§ 630.30 Measles Virus Vaccine Live

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

(b) Criteria for acceptable strains of attenuated measles virus. Strains of attenuated measles 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 measles virus as demonstrated by tissue culture neutralization tests. Strains used for the manufacture of Measles Virus Vaccine Live, shall have been shown to be safe and potent in man by field studies with experimental vaccines. The vaccine shall have been demonstrated as safe and potent in at least 10,000 susceptible persons. Susceptibility shall be shown by the absence of neutralizing or other antibodies against measles 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 measles virus used in the manufacture of measles virus 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 the following manner:

(i) Samples of each of the five lots of vaccine shall be tested in measles susceptible monkeys. Immediately prior to initiation of a test each monkey shall have been shown to be serologically negative for neutralizing antibodies by means of a tissue culture neutralization test with undiluted serum from each monkey tested at approximately 100 TCID$_{50}$ of Edmonston strain measles virus, or negative for measles virus antibodies as demonstrated by tests of equal sensitivity.

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

(iii) 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 lumber spinal cord enlargement.

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

(v) 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)(3)(i) through (iv) 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.

(vi) At the end of the observation period, each surviving monkey shall (a) be bled and the serum tested for evidence of serum antibody conversion to measles virus and (b) be autopsied and samples of cerebral cortex and of cervical and lumbar spinal cord enlargements shall be taken for virus recovery and identification if needed pursuant to paragraph (c)(3)(vii) of this section. Histological sections shall be prepared from both spinal cord enlargements and appropriate sections of the brain and examined.

(vii) 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 systems tissues previously removed from the animal.

(viii) 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) Wild virus controls. As a check against the inadvertent introduction of wild measles virus, at least four uninoculated measles susceptible control monkeys shall be maintained as either cage mates to, or within the same immediate area of, the 20 inoculated test animals for each lot of vaccine for
§ 630.31 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design, by a suitable route of administration of the product. Such clinical trials shall be conducted with five lots of measles virus vaccine which have been manufactured by the same methods. There shall be a demonstration under circumstances in which adequate clinical and epidemiological surveillance of illness has been maintained to show that the measles virus vaccine, when administered as recommended by the manufacturer, is free of harmful effect upon administration to approximately 1,000 susceptible individuals, in that there were no detectable neutralizing antibodies before vaccination and there was serological conversion after vaccination. The five lots of vaccine shall be distributed as evenly as possible among the 1,000 individuals tested. Demonstration shall be made of immunogenic effect by the production of specific measles neutralizing antibodies (i.e., sero-conversion from less than 1:4 to 1:8 or greater) in at least 90 percent of each of five groups of measles susceptible individuals, each having received a virus vaccine dose which is not greater than that which was demonstrated to be safe in field studies (§630.30(b)) when used under comparable conditions. Such clinical trials shall be conducted in compliance with part 56 of this chapter unless exempted under §56.104 or granted a waiver under §56.105, and with the requirements for informed consent set forth in part 50 of this chapter.

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§ 630.32 Manufacture of live, attenuated Measles Virus Vaccine.

(a) Virus cultures. Virus shall be propagated in chick embryo tissue cultures.

(b) Virus propagated in chick embryo tissue cultures. Embryonated chicken eggs used as the source of chick embryo tissue for the propagation of measles virus shall be derived from flocks certified to be free of Salmonella pullorum, avian tuberculosis, fowl pox, Rous sarcoma, avian leucosis, reticuloendotheliosis virus, and other adventitious agents pathogenic for chickens. If eggs are procured from flocks that are not so certified, tests shall be performed to demonstrate freedom of the vaccine from such agents. (See §630.35(a)(8) for test for avian leucosis.)

(c) [Reserved]

(d) Passage of virus strain in vaccine manufacture. Virus in the final vaccine shall represent no more than ten tissue culture passages beyond the passage used to perform the clinical trials (§630.30(b)) which qualified the manufacturer’s vaccine strain for license.