§ 600.20 Inspectors.

Inspections shall be made by an officer of the Food and Drug Administration having special knowledge of the methods used in the manufacture and control of products and designated for such purposes by the Commissioner of Food and Drugs, or by any officer, agent, or employee of the Department of Health and Human Services specifically designated for such purpose by the Secretary.

[38 FR 32048, Nov. 20, 1973]

§ 600.21 Time of inspection.

The inspection of an establishment for which a biologics license application is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a biologics license is desired. In case the license is denied following inspection for the original license, no reinspection need be made until assurance has been received that the faulty conditions which were the basis of the denial have been corrected. An inspection of each licensed establishment and its additional location(s) shall be made at least once every 2 years. Inspections may be made with or without notice, and shall be made during regular business hours unless otherwise directed.


§ 600.22 Duties of inspector.

The inspector shall:

(a) Call upon the active head of the establishment, stating the object of his visit,

(b) Interrogate the proprietor or other personnel of the establishment as he may deem necessary,

(c) Examine the details of location, construction, equipment and maintenance, including stables, barns, warehouses, manufacturing laboratories, bleeding clinics maintained for the collection of human blood, shipping rooms, record rooms, and any other structure or appliance used in any part of the manufacture of a product,

(d) Investigate as fully as he deems necessary the methods of propagation, processing, testing, storing, dispensing, recording, or other details of manufacture and distribution of each licensed product, or product for which a license has been requested, including observation of these procedures in actual operation,

(e) Obtain and cause to be sent to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in §600.2), adequate samples for the examination of any product or ingredient used in its manufacture,

(f) Bring to the attention of the manufacturer any fault observed in the course of inspection in location, construction, manufacturing methods, or administration of a licensed establishment which might lead to impairment of a product,

(g) Inspect and copy, as circumstances may require, any records required to be kept pursuant to §600.12,

(h) Certify as to the condition of the establishment and of the manufacturing methods followed and make recommendations as to action deemed appropriate with respect to any application for license or any license previously issued.


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. 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.** As defined in §606.3(c) of this chapter.

**Disability.** A substantial disruption of a person’s ability to conduct normal life functions.

**Life-threatening adverse experience.** Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

**Serious adverse experience.** Any adverse experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**Unexpected adverse experience:** Any adverse experience that is not listed in the current labeling for the biological product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ 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 thrombembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b) **Review of adverse experiences.** Any person having a biologics 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. Licensed manufacturers are not required to resubmit to FDA adverse product experience reports forwarded to the licensed manufacturer by FDA; licensed manufacturers, however, must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse experiences to FDA.

(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), or to the Center for Drug Evaluation and Research (see mailing addresses in §600.2). Submit all vaccine adverse experience reports to: Vaccine Adverse Event Reporting System (VAERS) (see mailing addresses in §600.2). FDA may waive the requirement for the second copy in appropriate instances.

(1)(i) **Postmarketing 15-day “Alert reports.”** The licensed manufacturer shall report each adverse experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar
days of initial receipt of the information by the licensed manufacturer.

(ii) Postmarketing 15-day “Alert reports”—followup. The licensed manufacturer shall promptly investigate all adverse experiences that are the subject of these postmarketing 15-day Alert reports and shall submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information. Postmarketing 15-day Alert reports and followups to them shall be submitted under separate cover.

(iii) Submission of reports. The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, shall also apply to any person 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. To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of persons other than the licensed manufacturer of the final biological product may be met by submission of all reports of serious adverse experiences to the licensed manufacturer of the final product. If a person elects to submit adverse experience reports to the licensed manufacturer of the final product rather than to FDA, the person shall submit each report to the licensed manufacturer of the final product within 5 calendar days of receipt of the report by the person, and the licensed manufacturer of the final product shall then comply with the requirements of this section. Under this circumstance, a person who submits reports to the licensed manufacturer of the final product 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 of the final product;

(B) The date the report was received by the person;

(C) The date the report was submitted to the licensed manufacturer of the final product; and—

(D) The name and address of the licensed manufacturer of the final product.

(iv) Report identification. 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 biologics 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 biologics license) and each annual report within 60 days of the anniversary date of the issuance of the biologics license. Upon written notice, FDA may extend or re-establish 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 expe-
riences (for example, labeling changes
or studies initiated).

(iii) Periodic reporting, except for in-
formation regarding 15-day Alert re-
ports, does not apply to adverse experi-
ence information obtained from post-
marketing studies (whether or not con-
ducted 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 ac-
accompanied by a copy of the published
article. The 15-day Alert reporting re-
quirements in paragraph (c)(1)(i) of this
section (i.e., serious, unexpected ad-
verse experiences) apply only to re-
ports found in scientific and medical
journals either as case reports or as the
result of a formal clinical trial.

(2) As with all reports submitted
under paragraph (c)(1)(i) of this sec-
tion, reports based on the scientific lit-
erature shall be submitted on the re-
porting form designated by FDA or
comparable format as prescribed by
paragraph (f) of this section. In cases
where the licensed manufacturer be-
lieves that preparing the form des-
ignated by FDA constitutes an undue
hardship, the licensed manufacturer
may arrange with the Division of Bio-
statistics and Epidemiology (HFM–210)
for an acceptable alternative reporting
format.

(e) Postmarketing studies. (1) Licensed
manufacturers are not required to sub-
mit a 15-day Alert report under para-
graph (c) of this section for an adverse
experience obtained from a post-
marketing clinical study (whether or
not conducted under a biological inves-
tigational new drug application) unless
the licensed manufacturer concludes
that there is a reasonable possibility
that the product caused the adverse ex-
perience.

(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 pro-
vided in paragraph (f)(3) of this section,
the licensed manufacturer shall com-
plete the reporting form designated by
FDA for each report of an adverse expe-
rience (FDA Form 3500A, or, for vac-
cines, a VAERS form; foreign events
including those associated with the use
of vaccines, may be submitted either
on an FDA Form 3500A or, if preferred,
on a CIOMS I form).

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

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

(i) The content of the alternative for-
mat is equivalent in all elements of in-
formation 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 Epide-
miology.

(4) Copies of the reporting form des-
ignated by FDA (FDA–3500A) for non-
vaccine biological products may be ob-
tained from
http://www.fda.gov/
medwatch/getforms.htm. Additional sup-
plies of the form may be obtained from
the Consolidated Forms and Publica-
tions 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 manu-
facturer should not include in reports
under this section any adverse experi-
ence that occurred in clinical trials if
they were previously submitted as part
of the biologics license application. If a
report refers to more than one biologi-
cal product marketed by a licensed
manufacturer, the licensed manufac-
turer should submit the report to the
biologics license application for the
product listed first in the report.

(h) Patient privacy. For nonvaccine bi-
ological products, a licensed manufac-
turer should not include in reports
under this section the names and ad-
dresses 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) Revocation of biologics 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 biologics license for such a product in accordance with the procedures of §601.5 of this chapter.

(k) 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.

(l) 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 to the Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research (see mailing addresses in §600.2), information about the quantity of the product distributed under the biologics 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.