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

PART 101—DEFINITIONS

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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.

Adverse event. Any observation in animals, whether or not the cause of the event is known, that is unfavorable and unintended, and that occurs after any use (as indicated on the label or any off-label use) of a biological product, including events related to a suspected lack of expected efficacy. For products intended to diagnose disease, adverse events refer to a failure in product performance that hinders an expected discovery of the correct diagnosis.

Adverse event report. Direct communication concerning the occurrence of an adverse event from an identifiable first-hand reporter which includes the following information:

(1) An identifiable reporter;
(2) An identifiable animal;
(3) An identifiable biologic product; and
(4) One or more adverse events.

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 de-
tection or measurement of antigens,
antibodies, nucleic acids, or immunity; or

(iii) Substances, at any stage of pro-
duction, 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), rep-
resentations, 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, dis-
brutes, or otherwise places in chan-
nels of trade, one or more biological
products he does not produce or im-
port.

Division. A marketing unit estab-
lished 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 li-
cense.

Guidelines. Guidelines establish prin-
ciples or practices related to test pro-
cedures, manufacturing practices,
product standards, scientific protocols,
labeling, and other technical or policy
considerations. Guidelines contain pro-
cedures or standards of general appli-
cability that are usually not regulatory
in nature, but that are related to mat-
ters 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, includ-
ing 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 subse-
quently housed at the common loca-
tion. 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 ani-
mals 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 examina-
tion or testing of biological products.

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

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

Licensee. A person to whom an estab-
lishment license and at least one prod-
uct license has been issued.

Microorganisms. Microscopic or sub-
microscopic 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 ori-
gin 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 bi-
ological products has been issued.

Person. Any individual, firm, partners-
ship, corporation, company, associa-
tion, educational institution, State or
local governmental agency, or other
organized group of any of the fore-
going, or any agent, officer, or em-
ployee of any thereof.

Premises. All buildings, appur-
tenances, and equipment used to
produce and store biological products
located within a particular land area.
§ 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(s).

(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.


§ 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.


§ 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 microorganisms 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.

(s) **Stability-indicating assay.** A stability-indicating assay is a validated quantitative analytical procedure that can detect changes over time in a pertinent property of the product.


§ 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.

§ 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

§ 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 unrevoke 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 unrevoke U.S. Veterinary Biologics Establishment License and at least one unexpired, unsuspended, and unrevoke 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.


§ 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.