(4) When a serial has been found unsatisfactory for potency by the test provided in paragraphs (e)(1), (2), and (3) of this section, the serial shall be withheld from the market and the following actions taken:

(i) The Administrator shall require that at least two additional serials prepared with the same Master Seed be subjected to similar animal potency tests by Animal and Plant Health Inspection Service or the licensee or both.

(ii) If another serial is found unsatisfactory for potency, the product shall be removed from the market while a reevaluation of the product is made and the problem is resolved.

[49 FR 22625, May 31, 1984, as amended at 56 FR 66784, 66786, Dec. 26, 1991; 62 FR 19038, Apr. 18, 1997]

§ 113.9 New potency test.

A potency test written into the filed Outline of Production for a product shall be considered confidential information by Animal and Plant Health Inspection Service until at least two additional product licenses are issued for the product or unless use of the test is authorized by the licensee, in which case, such potency test may be published as part of the Standard Requirement for the product.

(a) Until a potency test is published as part of the Standard Requirement for the product, reference to such a test shall be made in the filed Outline of Production and the test shall be conducted.

(b) When a potency test has been published as part of the Standard Requirement, such test shall be conducted unless the product is specifically exempted as provided in § 113.4.

[40 FR 14084, Mar. 28, 1975, as amended at 56 FR 66784, Dec. 26, 1991]

§ 113.10 Testing of bulk material for export or for further manufacture.

When a product is prepared in a licensed establishment for export in large multiple-dose containers as provided in § 112.8(d) or (e) of this subchapter or for further manufacturing purposes as provided in § 114.3(d) of this subchapter, samples of the bulk material shall be subjected to all required tests prescribed in the filed Outline of Production or Standard Requirements for the product. Samples of concentrated liquid product shall be diluted to a volume equal to the contents of the sample times the concentration factor prior to initiating potency tests.

[49 FR 45846, Nov. 21, 1984]

STANDARD PROCEDURES

§ 113.25 Culture media for detection of bacteria and fungi.

(a) Ingredients for which standards are prescribed in the United States Pharmacopeia, or elsewhere in this part, shall conform to such standards. In lieu of preparing the media from the individual ingredients, they may be made from dehydrated mixtures which, when rehydrated with purified water, have the same or equivalent composition as such media and have growth-promoting buffering, and oxygen tension-controlling properties equal to or better than such media. The formulas for the composition of the culture media prescribed in §§ 113.26 and 113.27 are set forth in the United States Pharmacopeia, 19th Edition.

(b) The licensee shall test each quantity of medium prepared at one time from individual ingredients and the first quantity prepared from each lot of commercial dehydrated medium for growth-promoting qualities. If any portion of a lot of commercial dehydrated medium is held for 90 days or longer after being so tested, it shall be retested before use. Two or more strains of micro-organisms that are exacting in their nutritive requirements shall be used. More than one dilution shall be used to demonstrate the adequacy of the medium to support the growth of a minimum number of micro-organisms.

(c) The sterility of the medium shall be confirmed by incubating an adequate number of test vessels and examining each for growth. Additional control may be used by incubation of representative uninoculated test vessels for the required incubation period during each test.

(d) A determination shall be made by the licensee for each biological product of the ratio of inoculum to medium which shall result in sufficient dilution of such product to prevent bacteriostatic and fungistatic activity.

The determination may be made by tests on a representative biological product for each group of comparable products containing identical preservatives at equal or lower concentrations. Inhibitors or neutralizers of preservatives, approved by the Administrator, may be considered in determining the proper ratio.

[35 FR 16039, Oct. 13, 1970, as amended at 37 FR 2430, Feb. 1, 1972; 41 FR 27715, July 6, 1976; 56 FR 66784, Dec. 26, 1991]

§ 113.26 Detection of viable bacteria and fungi except in live vaccine.

Each serial and subserial of biological product except live vaccines shall be tested as prescribed in this section unless otherwise specified by the Administrator. When cell lines, primary cells, or ingredients of animal origin used in the preparation of a biological product are required to be free of viable bacteria and fungi, they shall also be tested as prescribed in this section.

(a) The media to be used shall be as follows:

(1) Fluid Thioglycollate Medium with 0.5 percent beef extract shall be used to test for bacteria in biological products containing clostridial toxoids, bacterins, and bacterin-toxoids.

(2) Fluid Thioglycollate Medium with or without 0.5 percent beef extract shall be used to test for bacteria in biological products other than clostridial toxoids, bacterins, and bacterin-toxoids.

(3) Soybean-Casein Digest Medium shall be used to test biological products for fungi; provided, that Fluid Thioglycollate Medium without beef extract shall be substituted when testing biological products containing mercurial preservatives.

(b) Test procedure:

(1) Ten test vessels shall be used for each of two media selected in accordance with paragraph (a)(1), (a)(2), or (a)(3) of this section. Each test vessel shall contain sufficient medium to negate the bacteriostatic or fungistatic activity in the inoculum as determined in § 113.25(d).

(2) Inoculum:

(i) When completed product is tested, 10 final container samples from each serial and each subserial shall be tested. One ml from each sample shall be inoculated into a corresponding individual test vessel of culture medium: *Provided*, That, if each final container sample contains less than 2 ml, one-half of the contents shall be used as inoculum for each test vessel.

(ii) When cell lines, primary cells, or ingredients of animal origin are tested, at least a 20 ml test sample from each lot shall be tested. One ml shall be inoculated into each test vessel of medium.

(3) Incubation shall be for an observation period of 14 days at 30 °to 35 °C. to test for bacteria and 14 days at 20 °to 25 °C. to test for fungi.

(4) If the inoculum renders the medium turbid so that the absence of growth cannot be determined by visual examination, subcultures shall be made on the seventh to eleventh day from biological products prepared from clostridial toxoids, bacterins, and bacterin-toxoids and the third to seventh day for other biological products. Portions of the turbid medium in amounts of not less than 1.0 ml. shall be transferred to 20 to 25 ml. of fresh medium, and incubated the balance of the 14-day period.

(c) Examine the contents of all test vessels for macroscopic microbial growth during the incubation period. When demonstrated by adequate controls to be invalid, the test may be repeated. For each set of test vessels representing a serial or subserial in a valid test, the following rules shall apply:

(1) If no growth is found in any test vessel, the serial or subserial meets the requirements of the test.

(2) If growth is found in any test vessel, one retest to rule out faulty technique may be conducted using 20 unopened final container samples.

(3) If growth is found in any test vessel of the final test, the serial, subserial, or ingredients to be used in the preparation of a biological product, as the case may be, is unsatisfactory.

[35 FR 16039, Oct. 13, 1970, as amended at 37 FR 2430, Feb. 1, 1972; 39 FR 21042, June 18, 1974; 40 FR 758, Jan. 3, 1975; 40 FR 14084, Mar. 28, 1975; 56 FR 66784, Dec. 26, 1991]