license number of each must appear on the package label, and on the label of the container if capable of bearing a full label."

The agency is clarifying the reporting requirements in § 600.80(c)(1)(iii) by substituting the term "licensed manufacturer" for the term "manufacturer." The agency intends that the manufacturer licensed to prepare the final product for commercial distribution has the primary responsibility for reporting adverse experiences to FDA. To prevent duplicate reports, language has been added to § 600.80(c)(1)(iii) in this final rule to clearly delineate the responsibilities of the licensed manufacturer of the final product and other persons whose names may appear on the product label.

E. Reporting Requirements Section 600.80(c)

1. Failure of Pharmacologic Action

One comment on proposed § 600.80(c) requested that FDA not require single patient adverse experience forms for each failure of expected pharmacological action. The comment suggested that increased frequency analyses should not be performed on spontaneous lack of response reports because it is not possible for an appropriate baseline to be constructed using either domestic or foreign spontaneous reports in this setting.

FDA believes that the use of single patient adverse experience reporting forms provides the agency with information that may be helpful in assessing whether there is a need for further investigation of the reported lack of response. The agency also believes that increased frequency analyses and reports are useful to serve as an indicator that an investigation is needed to explore the issue further.

2. Followup Reports to 15-day Alerts

Two comments regarding proposed § 600.80(c)(1)(i) questioned the need for a report that briefly describes the steps taken to seek additional information about an adverse event and the reasons why such information could not be obtained. The comments stated that the proposed language placed an additional burden on licensed manufacturers by requesting not only that they make every effort to obtain such information but also that they write a report describing such efforts.

Under § 600.80(c) licensed manufacturers will be required to seek additional information and document the steps taken to comply with the rule in a manner consistent with § 314.80(c). The agency is not, at this time, specifying the format for this documentation. The agency must be able to verify the licensed manufacturer's efforts and advise licensed manufacturers of additional steps that should be pursued to retrieve the necessary information when appropriate. The proposed rule stated that this report should not be submitted to the agency unless so requested but should be maintained in the licensed manufacturer's files. This requirement differs from § 314.80(c)(1)(i). The agency believes it would reduce the burden for manufacturers who produce both biologics and drugs if § 600.80(c)(1)(i) is consistent with § 314.80(c)(1)(i). Therefore, the sentence in proposed § 600.80(c)(1)(i), "This report should be retained by the manufacturer in its files but not submitted as a followup to FDA unless so requested" has been deleted. Further discussion of changing the final disposition of these reports is included in the notice of proposed rulemaking found elsewhere in this issue of the **Federal Register.**

3. Increased Frequency Analysis

Two comments on proposed § 600.80(c)(1)(ii) requested information regarding the utility of increased frequency analysis. These comments suggest that the analysis is not of the increased frequency of adverse experiences but rather the analysis is of the increased frequency of reports of adverse experiences. One comment requested that the agency develop improved methods for determining increased frequency that would account for fluctuations in reporting.

FDA agrees that increased frequency of adverse experience reports does not necessarily correlate with an increase in adverse experiences. Case reports are used to alert the agency about areas which may need further investigation. FDA takes into account the fact that reporting rates vary over time in postmarketing surveillance when analyzing the reporting rate for an individual biologic. FDA does not assume that an increase in incidence of adverse experiences will automatically trigger an increase in reports of adverse experience. Nor does the agency assume that an increase in the number of reports of adverse experiences necessarily indicates an increase in incidence of adverse experiences. The agency believes that an increase in reporting rates, when taken into account with other relevant information, may indicate that an epidemiologic investigation is needed to explore the situation further.

4. Periodic Reports

Three comments on proposed § 600.80(c)(2) noted a discrepancy on when the reporting period begins. One comment requested that the interval for periodic reporting be extended to annually rather than quarterly. One comment requested that the agency extend the time for submitting periodic reports from 30 to 60 days after the end of the reporting period.

FDA believes that the reports need to be submitted in a timely manner because the public is continuing to be exposed to the products. Accordingly, FDA is retaining the proposed time schedule for submitting periodic reports in this final rule. In the notice of proposed rulemaking published elsewhere in this issue of the **Federal Register**, FDA is proposing to amend the regulations regarding when the reporting period begins and to amend

the schedule for submitting periodic reports.

5. Schedule for Submitting Reports

Four comments on proposed § 600.80(c)(2)(i) requested that the agency limit reporting requirements (other than 15-day alerts) to the first 3 or 10 years of marketing. These comments stated that the initial postmarketing period would provide the most benefit and that after an initial period these reports would offer little benefit and would be a burden to the agency and the licensed manufacturer.

FDA believes that there is a need for licensed manufacturers to continually monitor adverse experiences. The length of time a product is marketed does not guarantee that it will not be implicated in latent adverse experiences that were not recognized previously. Novel adverse experiences can occur when a biological product is used concomitantly with another drug or biological product. In addition, a product that has been on the market for many years can be implicated in adverse experiences that were either previously undetected or unknown in the scientific community. For these reasons, this requirement for periodic review and submission of reports of adverse experiences is necessary for the public safety. However, the licensed manufacturer can request a waiver under § 600.90 in order to decrease or eliminate the periodic reporting requirements for older products with a proven safety record.

Under § 600.80(c)(2)(i) the agency may also require more frequent reports for products if appropriate; for example, products with special safety or efficacy concerns. Similarly the agency may require less frequent reports or no reports for products with a history of continual safety.

6. Effect of Significant Change in Manufacturing on Reporting Requirements

One comment on proposed § 600.80(c)(2)(i) expressed concern that significant changes in the manufacturing process, as provided in the Product License Application (PLA), may lead FDA to require that the frequency of the periodic reports be maintained as quarterly reports. The example given in the comment was for influenza virus vaccine. The comments questioned whether this product would be considered a new product annually due to its inherent strain changes.

Influenza vaccine is an example of a product for which more frequent reports may be appropriate. The agency considers the influenza vaccine to be a new product annually because variations in influenza strains make it necessary to reformulate the influenza vaccine each year.

In the past, there have been many reports of adverse experiences associated with the influenza vaccine, including reports of Guillain-Barre Syndrome and false positive test results for other viral markers. In situations such as this, the agency may require more frequent reporting which will help it assess the magnitude and accuracy of reports of adverse experiences. In § 600.80(c)(2)(i) FDA may upon written notice extend or reestablish the requirement that a licensed manufacturer submit quarterly reports, or require that the license manufacturer submit reports under this section at different times than those stated. Prompt reporting of these adverse experiences will make it easier to either recall a problem lot or discredit a false rumor.

7. Requirement for Negative Periodic Reports

Two comments on proposed § 600.80(c)(2) requested that the agency clarify the discrepancy between the proposed rule and the draft guideline regarding periodic reports for products that had no adverse experiences reported. The proposed rule did not require periodic reports for products that had no adverse experiences reported. The guideline asked that a letter be sent stating that no adverse experiences were reported. These comments also stated that the negative report is an "undue burden."

The guideline has been changed to be consistent with the final rule in not requiring negative reporting at this time. However, the agency believes that the negative reports are appropriate for the agency to determine that the licensed manufacturer is focusing attention on whether there have been adverse experiences reported to FDA. Therefore, requirements regarding submission of negative reports are included in the notice of proposed rulemaking found elsewhere in this issue of the Federal Register.

8. Tabular Line Listing in Periodic Reports

Three comments on proposed § 600.80(c)(2)(ii)(C) regarding the tabular listing of adverse experiences required in the periodic reports stated that the requirements to list the patient's identification number, age, sex, and adverse experience terms in the tabular listing were viewed as unnecessary and excessive. Also noted were discrepancies regarding the tabular listing requirements between the guideline and the proposed rule.

The agency agrees that the age and sex are not necessary in the tabular listing. However, the agency believes that the adverse experience terms should be included in such a listing. The tabular line listing is intended to provide a synopsis of individual case histories previously submitted, to assist FDA in identifying potential issues and individual case histories for further review. The agency is amending § 600.80(c)(2) to require only the licensed manufacturer's patient identification number and adverse experience terms in the tabular listing.

9. Submission of Labeling

Two comments on proposed § 600.80(c)(2)(ii)(E) requested that the agency not require licensed manufacturers to submit with periodic reports a copy of the most current labeling, including container labels, carton labels, package inserts, and other materials distributed with the product. In addition, the comments stated that the current labeling is reviewed by FDA before use and licensed manufacturers should not be required to repeatedly submit this information with periodic reports. One comment stated that the only labeling useful for evaluating adverse experience reports is the package insert, unless the product is sold over-the-counter, then submission of directions for consumers on the container label may be justified.

The agency agrees with the comments and is amending § 600.80(c)(2)(ii)(C) of the final rule to require "a history of actions taken since the last report because of adverse experiences (for example, labeling changes or studies initiated)." This ensures that the review of the adverse experiences is conducted in the context of the latest information available.

10. Submission of Distribution Data

Ten comments related to various aspects of the requirements in proposed § 600.80(c)(2)(iv) for submission of distribution data for licensed biological products. Two comments stated that the request for foreign distribution data is a heavy burden. Three comments stated that the requirement to report dose distribution data is difficult and inappropriate for certain types of products and that this information is not required in § 314.80 for drugs. Two comments disagreed with a statement in the preamble that the quantity of a product distributed enables FDA to estimate more accurately the incidence of a product's adverse effects. The comments reasoned that distribution

data do not determine how much product is actually used. One comment questioned FDA's ability to keep the distribution information confidential. One comment stated that the proposed schedule for distribution reports places a hardship on manufacturers as it required quarterly reports for new biological products, annual reports for biological products licensed more than 3 years, and annual reports for drugs. Another comment requested guidance on the preferred format for distribution data. The agency agrees that foreign distribution data should not be required for biological products. Although the agency agrees that distribution data do not accurately estimate the incidence of a product's adverse effects, it is information needed to help FDA determine whether further study is needed. FDA, on its own initiative, is amending the final rule to parallel the drug regulations format by moving the requirements to submit distribution data to § 600.81. The agency has revised the schedule for submitting distribution reports in § 600.81 of the final rule. The reports will now be due on the semiannual and annual anniversary of the licensing of the product. Licensed manufacturers that believe that the requirements for submission of distribution data are inappropriate for certain types of products may request a waiver under § 600.90, as discussed elsewhere in this preamble. Until a waiver is granted the provisions specified in the final rule are applicable.

F. Review of Scientific Literature

One comment on § 600.80(d) requested that submission of reports from scientific literature be limited to those articles where the author believes the product is associated with the experience; i.e., "reasonable causation" by the author should be used in determining what adverse experiences from the literature need to be reported to FDA.

The agency believes that reports of adverse experiences in the literature where the author clearly states that the licensed manufacturer's product is not the cause do not need to be reported. Reports in the scientific literature where no conclusion is reached regarding causality should be further investigated by the licensed manufacturer and reported to FDA if the adverse experience is associated or remains possibly associated with the licensed biological product. The licensed manufacturer should document the information that determines the cause to be other than product related and retain this documentation.

G. Reporting Form FDA–1639

Five comments on proposed § 600.80(f) concerned the use of Form FDA–1639 for reporting adverse experiences. One comment stated that the form is inappropriate for their biological products, one comment asked that the form be updated, one comment requested that Form FDA–1639 be retained for VAERS reporting as well as for adverse experience reporting for drugs and biological products. Two comments questioned whether an approved alternate form for reporting adverse experiences for drugs must be resubmitted to CBER for approval. One comment requested that the agency not allow implementation of an alternative reporting form as it will cause a hardship in computerization of adverse experience data across the biological and pharmaceutical product lines. This comment requested that the same form (Form FDA–1639) be used for all adverse experience reports regardless of the nature of the product.

FDA has designed a new adverse experience reporting form (Form FDA–3500A) which, with the exception of reporting adverse experiences associated with vaccines, is ordinarily to be used to report under §§ 310.305, 312.32, 314.80, 600.80, and parts 803 and 807 regarding drugs, biological products, and devices, respectively. The new form will simplify and consolidate the reporting of adverse events and product problems and will enhance agency-wide consistency in the collection of postmarketing data. Any computer-generated forms will have to be submitted to MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852–9787, for approval to use in complying with this final rule. As one comment suggested, alternative formats will make computerization of adverse experience data across product lines difficult. Therefore, a licensed manufacturer should submit adequate justification for an alternative format.

Form FDA–3500A is referenced in § 600.80(f) of the final rule. The term "form designated by FDA" is used throughout the remainder of the final rule to accommodate any future changes in the form itself. For vaccines the designated form for reporting adverse experiences is Form VAERS–1. The form for VAERS is discussed in a published report in *Morbidity and Mortality Weekly Report* (see MMWR, 39:730–733, 1990).

H. Reporter Identification

One comment on proposed § 600.80(h) requested that if the reporter is the patient (or relative) that his or her name not be listed on the adverse experience form.

The agency concurs with this request for adverse experience reporting for licensed biological products other than vaccine-associated experiences being reported in accordance with NCVIA. Under NCVIA it would be appropriate to include the patient's name in the report because copies of this report may be made available to the vaccinee or legal representative of the vaccinee. For adverse experience reporting of licensed biological products other than vaccines being reported under NCVIA, the report should not include the name of the patient, but should assign a unique code number to each report. For adverse experience reporting of biological products, patient identifiers are not releasable to the public under FDA's public information regulations (21 CFR part 20). Section 600.80(h) is amended to reflect that VAERS reports are subject to the CDC Privacy Act System.

I. Unique Code Number

One comment concerning proposed § 600.80(h) requested that the agency increase the number of characters in the unique code number assigned to each report from eight characters in length to nine characters.

The agency encourages consistency by designating in the final rule a number of characters to be used, to simplify preparing and processing the reports. To allow some flexibility, note that § 600.80(h) in the final rule recommends but does not require use of a code number of eight characters or less.

J. Recordkeeping

Two comments on proposed § 600.80(i) related to the length of time a licensed manufacturer is required to keep adverse experience records. One comment requested clarification regarding whether form letters sent by the licensed manufacturer to the adverse experience reporter must be retained 10 years; another comment requested that the recordkeeping be limited to 1 year past the involved product's expiration date.

FDA believes that 10 years is a reasonable time to maintain such records. This requirement corresponds with existing regulations for drug products. If a form letter to the reporter is the documentation that the licensed manufacturer sought additional information about an adverse experience, then the form letter must be maintained in the file for 10 years. Any letters which are part of the correspondence regarding an adverse experience reporting must be maintained in the file for 10 years.

K. Exemptions

FDA has determined that § 600.80(l) should be amended to clarify that licensed manufacturers of in vitro diagnostic products, including assay systems for the detection of antibodies or antigens to retroviruses, report adverse experiences under the device reporting regulations. The best way to monitor product defects with these licensed biological devices is for them to be reported under the Medical Devices: Medical Device User Facility, Distributor, and Manufacturer Reporting, Certification, and Registration Regulations (see 56 FR 60024, November 26, 1991). To eliminate any confusion over how to report product defects with these products, the final rule is amended to state specifically that in vitro diagnostics, including assays to detect antibodies or antigens to retroviruses (such as HIV–1 and HIV–2), are exempt from this rule but are subject to the device reporting regulations.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). 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 agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The final rule codifies adverse experience reporting for biological products currently being practiced by licensed manufacturers on a voluntary basis. FDA believes that the information collection resulting from postmarket surveillance required by this final rule will be of benefit to the public health. FDA has prepared a Threshold Assessment to estimate the cost to comply with the final rule by the regulated industry. The estimation by FDA for the total annual cost to industry is $3,937,164. The agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) 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.

VI. Paperwork Reduction Act of 1980

Sections 600.80 and 600.81 of this final rule contain information collection requirements which are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1980. The title, description, and respondent description of the information collection 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 the collection of information.

Title: Adverse Experience Reporting Requirements for Licensed Biological Products.

Description: FDA is charged with the responsibility for determining that a biological product meets the statutory standards for safety, purity, and potency for initial and continued licensure. To carry out this mandate, the agency needs to be informed whenever a manufacturer of a licensed biological product receives or otherwise becomes aware of information about adverse experiences associated with the use of its product. Only if FDA is provided with such information will it be able to evaluate the risk, if any, associated with a biological product and take whatever action is necessary to reduce or eliminate the public's exposure. FDA is taking this action to provide a mechanism under which manufacturers would inform the agency, on a timely basis, of any unanticipated safety problems with marketed biological products. This action is similar to initiatives taken by FDA regarding new drugs and medical devices.

Description of Respondents: Businesses or other for-profit and small businesses or organizations.

As required by the Paperwork Reduction Act, FDA has submitted a copy of this rule to OMB with a request that it approve these information collection requirements.

ESTIMATED TOTAL ANNUAL REPORTING BURDEN

Section	Number of Respondents	Number of Respondents per Respondent	Total Annual Responses	Hours Per Response	Total Hours
600.81	63	175.12698	11,033	1.0	11,033

ESTIMATED TOTAL ANNUAL RECORDKEEPING BURDEN

Section	No. of Recordkeepers	Annual Hours Per Recordkeeper	Total Recordkeeping Hours
600.80(i)	63	0.5	31.5

This final rule also contains information collection requirements contained in § 600.80(c) that have been approved by OMB under OMB No. 0910–0291 with a total of 11,033 hours. It is estimated that the information requirements for this section under this final rule will add 11,064.5 hours to the burden estimate.

List of Subjects in 21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

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

PART 600—BIOLOGICAL PRODUCTS: GENERAL

1. The authority citation for 21 CFR part 600 is revised 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. A new subpart D consisting of §§ 600.80, 600.81, and 600.90 is added to read as follows:

Subpart D—Reporting of Adverse Experiences

Sec.

Subpart D—Reporting of Adverse Experiences

§ 600.80 Postmarketing reporting of adverse experiences.

(a) *Definitions.* The following definitions of terms apply to this section:

Adverse experience means any adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: an adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product, whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action.

Blood Component for this purpose has the same meaning as defined in § 606.3(c) of this chapter.

Increased frequency means an increase in the rate of occurrence of a particular adverse biological product experience, e.g., an increased number of reports of a particular adverse biological product experience after appropriate adjustment for biological product exposure.

Serious means an adverse experience associated with the use of a biological product that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

Unexpected means an adverse biological product experience that is not listed in the current labeling for the product and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.

(b) *Review of adverse experiences.* Any person having a product license under § 601.20 of this chapter shall promptly review all adverse experience information pertaining to its product obtained or otherwise received by the licensed manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.

(c) *Reporting requirements.* The licensed manufacturer shall report to FDA adverse experience information, as described in this section. The licensed manufacturer shall submit two copies of each report described in this section for nonvaccine biological products, to the Center for Biologics Evaluation and Research (HFM–210), Food and Drug Administration, 1401 Rockville Pike, suite 200 N., Rockville, MD 20852–1448. Submit all vaccine adverse experience reports to: Vaccine Adverse Event Reporting System (VAERS), P.O. Box 1100, Rockville, MD 20849–1100. FDA may waive the requirement for the second copy in appropriate instances.

(1) *Fifteen-day Alert reports.* (i) The licensed manufacturer shall report each adverse experience that is both serious and unexpected, regardless of source, as soon as possible but in any case within 15 working days of initial receipt of the information. These reports are required to be submitted, for nonvaccine biological products, on a form designated by FDA or a suitable format containing all of the data elements in the FDA designated reporting form, and, for vaccines on a VAERS form. The licensed manufacturer shall promptly investigate all adverse experiences that are the subject of these 15-day Alert reports and shall submit followup reports within 15 working days of receipt of new information or as requested by FDA. If additional information is not obtainable, a followup report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained. These 15-day Alert reports and followups to them are required to be submitted under separate cover and may not be included, except for summary or tabular purposes, in a periodic report.

(ii) The licensed manufacturer shall review periodically (at least as often as the periodic reporting cycle) the frequency of reports of adverse biological product experiences that are both serious and expected and reports of therapeutic failure (lack of effect), regardless of source, and report any significant increase in frequency as soon as possible but in any case within 15 working days of determining that a significant increase in frequency exists. Upon written notice, FDA may require that licensed manufacturers review the frequency of reports of serious, expected adverse biological product experiences at intervals different than the periodic reporting cycle. Reports of a significant increase in frequency are required to be submitted in narrative form (including the time period on which the increased frequency is based, the method of analysis, and the interpretation of the results), rather than using the form designated by FDA. Fifteen-day Alert reports based on increased frequency are required to be submitted under separate cover and may not be included, except for summary purposes, in a periodic report.

(iii) The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of Fifteen-day Alert reports, shall also apply to any person other than the licensed manufacturer of the final product whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing. In order to avoid unnecessary duplication in the initial and followup submission of reports to FDA, the obligations of a manufacturer other than the licensed manufacturer, may be met by submitting all reports to the licensed manufacturer of the final product. If a manufacturer other than the licensed manufacturer elects to submit reports to the licensed manufacturer rather than to FDA, it shall submit each report to the licensed manufacturer within 3 working days of its receipt, and the licensed manufacturer shall then comply with the requirements of this section. Under this circumstance, the manufacturer shall maintain a record of this action which shall include:

(A) A copy of all adverse biological product experience reports submitted to the licensed manufacturer,

(B) Date the report was received by the manufacturer,

(C) Date the report was submitted to the licensed manufacturer,

(D) Name and address of the licensed manufacturer.

(iv) Each report submitted under this paragraph shall bear prominent identification as to its contents, i.e., "15-day Alert report" or "15-day Alert report--followup."

(2) *Periodic adverse experience reports.* (i) The licensed manufacturer shall report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of issuance of the product license, and then at annual intervals. The licensed manufacturer shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of issuance of the product license) and each annual report within 60 days of the anniversary date of the issuance of the product license. Upon written notice, FDA may extend or reestablish the requirement that a licensed manufacturer submit quarterly reports, or require that the licensed manufacturer submit reports under this section at different times than those stated. Followup information to adverse experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report shall contain:

(A) A narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the licensed manufacturer's patient identification number, adverse reaction term(s), and date of submission to FDA);

(B) A form designated for Adverse Experience Reporting by FDA for each adverse experience not reported under paragraph (c)(1)(i) of this section (with an index consisting of a line listing of the licensed manufacturer's patient identification number and adverse reaction term(s)); and

(C) A history of actions taken since the last report because of adverse experiences (for example, labeling changes or studies initiated).

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) *Scientific literature.* (1) A 15-day Alert report based on information from the scientific literature shall be accompanied by a copy of the published article. The 15-day Alert reporting requirements in paragraph (c)(1)(i) of this section (i.e., serious, unexpected adverse experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial. The 15-day Alert reporting requirements in paragraph (c)(1)(ii) of this section (i.e., a significant increase in frequency of a serious, expected adverse experience or of a therapeutic failure) apply only to reports found in scientific and medical journals either as the result of a formal clinical trial, or from epidemiologic studies or analyses of experience in a monitored series of patients.

(2) As with all reports submitted under paragraph (c)(1)(i) of this section, reports based on the scientific literature shall be submitted on the reporting form designated by FDA or comparable format as prescribed by paragraph (f) of this section. In cases where the licensed manufacturer believes that preparing the form designated by FDA constitutes an undue hardship, the licensed manufacturer may arrange with the Division of Biostatistics and Epidemiology (HFM–210) for an acceptable alternative reporting format.

(e) *Postmarketing studies.* (1) Licensed manufacturers are not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse experience obtained from a postmarketing clinical study (whether or not conducted under a biological investigational new drug application) unless the licensed manufacturer concludes that there is a reasonable possibility that the product caused the adverse experience.

(2) The licensed manufacturer shall separate and clearly mark reports of adverse experiences that occur during a postmarketing study as being distinct from those experiences that are being reported spontaneously to the licensed manufacturer.

(f) *Reporting forms.* (1) Except as provided in paragraphs (c)(1)(ii), and (f)(3) of this section, the licensed manufacturer shall complete the reporting form designated by FDA (FDA–3500A, or, for vaccines, a VAERS form) for each report of an adverse experience.

(2) Each completed form should refer only to an individual patient or single attached publication.

(3) Instead of using a designated reporting form, a licensed manufacturer may use a computer-generated form or other alternative format (e.g., a computer-generated tape or tabular listing) provided that:

(i) The content of the alternative format is equivalent in all elements of information to those specified in the form designated by FDA; and

(ii) the format is approved in advance by MEDWATCH: The FDA Medical Products Reporting Program; or, for alternatives to the VAERS Form, by the Division of Biostatistics and Epidemiology.

(4) Copies of the reporting form designated by FDA (FDA–3500A) for nonvaccine biological products may be obtained from the Center for Biologics Evaluation and Research (address above). Additional supplies of the form may be obtained from the Consolidated Forms and Publications Distribution Center, 3222 Hubbard Rd., Landover, MD 20785. Supplies of the VAERS form may be obtained from VAERS by calling 1–800–822–7967.

(g) *Multiple reports.* A licensed manufacturer should not include in reports under this section any adverse experiences that occurred in clinical trials if they were previously submitted in the product license application. If a report refers to more than one biological product marketed by a licensed manufacturer, the licensed manufacturer should submit the report to the license for the product listed first in the report.

(h) *Patient privacy.* For nonvaccine biological products, a licensed manufacturer should not include in reports under this section the names and addresses of individual patients; instead, the licensed manufacturer should assign a unique code number to each report, preferably not more than eight characters in length. The licensed manufacturer should include the name of the reporter from whom the information was received. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse experience reports are not releasable to the public under FDA's public information regulations in part 20 this of chapter. For vaccine adverse experience reports, these data will become part of the CDC Privacy Act System 09–20–0136, "Epidemiologic Studies and Surveillance of Disease Problems." Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

(i) *Recordkeeping.* The licensed manufacturer shall maintain for a period of 10 years records of all adverse experiences known to the licensed manufacturer, including raw data and any correspondence relating to the adverse experiences.

(j) *Guideline.* FDA has prepared a guideline for the submission of reports of adverse experiences and suggested followup investigation of reports.

(k) *Revocation of license.* If a licensed manufacturer fails to establish and maintain records and make reports required under this section with respect to a licensed biological product, FDA may revoke the product license for such a product in accordance with the procedures of § 601.5 of this chapter.

(l) *Exemptions.* Manufacturers of the following listed products are not required to submit adverse experience reports under this section:

(1) Whole blood or components of whole blood.

(2) In vitro diagnostic products, including assay systems for the detection of antibodies or antigens to retroviruses. These products are subject to the reporting requirements for devices.

(m) *Disclaimer.* A report or information submitted by a licensed manufacturer under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the licensed manufacturer or FDA that the report or information constitutes an admission that the biological product caused or contributed to an adverse effect. A licensed manufacturer need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the biological product caused or contributed to an adverse effect. For purposes of this provision, this paragraph also includes any person reporting under paragraph (c)(1)(iii) of this section.

§ 600.81 Distribution reports.

The licensed manufacturer shall submit information about the quantity of the product distributed under the product license, including the quantity distributed to distributors. The interval between distribution reports shall be 6 months. Upon written notice, FDA may require that the licensed manufacturer submit distribution reports under this section at times other than every 6 months. The distribution report shall consist of the bulk lot number (from which the final container was filled), the fill lot numbers for the total number of dosage units of each strength or potency distributed (e.g., fifty thousand per 10-milliliter vials), the label lot number (if different from fill lot number), labeled date of expiration, number of doses in fill lot/label lot, date of release of fill lot/label lot for distribution at that time. If any significant amount of a fill lot/label lot is returned, include this information. Disclosure of financial or pricing data is not required. As needed, FDA may require submission of more detailed product distribution information. Upon written notice, FDA may require that the licensed manufacturer submit reports under this section at times other than those stated. Requests by a licensed manufacturer to submit reports at times other than those stated should be made as a request for a waiver under § 600.90.

§ 600.90 Waivers.

(a) A licensed manufacturer may ask the Food and Drug Administration to waive under this section any requirement that applies to the licensed manufacturer under §§ 600.80 and 600.81. A waiver request under this section is required to be submitted with supporting documentation. The waiver request is required to contain one of the following:

(1) An explanation why the licensed manufacturer's compliance with the requirement is unnecessary or cannot be achieved,

(2) A description of an alternative submission that satisfies the purpose of the requirement, or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The licensed manufacturer's compliance with the requirement is unnecessary or cannot be achieved,

(2) The licensed manufacturer's alternative submission satisfies the requirement, or

(3) The licensed manufacturer's submission otherwise justifies a waiver.

Dated: October 13, 1994.

William K. Hubbard,

Interim Deputy Commissioner for Policy.

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