REGULATION OF BIOLOGICAL PRODUCTS

August 1955

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

Regulation of Biological Products

August 1955

Supersedes Miscellaneous Publication No. 10

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

Division of Biologics Standards of the National Institutes of Health

Public Health Service Publication No. 437

August 1955

This publication supersedes Miscellaneous Publication No. 10: Regulations for the Sale, Barter, or Exchange of any Virus, Therapeutic Serum, Toxin, Antitoxin or Analogous Product, etc.

From the Division of Biologics Standards
National Institutes of Health
Bethesda 14, Maryland

UNITED STATES GOVERNMENT PRINTING OFFICE, WASHINGTON : 1955

INTRODUCTION

This publication contains an unofficial reprint of (a) excerpts from the Public Health Service Act, as amended (42 U. S. C. 201 et seq.), covering those portions primarily applicable to the control of biologic products and of (b) the regulations on biologic products adopted pursuant to such Act (42 C. F. R. Part 73).

Interstate shipment and the export or import of biologic products were originally subject to Federal control under the provisions of the Act of July 1, 1902; 32 Stat. 728, 729. In enacting the Public Health Service Act, this authority was consolidated with other laws relating to the Public Health Service by the Act of July 1, 1944, entitled "An Act to consolidate and revise the laws relating to the Public Health Service, and for other purposes" (Public Law 410, 78th Congress; 58 Stat. 682). Title III, Part F of the Public Health Service Act is the part that directly relates to the control of biologic products.

The Public Health Service Regulations consist of Title 42, Chapter I of the Code of Federal Regulations. This chapter was rearranged and reprinted in its entirety in the Federal Register of September 16, 1947, to integrate the numerous amendments and additions issuing since the original codification of Title 42 on June 1, 1938. The present publication includes Part 73, Biologic Products, of these Regulations and includes amendments and additions published in the Federal Register since September 16, 1947.

Reorganization Plan No. 1, 1953 (67 Stat. 631), transferred the Public Health Service to the Department of Health, Education, and Welfare, abolished the Federal Security Agency and the Office of Federal Security Administrator, and transferred all functions of the Administrator to the Secretary of the Department. The Plan was made effective April 11, 1953, by the Act of April 1, 1953 (Public Law 13, 83d Congress, 67 Stat. 18). Accordingly, for all actions subsequent to April 10, 1953, the references in the statute and regulations to the terms "Federal Security Agency," "Federal Security Administrator," or "Administrator" have respectively been changed in this reprint to "Department of Health, Education, and Welfare," "Secretary of the Department of Health, Education, and Welfare" and "Secretary."

PUBLIC HEALTH SERVICE ACT, As Amended

TITLE I—SHORT TITLE AND DEFINITIONS

SHORT TITLE

42 U. S. C., Note

SEC. 1. Titles I to VI inclusive, of this Act may be cited as the "Public Health Service Act." [1]

DEFINITIONS

42 U. S. C. 201

SEC. 2. When used in this Act—

(a) The term "Service" means the Public Health Service;

(b) The term "Surgeon General" means the Surgeon General of the Public Health Service;

(c) The term "Secretary" means the Secretary of the Department of Health, Education, and Welfare;

(d) The term "regulations," except when otherwise specified, means rules and regulations made by the Surgeon General with the approval of the Secretary;

(e) The term "executive department" means any executive department, agency, or independent establishment of the United States or any corporation wholly owned by the United States;

(f) The term "State" means a State or the District of Columbia, Hawaii, Alaska, Puerto Rico, or the Virgin Islands, except that as used in section 361 (d)[2] such term means a State, the District of Columbia, or Alaska;

(g) The term "possession" includes, among other possessions, Puerto Rico and the Virgin Islands.

TITLE II—ADMINISTRATION

PUBLIC HEALTH SERVICE

42 U. S. C. 202

SEC. 201. The Public Health Service in the Department of Health, Education, and Welfare shall be administered by the Surgeon General under the supervision and direction of the Secretary.

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[1] Section 1 was amended by section 4 of the Hospital Survey and Construction Act to add Title VI to the original five titles of the Public Health Service Act.

[2] Relates to Part G—Quarantine and Inspection, Control of Communicable Diseases.

ORGANIZATION

42 U. S. C. 203

SEC. 202. The Service shall consist of (1) the Office of the Surgeon General, (2) the National Institutes [1] of Health, (3) the Bureau of Medical Services, and (4) the Bureau of State Services. The Surgeon General is authorized and directed to assign to the Office of the Surgeon General, to the National Institutes [1] of Health, to the Bureau of Medical Services, and to the Bureau of State Services, respectively, the several functions of the Service, and to establish within them such divisions, sections, and other units as he may find necessary; and from time to time abolish, transfer and consolidate divisions, sections, and other units and assign their functions and personnel in such manner as he may find necessary for efficient operation of the Service. No division shall be established, abolished, or transferred, and no divisions shall be consolidated, except with the approval of the Secretary. The National Institutes [1] of Health shall be administered as a part of the field service. The Surgeon General may delegate to any officer or employee of the Service such of his powers and duties under this Act, except the making of regulations, as he may deem necessary or expedient.

TITLE III—GENERAL POWERS AND DUTIES OF PUBLIC HEALTH SERVICE

PART F—BIOLOGICAL PRODUCTS

REGULATION OF BIOLOGICAL PRODUCTS

42 U. S. C. 262

SEC. 351. (a) No person shall sell, barter, or exchange, or offer for sale, barter, or exchange in the District of Columbia, or send, carry, or bring for sale, barter, or exchange from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession, any virus, therapeutic serum, toxin, antitoxin, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man, unless (1) such virus, serum, toxin, antitoxin, or other product has been propagated or manufactured and prepared at an establishment holding an unsuspended and unrevoked license, issued by the Secretary as hereinafter authorized, to propagate or manufacture, and prepare such virus, serum, toxin, antitoxin, or

[1] Section 202 was amended by 6 (b) of the National Heart Act by adding an "s" to Institute.

other product for sale in the District of Columbia, or for sending, bringing, or carrying from place to place aforesaid; and (2) each package of such virus, serum, toxin, antitoxin, or other product is plainly marked with the proper name of the article contained therein, the name, address, and license number of the manufacturer, and the date beyond which the contents cannot be expected beyond reasonable doubt to yield their specific results. The suspension or revocation of any license shall not prevent the sale, barter, or exchange of any virus, serum, toxin, antioxin, or other product aforesaid which has been sold and delivered by the licensee prior to such suspension or revocation, unless the owner or custodian of such virus, serum, toxin, antitoxin, or other product aforesaid has been notified by the Secretary not to sell, barter, or exchange the same.

(b) No person shall falsely label or mark any package or container of any virus, serum, toxin, antitoxin, or other product aforesaid; nor alter any label or mark on any package or container of any virus, serum, toxin, antitoxin, or other product aforesaid so as to falsify such label or mark.

(c) Any officer, agent, or employee of the Department of Health, Education and Welfare, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any virus, serum, toxin, antitoxin, or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession.

(d) Licenses for the maintenance of establishments for the propagation or manufacture and preparation of products described in subsection (a) of this section may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products, prescribed in regulations made jointly by the Surgeon General, the Surgeon General of the Army, and the Surgeon General of the Navy, and approved by the Secretary, and licenses for new products may be issued only upon a showing that they meet such standards. All such licenses shall be issued, suspended and revoked as prescribed by regulations and all licenses issued for the maintenance of establishments for the propagation or manufacture and preparation, in any foreign country, of any such products for sale, barter, or exchange in any State or possession shall be issued upon condition that the licensees will permit the inspection of their establishments in accordance with subsection (c) of this section.

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(e) No person shall interfere with any officer, agent, or employee of the Service in the performance of any duty imposed upon him by this section or by regulations made by authority thereof.

(f) Any person who shall violate, or aid or abet in violating, any of the provisions of this section shall be punished upon conviction by a fine not exceeding $500 or by imprisonment not exceeding one year, or by both such fine and imprisonment, in the discretion of the court.

(g) Nothing contained in this Act shall be construed as in any way affecting, modifying, repealing, or superseding the provisions of the Federal Food, Drug, and Cosmetic Act (U. S. C., 1940 edition, title 21, ch. 9).

PREPARATION OF BIOLOGICAL PRODUCTS

42 U. S. C. 263

SEC. 352. (a) The Service may prepare for its own use any product described in section 351 and any product necessary to carrying out any of the purposes of section 301.

(b) The Service may prepare any product described in section 351 for the use of other Federal departments or agencies, and public or private agencies and individuals engaged in work in the field of medicine when such product is not available from establishments licensed under such section.

PUBLIC HEALTH SERVICE REGULATIONS

TITLE 42—PUBLIC HEALTH

CHAPTER I—PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE [1]

PART 73—BIOLOGIC PRODUCTS

[1] Headnote revised April 17, 1953, 18 F. R. 2176.
[2] § 73.15 added Oct. 26, 1948, 13 F. R. 6269.

AUTHORITY: §§ 73.1 to 73.96, inclusive, issued under sec. 351, 58 Stat. 702; 42 U. S. C., 262. Statutes giving special authority are cited in parentheses, at the end of affected sections.

DERIVATION: §§ 73.1 to 73.32, inclusive, contained in Regulations, Surgeon General of the Public Health Service, approved by Acting Federal Security Administrator, Jan. 16, 1947; §§ 73.35 to 73.96, inclusive, contained in Regulations, Surgeons General of the Army, Navy, and Public Health Service, approved by Acting Federal Security Administrator Jan. 16, 1947; §§ 73.1 to 73.96, inclusive, effective Feb. 21, 1947, 12 F. R. 411.

CROSS REFERENCE: Department of Health, Education, and Welfare regulations relating to drugs as defined in the Federal Food, Drug, and Cosmetic Act (21 U. S. C. 301 et seq.). See Food and Drug Administration, Department of Health, Education, and Welfare, 21 CFR, Chap. I, Parts 2, 135, 141, 144, 145, 146. Exemption from section 505 of the Federal Food, Drug, and Cosmetic Act (21 U. S. C. 355) of new drugs licensed under the Public Health Service Act; see 21 CFR, Chap. I, 2.109. Drugs intended solely for investigational use, see 21 CFR, Chap. I, 2.114.

CROSS REFERENCE: Bureau of Customs regulations relating to viruses, serums and toxins: See Customs Duties, 19 CFR, Cum. Supp., 12.21–12.23.

CROSS REFERENCE: Post Office regulations relating to importation and transportation of viruses, serums, and antitoxins by mail: See Postal Service, 39 CFR 6.14, 21.54.

DEFINITIONS

§ 73.1 *Definitions.*—As used in this part:

(a) "Act" means the Public Health Service Act (58 Stat. 682), approved July 1, 1944.

(b) "Secretary" means the Secretary of the Department of Health, Education, and Welfare.

(c) "Surgeon General" means the Surgeon General of the United States Public Health Service.

(d) "Institutes" means the National Institutes of Health in the Public Health Service.

(e) "State" means a State or the District of Columbia, Hawaii, Alaska, Puerto Rico, or the Virgin Islands.

(f) "Possession" includes, among other possessions, Puerto Rico and the Virgin Islands.

(g) "Biologic product" means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:

(1) A virus is a product containing the minute living cause of an infectious disease.

(2) A therapeutic serum is the product obtained from the blood of an animal by removing the clot or clot components and the blood cells and intended for administration by a route other than ingestion.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, fol-

lowing the injection of nonfatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous:

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum and intended for administration by a route other than ingestion.

(iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, for the prevention, treatment, or cure of diseases or injuries of man through specific immunization.

(h) "Trivalent organic arsenicals" means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.

(i) "Products" includes biologic products and trivalent organic arsenicals. A product is deemed "applicable to the prevention, treatment, or cure of diseases or injuries of man" irrespective of the mode of administration or application recommended, including use when intended, through administration or application to a person, as an aid in diagnosis or in evaluating the degree of susceptibility or immunity possessed by a person; and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biologic product.

(j) "Proper name," as applied to a product, means the name designated in the license for use upon each container of the product.

(k) "Dating period" means the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results.

(l) "Expiration date" means the date of termination of the dating period.

(m) The word "standards" means specifications and procedures applicable to an establishment or to the production, content, testing, labeling, or release of products prepared therein, which are prescribed in this part and which are designed to insure the continued safety, purity, and potency of such products.

(n) The word "continued" as applied to the safety, purity, and potency of products is interpreted to apply to the dating period.

(o) The word "safety" is interpreted to apply to the relative freedom from harmful effect to the recipient when a product is prudently administered, taking into consideration the character of the product in relation to the condition of the patient at the time.

(p) The word "purity" is interpreted to mean the degree of freedom from extraneous matter, whether harmful to the recipient, deleterious to the product, or otherwise, in the finished product.

(q) The word "potency" is interpreted to means the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

(r) "Manufacturer" includes any individual, trust or estate, association, partnership, or corporation engaged in the manufacture of a product subject to license under the act.

(s) "Establishment" means that portion of the properties of any manufacturer which is given over to the manufacture of a product subject to license, including equipment and animals used, and the personnel engaged in such manufacture.

(t) "Selling agent" or "distributor" means any person engaged in the unrestricted distribution, other than by sale at retail, of products, subject to license.

LICENSES; PROCEDURE

§ 73.2 *Applications.*—To obtain a license for any establishment, biologic product or trivalent organic arsenical, the manufacturer shall make application to the Surgeon General on forms prescribed for such purpose, and, in the case of an application for a product license, shall submit samples of the product and specimens of the labels, enclosures, and containers proposed to be used for such product.

§ 73.3 *Inspection of establishments and examination of products prior to licensing.*—Licenses shall be issued only after inspection of the establishment and examination of the product for which a product license is desired and upon a determination that the establishment and the product meet the standards prescribed in the regulations in this part. Additional product licenses shall be issued only upon examination of the product and a determination that the product meets the standards prescribed in the regulations in this part.

§ 73.4 *Form of license: domestic establishments.*—The following form of license is prescribed for establishments located in any State or possession of the United States:

Establishment License No. ------

This is to certify that ---------- of ----------, through the establishment identified as ---------- located at ---------- is hereby licensed, pursuant to section 351 of the Public Health Service Act, approved July 1, 1944 (58 Stat. 682), and regulations thereunder, to propagate or

manufacture, and to prepare for sale in the District of Columbia, or for sending, bringing or carrying from any State or possession into any other State or possession or into any foreign country any virus, serum, toxin, antitoxin, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound) for the propagation and manufacture of which the establishment holds an unsuspended and unrevoked license issued by the Secretary of the Department of Health, Education, and Welfare pursuant to said act and regulations.

Secretary of the Department of Health, Education and Welfare

Date ---

§ 73.5 *Product licenses.*—Each product license shall designate:

(a) The manufacturer.

(b) The establishment.

(c) The license number of the establishment.

(d) The proper name of the product, with additional specifications, if any, which may be approved or required for additional labeling purposes.

§ 73.6. *Changes to be reported.*—Important changes in location, equipment, management, and responsible personnel, or in production methods and labeling of any licensed product or of any product for which an application for a license is pending shall be immediately reported to the Institutes by any establishment holding a license, and, unless in case of an emergency, not less than 30 days in advance of the time such changes are made; failure to make such report shall constitute a ground for summary suspension of a license pending reinspection of the establishment or re-examination of the product.

§ 73.7 *Products under development.*—A biologic product or trivalent organic arsenical undergoing development, but not yet ready for a product license, may be shipped or otherwise delivered from one State or possession into another State or possession provided such shipment or delivery is not for sale, barter, or exchange and is in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder.[1]

§ 73.8 *Issuance, revocation, or suspension.*—A license shall be issued by the Secretary upon the recommendation of the Surgeon General and upon the finding by the Surgeon General that the establishment or the product, as the case may be, meets the standards established by the regulations in this part as herein prescribed or hereafter amended. Licenses shall be valid until suspended or revoked. An establishment or product license shall be revoked upon application of the manufacturer giving notice of intention to discontinue the manufacture of all products or of intention to discontinue the manufacture of a particular product for which a license is held. The Surgeon General

[1] Sec. 73.7 amended July 31, 1954, 19 F. R. 4722.

shall recommend to the Secretary that a license be suspended or revoked whenever he finds, after notice and opportunity for hearing, that the establishment or the product for which the license has been issued fails to conform to the standards in the regulations in this part as herein prescribed or hereafter amended to insure the continued safety, purity, and potency of the manufactured product. In case of suspension, if the faulty condition is not corrected within 60 days or within such other period as may be specified in the notice of suspension, he shall recommend that the license be revoked. Except as provided in § 73.10, prior to the institution of proceedings looking to the suspension or revocation of a license the licensee shall be advised in writing of the facts or conduct which may warrant such action and shall be accorded opportunity within a reasonable period prescribed by the Surgeon General to demonstrate or achieve compliance with the regulations in this part.

§ 73.9 *Licenses heretofore issued.*—Any license heretofore issued and in effect upon the effective date of the regulations in this part shall remain in effect unless and until superseded by a new license, or suspended or revoked, pursuant to the regulations in this part.

§ 73.10 *Summary suspension.*—Whenever the Surgeon General has reasonable ground to believe that an establishment or product for which a license has been issued fails to conform to the standards prescribed in the regulations in this part, and that by reason of such failure and of failure of the manufacturer to take prompt corrective measures on notice thereof, the distribution or sale of a licensed product would constitute a danger to health, or that the establishment and production methods have been so changed as to require in order to protect the public health a new showing that the establishment or product meets the standards prescribed in the regulations in this part, he may recommend to the Secretary that the license for the establishment or the product be summarily suspended and the manufacturer be required (a) to notify the selling agents and distributors to whom such product or products have been delivered of such suspension, (b) to furnish complete records of such deliveries and notice of suspension, and (c) to show cause within 60 days or such other period as may be specified in the order why the license should not be revoked.

§ 73.11 *Review Board.*—When deemed advisable by the Surgeon General, in matters involving the safety, purity and potency of licensed products or products for which an application for license is pending, the reports of inspection and laboratory examinations, together with any pertinent data the establishment may submit, shall be passed upon by a special board of three officers appointed by the Surgeon General for that purpose. The board shall report its findings to the Surgeon General who will forward its report, together with his findings and recommendations, to the Secretary.

§ 73.12 *Opportunity for hearing.*—Any manufacturer whose application for a license has been denied, or whose establishment or product license has been summarily suspended, without prior opportunity for hearing, may appeal from such denial or suspension and shall be entitled to a hearing thereon before a review body constituted as provided in § 73.11. The Surgeon General, upon review of the record, may affirm, reverse, or modify the findings of the review board, or may direct the taking of further testimony and shall forward his determinations and recommendations to the Secretary.

§ 73.13 *Suspension and revocation: publication.*—Notice of suspension or revocation of license, with statement of cause therefor, may be published by the Secretary.

§ 73.14 *Reissuance.*—An establishment license, previously revoked or suspended may be reissued or reinstated upon inspection of the establishment, or upon examination of the product showing that the reasons for revocation or suspension have been corrected, except that in case of a product license revoked upon application or because of failure to meet changes in standards prescribed by amendment to the regulations in this part after the issuance of such license, only such inspection and examination as may be considered advisable by the Institutes shall be required.

§ 73.15 *Products in short supply; initial processing at other than licensed establishment.*—Licenses issued to a manufacturer for an establishment shall authorize persons other than such manufacturer to conduct at places other than such establishment the initial and partial processing of a product for shipment solely to such manufacturer only to the extent that the names of such persons and places are registered with the Surgeon General and he finds, upon application of such manufacturer, that (a) the product is in short supply due either to the peculiar growth requirements of the organism involved or to the scarcity of the animal required for production purposes, and (b) such manufacturer has established with respect to such persons and places such procedures, inspections, tests, or other arrangements as will assure full compliance with the applicable regulations of this part related to continued safety, purity, and potency. Such persons and places shall be subject to all regulations of this part except §§ 73.2 to 73.14, 73.20 to 73.24, and 73.50 to 73.55. Failure of such manufacturer to maintain such procedures, inspections, tests or other arrangements, or failure of any person conducting such processing to comply with applicable regulations shall constitute a ground for summary suspension or revocation of the authority conferred pursuant to this section on the same basis as provided in §§ 73.10, 73.12, and 73.13 with respect to the summary suspension and the revocation of licenses.[1]

[1] § 73.15 added Oct. 26, 1948, 13 F. R. 6269.

FOREIGN ESTABLISHMENTS AND PRODUCTS

§ 73.20 *Licenses required; products for controlled investigation only.*—Any biologic or trivalent organic arsenical propagated or manufactured and prepared in any foreign country and intended for sale, barter, or exchange shall be refused entry by collector of customs unless produced in an establishment holding an unsuspended and unrevoked establishment license and license for the product. Unlicensed products which are not imported for sale, barter or exchange and which are intended solely for purposes of controlled investigation are admissible only if in accord with section 505 of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder.[2] (Sec. 215, 58 Stat. 690; 42 U. S. C. 216.)

§ 73.21 *Procedure.*—Except as otherwise provided in this part, licenses for foreign establishments and products shall be issued, suspended or revoked in the same manner as licenses for domestic establishments and products. Each foreign establishment holding a license and consigning any licensed biologic product or trivalent organic arsenical into any State or possession shall be required to file with the Surgeon General the name and address of any representative or representatives authorized by the establishment to distribute the product, and such representative or representatives shall keep such records of such distribution as are required of domestic licensed establishments, and failure to maintain such records shall constitute ground for revocation of license.

§ 73.22 *Form of license.*—Licenses for establishments located in foreign countries shall be in form similar to that for domestic establishments except that they shall authorize preparation for sending, carrying, or bringing for sale, barter or exchange from the foreign country designated in the license into any State or possession of the United States and shall specify that it is issued upon the condition that the licensee will permit the inspection during all reasonable hours of the establishment by any officer, agent, or employee of the Department of Health, Education, and Welfare authorized by the Secretary of the Department of Health, Education, and Welfare for such purpose.

§ 73.23 *Smallpox vaccine; importation prohibited.*—The importation of smallpox vaccine into any State or possession from any foreign country is prohibited except that smallpox vaccine may be sent from any foreign country, in containers indicating plainly the limited purpose intended, to the Institutes for test or research purposes or for vaccine production (Sec. 351, 58 Stat. 702; 42 U. S. C. 262).

§ 73.24 *Samples to accompany each importation.*—Each foreign importation of a biologic product or trivalent organic arsenical from a

[2] § 73.20 amended July 31, 1954, 19 F. R. 4722.

licensed establishment, whether or not intended for investigational use only, shall be accompanied by at least two final containers of each lot of any biologic product and by at least 15 final containers of each lot of any trivalent organic arsenical contained in the shipment. Such samples shall be forwarded by the collector of customs at the port of entry to the Institutes for examination. If separate samples are not found accompanying the shipment, samples shall be obtained from the shipment by the collector of customs and forwarded to the Institutes (Sec. 801, 52 Stat. 1058; 21 U. S. C. 381).

ESTABLISHMENT INSPECTION

§ 73.30. *Inspectors.*—Inspections shall be made by an officer of the Public Health Service having special knowledge of the methods used in the production and control of biologic products and designated for such purpose by the Surgeon General or by any officer, agent, or employee of the Department of Health, Education, and Welfare specifically designated for such purpose by the Secretary.

§ 73.31 *Time of inspection.*—The inspection of an establishment for which a license is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a product 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 shall be made at least once each year. Inspections may be made with or without notice, and shall be made during regular business hours unless otherwise directed.

§ 73.32 *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, production 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 propagation, manufacture, and preparation 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 processes in actual operation,

(e) Obtain and cause to be sent to the Institutes adequate samples for the examination of any product or ingredient used in its preparation,

(f) Bring to the attention of the manufacturer any fault observed in the course of inspection in location, construction, production 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 § 73.36,

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

ESTABLISHMENT STANDARDS

§ 73.35 *Responsible head.*—A responsible person shall be in permanent and full control of the establishment in all matters relating to the manufacture of products. A responsible person is one who has been trained in the manufacturing techniques employed and the fundamental scientific facts upon which the manufacture of products rests, who is capable of enforcing discipline among the employees under his supervision, and to whom sufficient authority has been delegated for such purpose.

§ 73.36 *Records, samples, cultures*—(a) *Production and distribution records.*—Records shall be kept, with dates of the various steps in the manufacture, testing, disposition, and distribution of each lot, so that at any time these steps as regards any lot number may be traced by an inspector. The records shall be retained for such interval beyond the expiration date as is considered necessary for the individual product to permit the return of any clinical report of unfavorable reactions. This interval will vary with the type of product and its geographic distribution. A minimum of 6 months after the expiration date with 5 years as the extreme interval under all circumstances is considered adequate. Records of distribution of each lot shall in any event be kept as long as the lot remains the property of the licensed manufacturer.

(b) *Records of recall.*—Complete records shall be maintained pertaining to the recall from distribution of any product upon notification from the Institutes of failure to conform with the standards prescribed in the regulations in this part, deterioration of the product or any other factor by reason of which the distribution of the product would constitute a danger to health.

(c) *Sterilization records.*—Records including the date, duration, and temperature of each sterilization shall be made by means of auto-

matic registering devices or under a system of recording which gives reasonable assurance of the accuracy and reliability of the record.

(d) *Animal necropsy records.*—A necropsy record shall be kept on each animal from which a biologic product has been obtained and which dies or is killed because of disease while employed in production of a product.

(e) *Retention of reference samples.*—Reference samples from each lot shall be retained by the manufacturer until the entire lot has become outdated and for 6 months thereafter. Exceptions may be authorized by the Institutes when the lot yields relatively few final containers and when such lots are prepared by the same method in large numbers and in close succession.

(f) *Cultures.*—Cultures and other materials while used in the production of licensed products shall be labeled and preserved in a safe and orderly manner.

(g) *Records in case of divided manufacturing responsibility.*—If two or more establishments participate in the manufacture of a product, the records of both establishments must show plainly the degree of responsibility of each in the manufacturing process.

§ 73.37 *Physical establishment; construction, equipment and care*—(a) *Work with spore-bearing organisms.*—All work with spore-bearing micro-organisms shall be carried out in (1) an entirely separate building with its own entrance, or (2) a portion of a building used for the manufacture of other products constructed in such a manner as to be completely walled-off so that admission to the special unit may be gained only through an entrance independent of the remainder of the building. All containers used shall be permanently marked so as to avoid the possibility of contamination of products.

(b) *Work of a diagnostic nature.*—Laboratory procedures of a clinical diagnostic nature involving possibly contaminated materials shall be in space set apart from that used for the production of licensed products, except that production space which is used only occasionally may be used for diagnostic work provided spore-bearing pathogenic micro-organisms are not involved and provided the space is thoroughly cleaned before production is resumed.

(c) *Laboratory and bleeding rooms.*—Laboratory rooms for the production of licensed products, including the bleeding rooms and other places where cleanliness is essential, shall be efficiently screened and kept free of flies and other insects or vermin. Building construction shall be such as to insure freedom from dust, smoke, and deleterious or obnoxious odors in the laboratory and bleeding rooms and such as to permit thorough cleaning and, when necessary, chemical disinfection of bleeding rooms and rooms for smallpox vaccine animals.

(d) *Stables.*—Stables shall be well lighted and well ventilated, and the floors shall be so constructed and cared for as to insure cleanliness.

(e) *Sterilization.*—Sterilization equipment and methods used shall be such as to insure the complete destruction of contaminating, living organisms, including living spores. The containers, filling apparatus, and other pieces of apparatus or materials which may come in contact with biologic products during manufacture shall be scrupulously clean. Such equipment shall be absolutely sterile unless the product is protected by subsequent sterilizing treatment.

(f) *Containers used in production.*—All containers used in preparation of biologic products shall be of such construction as will readily permit inspection for cleanliness.

(g) *Hot water available.*—Hot water shall be provided in bleeding rooms and stables for smallpox vaccine animals.

(h) *Disposal of manure.*—No manure shall be so stored as to permit the breeding of flies on the premises nor shall the establishment be located in close proximity to off-property manure storage capable of engendering fly breeding.

(i) *Isolation of hog cholera production.*—All personnel, animals, and equipment used in the production of hog cholera serum shall be kept entirely separate from personnel, animals, and materials used in the production of biologic products for human use.

§ 73.38 *Animals used in production*—(a) *Quarantine and care.*—Animals used in production of biologic products shall be kept under competent daily inspection and preliminary quarantine for a period of at least 7 days before use. Only healthy animals free from communicable disease shall be used for production purposes and at all times shall be adequately housed, fed, and humanely treated. Particular care shall be taken during the quarantine period to eliminate those animals of the equine genus which may be infected with glanders, and those of the bovine genus which may be infected with tuberculosis.

(b) *Immunization against tetanus.*—All horses used in the production of biologic products, except those which are under active immunization for the production of tetanus antitoxin, shall receive injections of tetanus toxoids in such amounts and at such intervals as experience has shown adequate to insure immunity to tetanus.

(c) *Disposal of used animals.*—No animal used for production or testing of products shall be removed from the premises while it is capable of transmitting disease. An animal which is unsuitable because of its physical condition for the production or testing of a product shall not be removed from the premises alive except for the purpose of being utilized for animal by-products. No animal shall be allowed to continue to live unnecessarily when to do so would be an inhumane act.

(d) *Reporting of certain diseases required.*—In case of actual or suspected infection with foot-and-mouth disease, glanders, tetanus, anthrax, gas gangrene, equine infectious anemia, or equine encephalomyelitis among animals intended for use or used for the production of biologic products, the manufacturer shall immediately notify the Institutes.

(e) *Smallpox vaccine production animals.*—Animals used for propagation of smallpox vaccine shall be thoroughly cleaned with soap and water at the beginning of the quarantine and at its conclusion. No area of the animal shall be vaccinated which is liable to be contaminated by feces.

(f) *Treatment of vaccinated animals.*—Preliminary to taking smallpox vaccine material from vaccinated animals, such animals shall be killed or rendered insensible to pain.

(g) *Restriction on attendants.*—Personnel while caring for smallpox vaccine animals shall be excluded from horse stables and paddocks and from contact with horses.

§ 73.39 *Human blood donors.*—Only those persons may serve as a source of the whole blood for use in preparing a licensed product whose physical condition is such that the withdrawal of the desired amount of blood will not endanger their health and who are certified by a qualified doctor of medicine as being free of disease transmissible by blood transfusion as far as can be determined from the donor's personal history, from physical examination and such clinical tests as appear necessary for each donor on the day upon which the blood is withdrawn from the donor, except that this requirement may be modified by the Institutes if the licensed product is processed by a method which insures the destruction or complete removal of the causative agent of such disease.

STANDARDS FOR PRODUCTS: LABELS

§ 73.50 *Container labels.*—The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(a) The proper name of the product;

(b) Name, address, and license number of manufacturer;

(c) Lot number;

(d) The expiration date.

If the final container is capable of bearing only a partial label, the final container shall show as a minimum the name (expressed either as the proper or common name), the lot number, and the name of the manufacturer and, if the final container is incapable of bearing any label, the items shall appear only on the outside label.

If the final container is a multiple-dose container, the container label must indicate the recommended dose. When the label has been affixed to the container a sufficient area of the container must remain uncovered for its full length or circumference to permit inspection of the contents.

§ 73.51 *Proper name on outside label.*—The proper name in the form designated in the product license for such purpose must appear upon the outside label in legible type and shall be given precedence in position and prominence over any trade-mark or trade name used:

(a) The "outside label" is the label of the carton enclosing one or more final containers, except that if no such carton is used the label of the individual final container is regarded as the outside label.

(b) "Legible type" includes only type of a size and character which can be read with ease when held in a good light and with normal vision.

(c) "Precedence in position" of the proper name will have been observed if it is placed above any trade-mark or trade name and provided it is symmetrically arranged with respect to other printing on the label.

(d) "Precedence in prominence" of the proper name will have been observed if the style of type is of the same or greater point size and of equal face, or heavier, than that used in printing the trade-mark or trade name, and if the contrast in color value between the proper name and the background is not less than that between the trade-mark or trade name and the background.

§ 73.52 *Outside label; additional items.*—The label affixed to the outside carton shall include, in addition to the proper name and the items required on the label of the final container, the following:

(a) The preservative used and its concentration,

(b) The volume of the contents, if a liquid, or the weight, if a solid, and the potency or dosage if more than one strength is dispensed.

(c) The recommended storage temperature,

(d) The words "Shake Well," or equivalent, when indicated by the character of the product,

(e) The dose and route of administration recommended or reference to such directions in an enclosed circular,

(f) The source of the product when a factor in safe administration,

(g) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no standard of potency has been prescribed, the words "No U. S. standard of potency."

§ 73.53 *Divided manufacturing responsibility to be shown.*—If two or more establishments participate in the manufacturing process, the name, address, and license number of each must appear on the label of the final container, if capable of bearing a full label, and on the outside label.

§ 73.54 *Name of selling agent or distributor.*—The name and address of the selling agent or distributor of a product may appear on the label under the designation of "selling agent" or "distributor" provided that the name and address of the manufacturer is given precedence in prominence.

§ 73.55 *Products for export.*—Labels on packages or containers of products for export may be adapted to meet specific requirements of the regulations of the country to which the product is to be exported provided that in all such cases the minimum label requirements prescribed in § 73.50 are observed.

STANDARDS FOR PRODUCTS: GENERAL

§ 73.70 *Tests prior to release*—(a) *Required for each lot.*—No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with the standards applicable to such product.

(b) *Potency.*—Tests for potency shall be made on each lot only after completion of those processes of manufacture which may affect the potency of the final product. The tests shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in § 73.1 (q).

(c) *Identity and safety.*—The contents of a final container of each filling of each lot shall be tested for identity and for safety either after the labels have been affixed to the final container or affixed, both outside and inside, to the multiple container storage receptacle just prior to its sealing for storage purposes, except that exceptions to this procedure may be authorized by the Institutes to apply when the volume of the final container is very large and when more than one lot is processed each day.

The identity test shall be specific for each product in a manner which will adequately identify it and distinguish it from any other product being processed in the same laboratory. In general, identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.

In general, the safety test shall consist of the parenteral injection of the maximum volume tolerated, but not more than 0.5 ml. into mice weighing approximately 20 grams each and 5.0 ml. into guinea pigs weighing approximately 350 grams each. When the injections are made into at least two animals of each species, there shall result neither significant symptoms nor death during an observation period of not less than 7 days. Variations from this test, either in the volume injected or in the species of test animal used shall be made whenever

required because of the human dose level demanded of the product or because of any individual demands of the product itself.

(d) *Sterility.*—Samples from final containers selected at random after each filing from each lot of each product shall be tested for sterility. The random sampling shall be made in such a manner that all stages of the filling from the bulk container will have equal chance of being represented. Three final containers shall be selected from each filling from each lot if the total number filled is 100 or less and, if greater, one additional container shall be selected for each additional 50 containers or fraction thereof, but not more than 10 samples need be tested. If the volume of the final container is 1.0 ml. or less, the entire contents of the container shall be cultured. If the volume of the final container is greater than 1.0 ml., the volume cultured shall be not less than 1.0 ml. when each injection is 1.0 ml. or less, and not less than the largest single injection recommended when greater than 1.0 ml., but need not be more than 10 ml. The culture shall be made in one or more tubes of fluid thioglycollate medium, and incubation shall be at 35° to 37° C. with observation for not less than 7 days. The manner of performing the sterility test may vary from the pattern prescribed in this paragraph when the nature of the product necessitates a change and when this need has been recognized by the Institutes.

(e) *Purity.*—The purity of a product, as defined in § 73.1 (p), includes the relative freedom from residual moisture and pyrogenic substances whenever these are factors of significance in the safe use of the product. The relative freedom from residual moisture shall be determined by a procedure which will accurately measure the amount of uncombined water or other volatile liquid present in the finished product. The relative freedom from pyrogenic substances shall be determined by the intravenous injection into normal rabbits of not less than 3.0 ml. per kilo of body weight, following which the thermal response shall not exceed 1.1° C. More rigid requirements for the pyrogen test shall be observed when the character of the product and the manner of its prophylatic or therapeutic use make this necessary to meet requirements of safety as defined in § 73.1 (o).[1]

§ 73.71 *Tests: by whom made.*—Tests for safety, purity and potency applicable to the product shall be completed for each lot of any licensed product prior to its release by the manufacturer, and samples of any lot of any licensed product, together with the protocols showing the results of applicable tests, may at any time be riquired to be sent to the Institutes for examination.[1]

§ 73.72 *Ingredients, preservatives, diluents.*—All ingredients used in a licensed product, and any diluent provided as an aid in the

[1] §§ 73.70 and 73.71 amended Feb. 7, 1948, 13 F. R. 114.

administration of the product shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used shall not denature the specific substances in the product below the minimum acceptable potency within the dating period when stored at the recommended temperature.

§ 73.73 *Total solids in serums.*—Except as otherwise provided by regulation, no liquid serum or antitoxin shall contain more than 20 percent total solids.

§ 73.74 *Permissible combinations.*—Licensed products may not be combined with other licensed products, either therapeutic, prophylactic or diagnostic, except as a license is obtained for the combined product. Licensed products may not be combined with nonlicensable therapeutic, prophylactic, or diagnostic substances except as a license is obtained for such combination.

§ 73.75 *Container and closure.*—Glass used in the container of a licensed product intended for administration by injection shall be colorless and fully transparent. The quality of the glass and of the closure used shall be such as will not hasten the deterioration of the licensed product or render it less suitable for the use intended within the dating period.

§ 73.76 *Standard units or samples.*—Standard units or samples for comparison made available by the Institutes shall be applied in testing for potency all forms of diphtheria antitoxin, tetanus antitoxin, botulism antitoxin Type A, botulism antitoxin Type B, perfringens antitoxin, scarlet fever streptococcus antitoxin, vibrion septique antitoxin, antipneumococcic serum (Types I, II, V, VII, and VIII), dysentery antitoxin (Shiga), staphylococcus antitoxin, histolyticus antitoxin, oedematiens antitoxin, and sordelli antitoxin and other products for which such units are available.

§ 73.77 *Standards of potency; particular products.*—Diphtheria antitoxin shall have a potency of not less than 500 units per milliliter. Tetanus antitoxin shall have a potency of not less than 400 units per milliliter. Scarlet fever streptococcus antitoxin shall have a potency of not less than 400 units per milliliter. Antitoxins dispensed in the dried state shall represent liquid antitoxins of not less than these potencies.

§ 73.78 *Dating period; date of manufacture.*—The dating period shall be determined with reference to the date of manufacture which shall be:

(a) For products for which an official standard of potency exists or which are subject to official potency tests, the last date of satisfactorily passing a potency test;

(b) For products for which no official standard of potency exists or which are not subject to official potency tests,

(1) The date of removal from the animal in case of animal products;

(2) The date of extraction in the case of products used for specific desensitization;

(3) The date of solution in case of venoms, and

(4) The date of cessation of growth in case of other products;

(c) For products which are submitted to the Institutes for approval prior to release, the date of official release notice.

§ 73.79 *Dating period; products in cold storage.*—The dating period may be determined with reference to the period of issue from cold storage, *Provided*, That, except as may be otherwise prescribed for individual products, the date of such issue is not more than 6 months after the date of manufacture and the product is kept constantly at a temperature not exceeding 10° C., or not more than 1 year after the date of manufacture if the product is kept constantly at a temperature not exceeding 5° C., or not more than 2 years if the product is kept constantly at a temperature not exceeding 0° C.

ADDITIONAL STANDARDS: TRIVALENT ORGANIC ARSENICALS

§ 73.90 *Tests prior to release.*—Tests required to be made, prior to the release of each lot of licensed product, shall be supplemented in the case of the trivalent organic arsenicals by tests for:

(a) Stability.

(b) Solubility.

(c) Arsenic content.

(d) Moisture.

(e) Relative nontoxicity.

§ 73.91 *Pretesting by Institutes; samples of each lot.*—Prior to the release of any lot of the product, the manufacturer shall forward to the Institutes no less than 15 ampoules of the largest single-dose size in such lot, together with protocols showing the results of each test required prior to release.

§ 73.92 *Expiration date.*—Notification from the Institutes that lot samples forwarded in accordance with § 73.91 have satisfactorily passed prescribed tests shall indicate a date which may be taken as the date of manufacture for the purpose of fixing the expiration date. The date of issue shall be the same as the date of manufacture.

§ 73.93 *Composition of product.*—Solutions or solutions of mixtures in the concentrations recommended for clinical administration shall be of such hydrogen ion value and tonicity as to be physiologically compatible with human blood.

§ 73.94 *Container.*—The product shall be hermetically sealed under vacuum or under a dry non-oxidizing gas in ampoules prepared from glass of the quality prescribed in § 73.75. The contents of any final container shall not exceed 10 maximum human doses.[1]

§ 73.95 *Final container label.*—In addition to the labeling requirements stated in § 73.50 the final container label of the trivalent organic arsenicals shall bear the statements required in § 73.96 (b) and (c) and an additional statement giving the amount of the drug contained in the ampoule.

§ 73.96 *Outside label.*—The outside label, in addition to the complete proper name and all other items required for products generally shall show conspicuously: (a) If the product is dispensed as a mixture or solution, the name of all admixed substances,

(b) If the ampoule is a multiple dose container, the fact that it is a multiple dose container,

(c) Specific method of preparation, if any, required prior to administration, as, for example, alkalinization.

[1] § 73.94 amended Feb. 7, 1948, 13 F. R. 113.

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Public Health Service Publication No. 437