§ 113.53 Requirements for ingredients of animal origin used for production of biologics.

Each lot of ingredient of animal origin which is not subjected to heat sterilization or other sterilization methods acceptable to Animal and Plant Health Inspection Service (APHIS), such as, but not limited to serum and albumin, used to prepare a biological product shall be tested as prescribed in this section by the licensee or a laboratory acceptable to VS. Results of all tests shall be recorded by the testing laboratory and made a part of the licensee’s records. A lot of ingredient found unsatisfactory by any prescribed test shall not be used to prepare a biological product. A serial of biological product shall not be released if produced using an ingredient that is found unsatisfactory by any prescribed test.

(a) Samples of each lot of ingredient of animal origin which is not subjected to heat sterilization, used to prepare a biological product shall be shown free of mycoplasma by the method prescribed in §113.28.

(b) Samples of each lot of ingredient or animal origin which is not subjected to heat sterilization of other sterilization methods acceptable to APHIS used to prepare a biological product shall be shown free of bacteria and fungi as prescribed in §113.36.

(c) Samples of each lot of ingredient of animal origin, except porcine trypsin, which is not subjected to heat sterilization or other viricidal procedure acceptable to APHIS used in the preparation of biological products shall be tested as prescribed in this paragraph:

(1) Monolayers at least 75 cm² of Vero (African green monkey kidney) cell line and of primary cells or a cell line of the same species of origin as the ingredient shall be used in the test. Cell lines used shall have been found satisfactory when tested as prescribed in §§113.52 and primary cells used shall have been found satisfactory when tested as prescribed in §113.51.

(2) At least 3.75 ml or 15 percent of the ingredient shall be used in the growth medium for the preparation of at least 75 cm² test monolayers. The ingredient shall also be used in the growth medium when monolayers are subcultured. If the ingredient being tested is cytotoxic when tested in this manner, other procedures may be used if approved by APHIS.

(3) The test monolayers shall be maintained for at least 21 days.

(4) Cells shall be subcultured at least two times during the maintenance period. All but the last subculture shall result in at least one new monolayer of at least 75 cm². The last subculture shall meet the minimum area requirements specified in §§113.46 and 113.47.

(5) Monolayers shall be examined regularly throughout the 21-day maintenance period for evidence of cytopathogenic agent. If evidence of a cytopathogenic agent is found, the ingredient is unsatisfactory.

(6) At the conclusion of the 21-day maintenance period, monolayers shall be tested for:

(i) Cytopathogenic and/or hemadsorbing agents as prescribed in §113.46; and
§ 113.55 Detection of extraneous agents in Master Seed Virus.

Unless otherwise prescribed in a Standard Requirement or in a filed Outline of Production, each Master Seed Virus (MSV) shall be tested as prescribed in this section. A MSV found unsatisfactory by any prescribed test shall not be used. A serial of biological product shall not be released if produced from a MSV that is found unsatisfactory by any prescribed test.

(a) At least a 1.0 ml aliquot per cell culture of MSV shall be dispensed onto monolayers (at least 75 cm² in area) of:

1. Vero (African green monkey kidney) cell line;

2. Embryonic cells, neonatal cells, or a cell line of the species for which the vaccine is recommended; and

3. Embryonic cells, neonatal cells, or a cell line of the species of cells in which the MSV is presently being propagated if different than prescribed in paragraphs (a)(1) and (a)(2) of this section. Cell lines used shall have been found satisfactory when tested as prescribed in §113.52 and primary cells used shall have been found satisfactory when tested as prescribed in §113.51. If the MSV is cytopathic for or causes hemadsorption in the cells in which it is to be tested, the MSV shall be neutralized with monospecific antiserum supplied or approved by Animal and Plant Health Inspection Service (APHIS) or counteracted by a method approved by APHIS.

(b) At least one monolayer of each cell type used in the test shall be maintained as an uninoculated control.

(c) Each monolayer shall be maintained at least 14 days.

§ 113.54 Sterile diluent.

Sterile Diluent shall be supplied in a final container by the licensee when such diluent is required for rehydration or dilution of the vaccine.

(a) Sterile Diluent may be distilled or deionized water or it may be a special liquid solution formulated in accordance with an acceptable outline on file with Animal and Plant Health Inspection Service.

(b) Each quantity prepared at one time in a single container and bottled into final containers shall be designated as a serial. Each serial shall be given a number which shall be used in records, test reports, and on the final container label.

(c) Final container samples from each serial shall be tested for bacteria and fungi in accordance with the test provided in §113.26. Any serial found to be unsatisfactory shall not be released. [39 FR 27428, July 29, 1974, as amended at 56 FR 66784, Dec. 26, 1991]