§ 630.50

Mumps Virus Vaccine Live.

(a) Proper name and definition. The proper name of this product shall be Mumps Virus Vaccine Live, which shall consist of a preparation of live, attenuated mumps virus.

(b) Criteria for acceptable strains of attenuated mumps virus. Strains of attenuated mumps virus used in the manufacture of vaccine shall be identified by (1) historical records including origin and manipulation during attenuation, (2) antigenic specificity as mumps virus as demonstrated by tissue culture neutralization tests. Strains used for the manufacture of Mumps Virus Vaccine Live shall have been shown to be safe and potent in at least 5,000 susceptible individuals by field studies with experimental vaccines. Susceptibility shall be shown by the absence of neutralizing or other antibodies against mumps virus, or by other appropriate methods. Seed virus used for vaccine manufacture shall be free of all demonstrable extraneous viable microbial agents except for unavoidable bacteriophage.

(c) Neurovirulence safety test of the virus seed strain in monkeys—(1) The test. A demonstration shall be made in monkeys of the lack of neurotropic properties of the seed strain of attenuated mumps virus used in the manufacture of mumps vaccine. For this purpose and to establish consistency of manufacture of the vaccine, vaccine from each of five consecutive lots shall be tested separately in monkeys shown to be serologically negative for mumps virus antibodies in the following manner:

(i) A test sample of vaccine removed after clarification but before final dilution for standardization of virus content shall be used for the test.

(ii) Vaccine shall be injected by combined intracerebral, intraspinal, and intramuscular routes into not less than 20 Macaca or Cercopithecus monkeys or a species found by the Director, Center for Biologics Evaluation and Research, to be equally suitable for the purpose. The animals shall be in overt good health and injected under deep barbiturate anesthesia. The intramuscular injection shall consist of 1.0 milliliter of test sample into the right leg muscles. At the same time, 200 milligrams of cortisone acetate shall be injected into the left leg muscles, and 1.0 milliliter of procaine penicillin (300,000 units) into the right arm muscles. The intracerebral injection shall consist of 0.5 milliliter of test sample into each thalamic region of each hemisphere. The intraspinal injection shall consist of 0.5 milliliter of test sample into the lumbar spinal cord enlargement.

(iii) The monkeys shall be observed for 17–21 days and symptoms of paralysis as well as other neurologic disorders shall be recorded.

(iv) At least 90 percent of the test animals must survive the test period without losing more than 25 percent of their weight except that, if at least 70 percent of the test animals survive the first 48 hours after injection, those animals which do not survive this 48-hour test period may be replaced by an equal number of qualified test animals which are tested pursuant to paragraphs (c)(1)(i) through (iii) of this section. At least 80 percent of the injected animals surviving beyond the first 48 hours must show gross or microscopic evidence of inoculation trauma in the thalamic area and microscopic evidence of inoculation trauma in the lumbar region of the spinal cord. If less than 70 percent of the test animals survive the first 48 hours, or if less than 80 percent of the animals meet the inoculation criteria prescribed in this paragraph, the test must be repeated.

(v) At the end of the observation period, each surviving animal shall be autopsied and samples of cerebral cortex and of cervical and lumbar spinal cord enlargements shall be taken for virus recovery and identification if
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needed pursuant to paragraph (c)(1)(vi) of this section. Histological sections shall be prepared from both spinal cord enlargements and appropriate sections of the brain and examined.

(vi) Doubtful histopathological findings necessitate (a) examination of a sample of sections from several regions of the brain in question, and (b) attempts at virus recovery from the nervous system tissues previously removed from the animals.

(vii) The lot is satisfactory if the histological and other studies demonstrate no evidence of changes in the central nervous system attributable to unusual neurotropism of the seed virus or of the presence of extraneous neurotropic agents.

(2) Test results. The mumps virus seed has acceptable neurovirulence properties for use in vaccine manufacture only if for each of the five lots (i) 90 percent of the monkeys survive the observation period, (ii) the histological and other studies produce no evidence of changes in the central nervous system attributable to unusual neurotropism or replication of the seed virus and (iii) there is no evidence of the presence of extraneous neurotropic agents.

(3) Need for additional neurovirulence safety testing. A neurovirulence safety test as prescribed in this paragraph shall be performed on vaccine from five consecutive lots whenever a new production seed lot is introduced or whenever the source of cell culture substrate must be reestablished and recertified as prescribed in §630.52(a).


§ 630.51 Clinical trials to qualify for license.

To qualify for license, the antigenicity of Mumps Virus Vaccine Live shall be determined by clinical trials, conducted in compliance with part 56 of this chapter unless exempted under §56.104 or granted a waiver under §56.105, and with part 50 of this chapter, that follow the procedures prescribed in §630.31, except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of mumps-susceptible individuals, each having received the parenteral administration of a virus vaccine dose not greater than that demonstrated to be safe in field studies (§630.50(b)) when used under comparable conditions.


§ 630.52 Manufacture of Mumps Virus Vaccine Live

(a) Virus cultures. Mumps virus shall be propagated in chick embryo cell cultures. The embryonated chicken eggs used as the source of chick embryo tissue for the propagation of mumps virus shall be derived from flocks certified or tested as prescribed in §630.32(b).

(b) Passage of virus strain in vaccine manufacture. Virus in the final vaccine shall represent no more than five cell culture passages beyond the passage used to perform the clinical trials (§630.50(b)) which qualified the manufacturer's vaccine strain for license.

(c) Cell culture preparation. Only primary cell cultures shall be used in the manufacture of mumps virus vaccine. Continuous cell lines shall not be introduced or propagated in mumps virus vaccine manufacturing areas.

(d) Control vessels. From the tissue used for the preparation of cell cultures for growing attenuated mumps virus, an amount of processed cell suspension equivalent to that used to prepare 500 ml. of cell culture shall be used to prepare uninfected tissue control materials which shall be prepared and tested by following the procedures prescribed in §630.32(f).

(e) Test samples. Test samples of mumps virus harvests or pools shall be withdrawn and maintained by following the procedures prescribed in §630.32(g).

[38 FR 32068, Nov. 20, 1973, as amended at 50 FR 4138, Jan. 29, 1985]

§ 630.53 Reference virus.

An NIH Reference Mumps Virus, Live, shall be obtained from the Center for Biologics Evaluation and Research
§ 630.54 Potency test.

The concentration of live mumps virus shall constitute the measure of potency. The titration shall be performed in a suitable cell culture system, free of wild viruses, using either the Reference Mumps Virus, Live, or a calibrated equivalent strain as a titration control. The concentration of live mumps virus contained in the vaccine of each lot under test shall be no less than the equivalent of 5,000 TCID 50 of the reference virus per human dose.

§ 630.55 Test for safety.

(a) Tests prior to clarification. Prior to clarification, the following tests shall be performed on each mumps virus pool prepared in chick embryo cell culture:

(1) Inoculation of adult mice. The test shall be performed in the volume and following the procedures prescribed in § 630.35(a)(1), and the virus pool is satisfactory only if equivalent test results are obtained.

(2) Inoculation of suckling mice. The test shall be performed in the volume and following the procedures prescribed in § 630.35(a)(2), and the virus pool is satisfactory only if equivalent test results are obtained.

(3) Inoculation of monkey cell cultures. A mumps virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in § 630.35(a)(3), and the virus pool is satisfactory only if equivalent test results are obtained.

(4) Inoculation of other cell cultures. The mumps virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in § 630.35(a)(3), in rhesus or cynomolgus monkey kidney, in whole chick embryo, and in human cell cultures. In addition, each virus pool shall be tested in chick embryo kidney in the same manner except that the volume tested in each cell culture shall be equivalent to 250 human doses or 25 milliliters, whichever represents a greater volume. The mumps virus pool is satisfactory only if results equivalent to those in § 630.35(a)(3) are obtained.

(5) Inoculation of embryonated chicken eggs. A neutralized suspension of each undiluted mumps virus pool shall be tested in the volume and following the procedures prescribed in § 630.35(a)(5), and the virus pool is satisfactory only if there is no evidence of adventitious agents.

(6) Bacteriological tests. In addition to the tests for sterility required pursuant to § 610.12 of this chapter, bacteriological tests shall be performed on each mumps virus pool for the presence of M. tuberculosis, both avian and human, by appropriate culture methods. The virus pool is satisfactory only if found negative for M. tuberculosis, both avian and human.

(b) Clarification. The mumps virus fluids shall be clarified by following the procedures prescribed in § 630.35(c).

§ 630.56 General requirements.

(a) Final container tests. In addition to the tests required pursuant to § 610.14 of this chapter, an immunological and virological identity test shall be performed on the final container if it was not performed on each pool or the bulk vaccine prior to filling.

(b) Dose. These standards are based on an individual human immunizing dose of no less than 5,000 TCID 50 of Mumps Virus Vaccine Live, expressed in terms of the assigned titer of the Reference Mumps Virus, Live.

(c) Labeling. In addition to the items required by other applicable labeling provisions of this part, single dose container labeling for vaccine which is not protected against photochemical deterioration shall include a statement cautioning against exposure to sunlight.

(d) [Reserved]
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(e) Photochemical deterioration; protection. Mumps Virus Vaccine Live, in multiple dose containers, shall be protected against photochemical deterioration in accordance with the procedures prescribed in §630.36(g).

(f) Samples and protocols. For each lot of vaccine, the following materials shall be submitted to the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892:

1. A protocol which consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Center for Biologics Evaluation and Research.

2. A total of no less than two 25-milliliter volumes, in a frozen state (−60°C), of preclarification bulk vaccine containing no preservative, stabilizer, or adjuvant.

3. A total of no less than 30 containers of the vaccine from each filling of each bulk lot of single-dose containers. A total of no less than six 50-dose containers or ten 10-dose containers of the vaccine from each filling of each bulk lot of multiple-dose containers.


Subpart G—Rubella Virus Vaccine Live

§ 630.60 Rubella Virus Vaccine Live.

(a) Proper name and definition. The proper name of this product shall be Rubella Virus Vaccine Live, which shall consist of a preparation of live, attenuated rubella virus.

(b) Criteria for acceptable strains of attenuated rubella virus. Strains of attenuated rubella virus used in the manufacture of vaccine shall be identified by (1) historical records including origin and manipulation during attenuation and (2) antigenic specificity as rubella virus as demonstrated by tissue culture neutralization tests.

(c) Extraneous agents. Seed virus used for vaccine manufacture shall be free of all demonstrable extraneous viable microbial agents except for unavoidable bacteriophage.

(d) Field studies with experimental vaccines. (1) Strains used for the manufacture of Rubella Virus Vaccine Live, shall have been shown in field studies with experimental vaccines to be safe and potent in the group of individuals inoculated, which must include at least 10,000 susceptible individuals. Susceptibility shall be shown by the absence of neutralizing or hemagglutination-inhibiting antibodies against rubella virus or by other appropriate methods.

2. The virus strain used in the field studies shall be propagated in the same cell culture system that will be used in the manufacture of the product.

3. The field studies shall be so conducted that at least 5,000 of the susceptible individuals must reside in areas where health related statistics are regularly compiled in accordance with procedures such as those used by the National Center for Health Statistics. Data in such form as will identify each inoculated person shall be furnished to the Director, Center for Biologics Evaluation and Research.

4. Inoculated persons shall be shown not to be contagious for contacts through surveillance of rubella susceptible contacts of the inoculated persons.

(e) Neurovirulence safety test of the virus seed strain in monkeys—(1) The test. A demonstration shall be made in monkeys of the lack of neurotropic properties of the seed strain of attenuated rubella virus used in the manufacture of rubella vaccine. For this purpose and to establish consistency of manufacture of the vaccine, vaccine from each of five consecutive lots shall be tested separately in monkeys shown to be serologically negative for rubella virus antibodies in the following manner:

(i) A test sample of vaccine removed after clarification but before final dilution for standardization of virus content shall be used for the test.

(ii) Vaccine shall be injected by combined intracerebral, intraspinal, and intramuscular routes into not less than 20 Macaca or Cercopithecus monkeys or a species found by the Director, Center for Biologics Evaluation and Research, to be equally suitable for the purpose. The animals shall be in over