SUBCHAPTER E—VIRUSES, SERUMS, TOXINS, AND ANALOGOUS PRODUCTS; ORGANISMS AND VECTORS

PART 101—DEFINITIONS

Sec.

AUTHORITY: 21 U.S.C. 151–159; 7 CFR 2.22, 2.80, and 371.4.

SOURCE: 38 FR 8426, Apr. 2, 1973, unless otherwise noted.

§ 101.1 Applicability.

When used in parts 101 through 117 of this subchapter, the meaning of the words and phrases listed shall be as defined in this part.

§ 101.2 Administrative terminology.

The following administrative words and phrases shall mean:

Adjacent herd. Adjacent herds are herds physically contiguous to the herd of origin; there are no herds between an adjacent herd and the herd of origin.

Administrator. The Administrator, Animal and Plant Health Inspection Service, or any person authorized to act for the Administrator.

Animal and Plant Health Inspection Service. The agency in the Department of Agriculture responsible for administering the Virus-Serum-Toxin Act.

Biological products. The term *biological products*, also referred to in this subchapter as biologics, biologicals, or products, shall mean all viruses, serums, toxins (excluding substances that are selectively toxic to microorganisms, e.g., antibiotics), or analogous products at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response. The term ''biological products'' includes but is not limited to vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, certain cytokines, antigenic or immunizing components of live organisms, and diagnostic components, that are of natural or synthetic origin, or that are derived from synthesizing or altering various substances or components of substances such as microorganisms, genes or genetic sequences, carbohydrates, proteins, antigens, allergens, or antibodies.

(1) A product's intended use shall be determined through an objective standard and not a subjective one, and would be dependent on factors such as representations, claims (either oral or written), packaging, labeling, or appearance.

(2) The term *analogous products* shall include:

(i) Substances, at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals and which are similar in function to biological products in that they act, or are intended to act, through the stimulation, supplementation, enhancement, or modulation of the immune system or immune response; or

(ii) Substances, at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals through the detection or measurement of antigens, antibodies, nucleic acids, or immunity; or

(iii) Substances, at any stage of production, shipment, distribution, or sale, which resemble or are represented as biological products intended for use in the treatment of animals through appearance, packaging, labeling, claims (either oral or written), representations, or through any other means.

(3) The term *treatment* shall mean the prevention, diagnosis, management, or cure of diseases of animals.

Department. The U.S. Department of Agriculture.

Distributor. A person who sells, distributes, or otherwise places in channels of trade, one or more biological

products he does not produce or import.

Division. A marketing unit established by the licensee which may be named on labels, advertisements and promotional material in addition to the name and address of the producer.

Domestic animals. All animals, other than man, including poultry.

Establishment. One or more premises designated on the establishment license.

Guidelines. Guidelines establish principles or practices related to test procedures, manufacturing practices, product standards, scientific protocols, labeling, and other technical or policy considerations. Guidelines contain procedures or standards of general applicability that are usually not regulatory in nature, but that are related to matters that fall under the Virus-Serum-Toxin Act. Guidelines issued by the agency include Veterinary Biologics Licensing Considerations, Memoranda, Notices, and Supplemental Assay Methods.

Herd. Any group of animals, including birds, fish, and reptiles, maintained at a common location (e.g. lot, farm or ranch) for any purpose. The herd (or flock) includes all animals subsequently housed at the common location. If the principal animals of a group are moved to a different location, the group is still considered the same herd.

Herd of origin. The herd from which the microorganism used as seed for production of an autogenous biologic is isolated. Offspring and excess breeding stock (not the principal animals) moved or sold from one group of animals to another have changed herds and are no longer considered part of the herd they originated from. Groups of animals under the same ownership but at different locations are separate herds.

Inspection. An examination made by an inspector to determine the fitness of animals, establishments, facilities, and procedures used in connection with the preparation, testing, and distribution of biological products and the examination or testing of biological products.

Inspector. Any officer or employee of Animal and Plant Health Inspection Service who is authorized by the Administrator to do inspection work.

Licensed establishment. An establishment operated by a person holding an unexpired, unsuspended, and unrevoked U.S. Veterinary Biologics Establishment License.

Licensee. A person to whom an establishment license and at least one product license has been issued.

Microorganisms. Microscopic or submicroscopic organisms, which are sometimes referred to as organisms, which may introduce or disseminate disease of animals.

Nonadjacent herd. Nonadjacent herds are all herds other than the herd of origin and other than herds adjacent to the herd of origin. Herds adjacent to the herd of origin but in a different State from the herd of origin are also considered nonadjacent herds.

Permittee. A person who resides in the United States or operates a business establishment within the United States, to whom a permit to import biological products has been issued.

Person. Any individual, firm, partnership, corporation, company, association, educational institution, State or local governmental agency, or other organized group of any of the foregoing, or any agent, officer, or employee of any thereof.

Premises. All buildings, appurtenances, and equipment used to produce and store biological products located within a particular land area shown on building plans or drawings furnished by the applicant or the licensee and designated by an address adequate for identification.

Prepare or preparation. Sometimes referred to as manufacture or produce, means the steps and procedures used in the processing, testing, packaging, labeling, and storing of a biological product.

Regulations. The provisions in parts 101 through 118 of this subchapter.

Research investigator or research sponsor. A person who has requested authorization to ship an experimental biological product for the purpose of evaluating such product, or has been granted such authorization.

Secretary. The Secretary of Agriculture of the United States or any officer or employee of the Department to whom authority has heretofore been delegated, or to whom authority may

hereafter be delegated, to act in his stead.

Subsidiary. A corporation in which a corporate licensee owns in excess of 50 percent of the voting stock.

Veterinary Services. Veterinary Services unit of Animal and Plant Health Inspection Service of the Department.

Virus-Serum-Toxin Act. The Act of March 4, 1913, 37 Stat. 832–833; as amended December 23, 1985, Public Law 99–198, 99 Stat. 1654–1655; and as further amended September 28, 1988, Public Law 100–449, 102 Stat. 1868; 21 U.S.C. 151–159.

U.S. Veterinary Biological Product License. A document, sometimes referred to as a product license, which is issued pursuant to part 102 of this subchapter to the holder of an establishment license, as a part of and ancillary to the establishment license, and which authorizes production of a specified biological product in the designated licensed establishment.

U.S. Veterinary Biological Product Permit. A document, sometimes referred to as a permit, issued to a person authorizing the importation of specified biological products subject to restrictions and controls as provided in the regulations.

U.S. Veterinary Biologics Establishment License. A document referred to as an establishment license, which is issued pursuant to part 102 of this subchapter, authorizing the use of designated premises for production of biological products specified in one or more unexpired, unsuspended, and unrevoked product license(s).

[38 FR 8426, Apr. 2, 1973; 38 FR 9221, Apr. 12, 1973, as amended at 40 FR 46093, Oct. 6, 1975; 41 FR 44358, Oct. 8, 1976; 49 FR 22624, May 31, 1984; 52 FR 30131, Aug. 13, 1987; 56 FR 66782, 66783, Dec. 26, 1991; 57 FR 38756, Aug. 27, 1992; 62 FR 31328, June 9, 1997; 64 FR 43044, Aug. 9, 1999]

§ 101.3 Biological products and related terms.

When used in conjunction with or in reference to a biological product, the following terms shall mean:

(a) *Licensed biological product*. A biological product prepared within a licensed establishment by a person holding an unexpired, unsuspended, and unrevoked product license for such product.

(b) *Experimental biological product*. A biological product which is being evaluated to substantiate an application for a product license or permit.

(c) *Completed product*. A biological product in bulk or final container produced in compliance with the regulations to final form and composition.

(d) *Finished product*. A completed product which has been bottled, sealed, packaged, and labeled as required by the regulations.

(e) *Released product*. A finished product released for marketing after all requirements have been satisfactorily complied with.

(f) *Fraction*. A specific antigen, its antibodies, or its antitoxin which constitutes a component of a biological product.

(g) *Diluent*. A liquid used to rehydrate a desiccated product or a liquid used to dilute another substance.

(h) *Serial*. The total quantity of completed product which has been thoroughly mixed in a single container and identified by a serial number: *Provided*, That, when all or part of a serial of liquid biological product is packaged as diluent for all or part of a serial of desiccated product, the resulting combination packages shall be considered a serial of the multiple fraction product.

(i) *Subserial*. Each of two or more properly identified portions of a serial which are further processed at different times or under different conditions such as, but not limited to, being desiccated in different size final containers and/or at different times.

(j) *Outline of production*. A detailed protocol of methods of manufacture to be followed in the preparation of a biological product and which may sometimes be referred to as an outline.

(k) *Product Code Number*. A number assigned by Animal and Plant Health Inspection Service to each type of licensed biological product.

(l) *Harvest date*. Unless otherwise specified in a filed Outline of Production, the harvest date shall be the date blood or tissues are collected for production or the date cultures of living microorganisms are removed from production incubators.

(m) *Bacterin.* An inactivated bacterial product consisting of an antigenic suspension of organisms or particulate parts of organisms, representing a whole culture or a concentrate thereof, with or without the unevaluated growth products, which has been inactivated as demonstrated by acceptable tests written into the filed Outline of Production for the product.

(n) *Toxoid.* An inactivated bacterial product which consists of a sterile, antigenic toxin or toxic growth product, which has resulted from the growth of bacterial organisms in a culture medium from which the bacterial cells have been removed, which has been inactivated without appreciable loss of antigenicity as measured by suitable tests, and which is nontoxic as demonstrated by acceptable tests written into the filed Outline of Production.

(o) *Bacterin-toxoid.* An inactivated bacterial product which is either:

(1) A suspension of organisms, representing a whole culture or a concentrate thereof, with the toxic growth products from the culture which has been inactivated without appreciable loss of antigenicity as measured by suitable tests, the inactivation of organisms and toxins being demonstrated by acceptable tests written into the filed Outline of Production: *Provided,* That it shall contain cellular antigens and shall stimulate the development of antitoxin; or

(2) A combination product in which one or more toxoids or bacterin-toxoids is combined with one or more bacterins or one or more bacterin-toxoids.

(p) *Bacterial extract.* An inactivated bacterial product which consists of the sterile, nontoxic, antigenic derivatives extracted from bacterial organisms or from culture medium in which bacterial organisms have grown.

(q) *Combination package.* Biological product consisting of two or more licensed biological products. Each completed product in final container is packaged together and mixed prior to administration. A combination package is issued a separate U.S. Veterinary Biological Product License and assigned a product code number to distinguish it from its component products, which also may be marketed individually unless otherwise restricted.

[38 FR 8426, Apr. 2, 1973, as amended at 42 FR 63770, Dec. 20, 1977; 50 FR 24903, June 14, 1985; 56 FR 66782, Dec. 26, 1991; 60 FR 14354, Mar. 17, 1995; 81 FR 59433, Aug. 30, 2016]

§ 101.4 Labeling terminology.

Terms pertaining to identification and packaging of biological products shall mean:

(a) *Label.* All written, graphic, or printed matter:

(1) Upon or attached to a final container of a biological product;

(2) Appearing upon any immediate carton or box used to package such final container; and

(3) Appearing on any accompanying enclosures (leaflets, inserts, or circulars) on which required information or directions as to the use of the biological product shall be found.

(b) *Labeling.* All labels and other written, printed, or graphic matter accompanying the final container.

(c) *Final container.* The unit, bottle, vial, ampule, tube, or other receptacle into which any biological product is filled for distribution and sale.

(d) *True name.* The name entered on the product license or permit at the time of issuance to differentiate the biological product from others: *Provided,* That, the principal part of such name shall be emphasized on such license or permit by being more prominently lettered than descriptive terms which may be necessary to complete the differentiation.

(e) *Serial number.* Numbers or numbers and letters used to identify and distinguish one serial from others.

(f) *Expiration date.* A date designating the end of the period during which a biological product, when properly stored and handled, can be expected with reasonable certainty, to be efficacious.

(g) *Label number.* A number assigned by Animal and Plant Health Inspection Service to each label or sketch submitted for review.

(h) *Master label.* The finished carton, container, or enclosure label for the smallest size final container that is authorized for a biological product, that serves as the Master template label applicable to all other size containers or cartons of the same product that is

marketed by a licensee, subsidiary, division, or distributor.

[38 FR 8426, Apr. 2, 1973, as amended at 42 FR 63770, Dec. 20, 1977; 56 FR 66782, Dec. 26, 1991; 61 FR 29464, June 11, 1996]

§ 101.5 Testing terminology.

Terms used when evaluating biological products shall mean:

(a) *Standard Requirement.* Test methods, procedures, and criteria established by Animal and Plant Health Inspection Service for evaluating biological products to be pure, safe, potent, and efficacious, and not to be worthless, contaminated, dangerous, or harmful under the Act.

(b) *Log.* Logarithm computed to the base 10.

(c) *Pure or purity.* Quality of a biological product prepared to a final form relatively free of extraneous micro-organisms and extraneous material (organic or inorganic) as determined by test methods or procedures established by Animal and Plant Health Inspection Service in Standard Requirements or in the approved Outline of Production for such product, but free of extraneous microorganisms or material which in the opinion of the Administrator adversely affects the safety, potency, or efficacy of such product.

(d) *Safe or safety.* Freedom from properties causing undue local or systemic reactions when used as recommended or suggested by the manufacturer.

(e) *Sterile or sterility.* Freedom from viable contaminating microorganisms as demonstrated by procedures prescribed in part 113 of this subchapter, Standard Requirements, and approved Outlines of Production.

(f) *Potent or potency.* Relative strength of a biological product as determined by test methods or procedures as established by Animal and Plant Health Inspection Service in Standard Requirements or in the approved Outline of Production for such product.

(g) *Efficacious or efficacy.* Specific ability or capacity of the biological product to effect the result for which it is offered when used under the conditions recommended by the manufacturer.

(h) *Dose.* The amount of a biological product recommended on the label to be given to one animal at one time.

(i) *Vaccinate.* An animal which has been inoculated, injected, or otherwise administered a biological product being evaluated.

(j) *Control animal.* An animal, which may be referred to as a control, used in a test procedure for purposes of comparison or to add validity to the results.

(k) *Day.* Time elapsing between any regular working hour of one day and any regular working hour of the following day.

(l) *Test results.* Terms used to designate testing results are as follows:

(1) *No Test.* Designation used when a deficiency in the test system has rendered a test unsuitable for drawing a valid conclusion.

(2) *Satisfactory.* Designation is a final conclusion given to a valid test with results that meet the release criteria stated in the filed Outline of Production or Standard Requirement.

(3) *Unsatisfactory.* Designation is a final conclusion given to a valid test with results that do not meet the release criteria stated in the filed Outline of Production or Standard Requirement.

(4) *Inconclusive.* Designation used for an initial test when a sequential test design established in the filed Outline of Production or Standard Requirement allows further testing if a valid initial test is not satisfactory.

(m) *Healthy.* Apparently normal in all vital functions and free of signs of disease.

(n) *Unfavorable reactions.* Overt adverse changes which occur in healthy test animals subsequent to initiation of a test and manifested during the observation period prescribed in the test protocol which are attributable either to the biological product being tested or to factors unrelated to such product as determined by the responsible individual conducting the test.

(o) *Master reference.* A Master Reference is a reference whose potency is correlated, directly or indirectly, to host animal immunogenicity. The Master Reference may be used as the working reference in in vitro tests for relative potency. The Master Reference

may also be used to establish the relative potency of a serial of product used in requalification studies and to establish the relative potency of working references. The preparation of a Master Reference as described in a filed Outline of Production may be:

(1) A completed serial of vaccine or bacterin prepared in accordance with a filed Outline of Production;

(2) A purified preparation of a protective immunogen or antigen; or

(3) A nonadjuvanted harvested culture of microorganisms.

(p) *Working reference.* A Working Reference is the reference preparation that is used in the in vitro test for the release of serials of product. Working References may be:

(1) Master References; or

(2) Serials of product that have been prepared and qualified, in a manner acceptable to Animal and Plant Health Inspection Service for use as reference preparations.

(q) *Qualifying serial.* (1) A serial of biological product used to test for immunogenicity when the Master or Working Reference is a purified antigen or nonadjuvanted harvest material. Qualifying serials shall be produced in accordance with the filed Outline of Production, tested for immunogenicity in accordance with methods deemed appropriate by the Animal and Plant Health Inspection Service, and have a geometric mean relative potency, when compared to the Master Reference, of not greater than 1.0 as established by: independent parallel line assays with five or more replicates; or other valid assay methods for determining relative antigen content which demonstrate linearity, specificity, and reproducibility at least equivalent to the parallel line assay and are acceptable to the Animal and Plant Health Inspection Service.

(2) Qualifying serials used to requalify or extend the dating period of a Master Reference shall be determined to be immunogenic in accordance with methods deemed appropriate by the Animal and Plant Health Inspection Service as provided in paragraph (a)(1) of this section, and, in addition, shall be within their permitted dating period and have been prepared in accordance with the production method described in the currently filed Outline of Production.

(r) *Immunogenicity.* The ability of a biological product to elicit an immune response in animals as determined by test methods or procedures acceptable to the Animal and Plant Health Inspection Service.

[38 FR 8426, Apr. 2, 1973, as amended at 40 FR 45419, Oct. 2, 1975; 41 FR 6751, Feb. 13, 1976; 43 FR 3701, Jan. 27, 1978; 56 FR 66782, 66783 Dec. 26, 1991; 62 FR 19037, Apr. 18, 1997; 79 FR 55969, Sept. 18, 2014]

§ 101.6 Cell cultures.

When used in conjunction with or in reference to cell cultures, which may be referred to as tissue cultures, the following terms shall mean:

(a) *Batches of primary cells.* A pool of original cells derived from normal tissue up to and including the 10th subculture.

(b) *Cell line.* A pool of cells which are 11 or more subcultures from the tissue of origin.

(c) *Subculture.* Each flask to flask transfer or passage regardless of the number of cell replications.

(d) *Master Cell Stock (MCS).* The supply of cells of a specific passage level from which cells for production of biologics originate.

[38 FR 8426, Apr. 2, 1973, as amended at 40 FR 45419, Oct. 2, 1975; 49 FR 22624, May 31, 1984]

§ 101.7 Seed organisms.

When used in conjunction with or in reference to seed organisms, the following shall mean:

(a) *Master Seed.* An organism at a specific passage level which has been selected and permanently stored by the producer from which all other seed passages are derived within permitted levels.

(b) *Working Seed.* An organism at a passage level between Master Seed and Production Seed.

(c) *Production Seed.* An organism at a specified passage level which is used without further propagation for initiating preparation of a fraction.

[49 FR 22625, May 31, 1984]

PART 102—LICENSES FOR BIOLOGICAL PRODUCTS

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AUTHORITY: 21 U.S.C. 151–159; 7 CFR 2.22, 2.80, and 371.4.

§ 102.1 Licenses issued by the Administrator.

Each establishment qualified to prepare biological products under the Virus-Serum-Toxin Act shall hold an unexpired and unrevoked U.S. Veterinary Biologics Establishment License issued by the Administrator and a U.S. Veterinary Biological Product License for each product prepared in such establishment unless the product is subject to the provisions of 9 CFR parts 103 or 106 of this subchapter.

[60 FR 48021, Sept. 18, 1995]

§ 102.2 Licenses required.

(a) Every person who prepares biological products subject to the Virus-Serum-Toxin Act shall hold an unexpired, unsuspended, and unrevoked U.S. Veterinary Biologics Establishment License and at least one unexpired, unsuspended, and unrevoked U.S. Veterinary Biological Product License issued by the Administrator to prepare a biological product.

(b) An applicant who applies for an establishment license must also apply for at least one product license. An establishment license will not be issued without a license authorizing the production of a biological product in the establishment.

[52 FR 11026, Apr. 7, 1987, as amended at 56 FR 66783, Dec. 26, 1991; 61 FR 52873, Oct. 9, 1996]

§ 102.3 License applications.

(a) *U.S. Veterinary Biologics Establishment License.* (1) The operator of each establishment of the kind specified in § 102.2 shall make written application to the Administrator for a license. Blank forms of application will be furnished upon request to Animal and Plant Health Inspection Service.

(2) When a person conducts more than one establishment, a separate application shall be made for each establishment.

(3) Whenever subsidiaries are to operate in an establishment for which license application is made, the applicant shall apply for permission for such subsidiaries to operate in the establishment and furnish therewith a complete statement regarding the relationship between the applicant and the subsidiaries.

(4) Facilities documents, prepared as prescribed in part 108 of this subchapter, shall accompany the application for license unless previously filed with Animal and Plant Health Inspection Service.

(5) Each application for a U.S. Veterinary Biologics Establishment License shall be accompanied by an application for one or more U.S. Veterinary Biological Product Licenses and the supporting documents required by paragraph (b)(2) of this section.

(6) A new application shall be made when a change of ownership, operation, or location of an establishment occurs; or prior to the expiration of a U.S. Veterinary Biologics Establishment License issued for an interim period of time.

(b) *U.S. Veterinary Biological Product License.* (1) The licensee of each establishment or applicant for an establishment license shall make written application to the Administrator for a U.S. Veterinary Biological Product License for each biological product to be prepared in the licensed establishment.

(2) Each application for a U.S. Veterinary Biological Product License shall be supported by:

(i) At least two copies of an Outline of Production prepared in accordance with §§ 114.8 and 114.9 of this subchapter; and

(ii) At least three copies of test reports and research data sufficient to establish purity, safety, potency, and efficacy of the product; and

(iii) Legends prepared as prescribed in § 108.5 of this subchapter designating which facilities are to be used in the preparation of each fraction; and