DRAFT REVISED MONOGRAPH FOR COMMENTS

This draft revised monograph contain text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to further revisions prior to publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Comments received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in/ biologics-ipc@gov.in **before the last date for comments.**

Document History and Schedule for the Adoption Process

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Ranikhet Disease Vaccine, Live (Lentogenic Strain)

Newcastle Disease Vaccine, Live (Lentogenic strain)

Definition

Ranikhet Disease Vaccine Live (Lentogenic Strain) is apreparation of a suitable strain of Newcastle disease/Ranikhet disease virus (avian paramyxovirus l**).** This monograph applies to vaccines intended for administration to chickens and/or other avian species for active immunization.

Production

Preparation of the vaccine

The vaccine virus is grown in embryonated hens' eggs or in cell cultures.

Substrate for virus propagation

The vaccine virus is grown in embryonated SPF eggs (2.7.7) or in cell cultures derived from SPF flocks (2.7.13).If the vaccine virus is grown in embryonated hens' eggs, they are obtained from flocks free from specified pathogens (SPF) (2.7.7).If the vaccine virus is grown in cell cultures, they comply with the requirements for cell cultures for the production of vaccines for veterinary use (*2.7.13)*.

Seed lots

The master seed lot complies with the tests for extraneous agents as described in the General monograph for Veterinary Vaccines (2.7.10).

Identification

Immunogenicity test in master seed can serve as an identification test.

Choice of vaccine virus

The vaccine virus shall be shown to be satisfactory with respect to safety (2.7.17) and efficacy (*2.7.12)* for the birds for which it is intended.

The following tests for intracerebral pathogenicity index (ICPI), amino-acid sequence, safety and increase in virulence and immunogenicity may be used during the demonstration of safety and efficacy of the vaccine.

Intra-cerebral pathogenicity index

Use vaccine virus at the least attenuated passage level that will be present between the master seed lot and a batch of the vaccine. Inoculate the vaccine virus into the allantoic cavity of embryonated hens' eggs, 9- to 11- days-old, from an SPF flock (*2.7.7*). Incubate the inoculated eggs for a suitable period and harvest and pool the allantoic fluids.

Use not fewer than ten 1-day-old chickens (i.e. more than 24 h but less than 40 h after hatching), from an SPF flock (*2.7.7*). Administer by the intracerebral route to each chick 0.05 ml of the pooled allantoic fluids containing not less than $10^{8.0}$ EID_{50} or, if this virus quantity cannot be achieved, not less than $10^{7.0}$ EID_{50}. Observe the chickens at least once daily for 8 days after administration and score them once every 24 h. A score of 0 is attributed to a chicken if it is clinically normal, 1 if it shows clinical signs of disease and 2 if it is dead.

The intracerebral pathogenicity index (ICPI), is the mean of the scores per chicken per observation over the 8-day period.

If an inoculum of not less than $10^{8.0}$ EID_{50} is used, the vaccine virus complies with the test if its intracerebral pathogenicity index is not greater than 0.5; if an inoculum of not less than $10^{7.0}$ EID_{50} but less than $10^{8.0}$ EID_{50} is used, the vaccine virus complies with the test if its intracerebral pathogenicity index is not greater than 0.4.

Safety

Carry out the test for each route and method of administration to be recommended for vaccination and in each avian species for which the vaccine is intended, using in each case birds not older than the minimum age to be recommended for vaccination. If the test is performed in chickens, use chickens from an SPF flock (*2.7.7*) or healthy susceptible chickens (2.7.18). If the test is performed in birds other than chickens, use birds that do not have antibodies against Ranikhet disease virus. Use vaccine virus at the least attenuated passage level that will be present in a batch of the vaccine.

For vaccines recommended for use in healthy susceptible chickens, use not less than 10 SPF chickens (2.7.7,Table 3) or healthy susceptible chickens demonstrated to be free from antibodies to Ranikhetdisease virus and of the youngest age recommended for vaccination. For vaccines recommended for use only in avian species other than the chicken, use not less than 10 birds of the species likely to bemost sensitive to Ranikhetdisease, which do not haveantibodies against Ranikhetdisease virus and of the minimumage recommended for vaccination. Administer to each bird byeye-drop, or parenterally if only parenteral administration isrecommended, 10 doses of the vaccine in a volume suitablefor the test. Observe the birds at least daily for 21 days. The test is not valid if more than 20 per cent of the birds show abnormal clinical signs or die from causes not attributable tothe vaccine. The vaccine complies with the test if no birdshows notable clinical signs of disease or dies from causesattributable to the vaccine.

Increase in virulence

Carry out the test using birds not more than 2 weeks old. If the properties of the vaccine virus allow sequential passage through 5 groups via natural spreading, this method may be used, otherwise passage is carried out as described below:

Carry out the test in a target species, using chickens if it is one of the target species. For the test in chickens, use chickens from an SPF flock (2.7.7). For other species, carry out the test in birds that do not have antibodies against Ranikhet disease virus. Administer to each bird of the 1st group by eye-drop a quantity of the vaccine virus that will allow recovery of virus for the passages described below. Observe the birds for the period shown to correspond to maximum replication of the vaccine virus, euthanise them and prepare a suspension from the brain of each bird and from a suitable organ depending on the tropism of the strain (for example, mucosa of the entire trachea, intestine, pancreas), and pool the samples. Administer 0.05 ml of the pooled samples by eye-drop to each bird of the next group. Carry out this passage operation not fewer than 4 times; verify the presence of the virus at each passage. If the virus is not found at a passage level, repeat the passage by administration to a group of 10 birds.

A. Carry out the test for intracerebral pathogenicity index using the material used for the 1st passage and the virus at the final passage level.

B. Carry out the test for amino-acid sequence using unpassaged vaccine virus, the material used for the 1st passage and the virus at the final passage level.
C. Carry out the test for safety using the material used for the 1st passage and the virus at the final passage level.

Administer the virus by the route to be recommended for vaccination likely to be the least safe and to the avian species for which the vaccine is intended that is likely to be the most susceptible to Ranikhet disease.
The vaccine virus complies with the test if, in the tests A, B and C, no indication of increase in virulence of the virus recovered from the final passage compared with the material used for the 1st passage is observed. If virus is not recovered after an initial passage in 5 birds and a subsequent repeat passage in 10 birds, the vaccine virus also complies with the test.

Immunogenicity
For each avian species for which the vaccine is intended, a test is carried out for each route and method of administration to be recommended using in each case, birds not older than the minimum age to be recommended for vaccination. The quantity of the vaccine virus administered to each bird is not greater than the minimum titre to be stated on the label and the virus is at the most attenuated passage level that will be present in a batch of the vaccine.

Vaccines for use in chickens: Use not fewer than 30 chickens of the same origin and from an SPF flock (*2.7.7*). Vaccinate by a route to be recommended not fewer than 20 chickens. Maintain not fewer than 10 chickens as controls. Challenge each chicken after 21 days by the intramuscular route with not less than $10^{5.0}$ embryo LD_{50} of Ranikhet disease virus (vellogenic challenge virus). Observe the chickens at least daily for 14 days after challenge. Record the deaths and the number of surviving chickens that show clinical signs of disease.

The test is not valid if 6 days after challenge fewer than 100 per cent of the control chickens have died or if during the period between vaccination and challenge more than 10 per cent of the vaccinated or control chickens show abnormal clinical signs or die from causes not attributable to the vaccine.

The vaccine virus complies with the test if during the observation period after challenge not fewer than 90 per cent of the vaccinated chickens survive and show no notable clinical signs of Ranikhet disease virus.

Vaccines for use in avian species other than chickens. Use not fewer than 30 birds of the species for which the vaccine is intended for Ranikhet disease, of the same origin and that do not have antibodies against avian paramyxovirus 1. Vaccinate by a route to be recommended not fewer than 20 birds. Maintain not fewer than 10 birds as controls. Challenge each bird after 21 days by the intramuscular route with a sufficient quantity of virulent avian paramyxovirus 1. Observe the birds at least once daily for 21 days after challenge. Record the deaths and the surviving birds that show clinical signs of disease.

The test is not valid if:

— during the observation period after challenge fewer than 90 per cent of the control birds die or show severe clinical signs of Ranikhet disease;

— or if during the period between the vaccination and challenge more than 10 per cent of the vaccinated or control birds show abnormal clinical signs or die from causes not attributable to the vaccine.

The vaccine virus complies with the test if during the observation period after challenge not fewer than 90 per cent of the vaccinated birds survive and show no notable clinical signs of Ranikhet disease. For species where

there is published evidence that it is not possible to achieve this level of protection, the vaccine complies with the test if there is a significant reduction in morbidity and mortality of the vaccinated birds compared with the control birds.

Batch tests

Identification

Identification of the vaccine virus. The vaccine, diluted if necessary, is identified using a suitable method. For example, when mixed with a monospecific Ranikhet disease virus antiserum, it is no longer able to provoke haemagglutination of chicken red blood cells, or to infect embryonated hens' eggs from an SPF flock (2.7.7) or susceptible cell cultures (*2.7.13*) into which it is inoculated.

Identification of the virus strain. The strain of vaccine virus is identified by a suitable validated method, for example using monoclonal antibodies.

Duly validated molecular biology (NAT) technique can also be applied for identification of vaccine virus

Bacteria and fungi. Vaccines intended for administration by injection comply with the test for sterility (2.2.11)

Frozen or freeze-dried vaccines produced in embryonated eggs and not intended for administration by injection comply either with the test for sterility (2.2.11) or with the following test: carry out a quantitative test forbacterial and fungal contamination; carry out identification tests for micro-organisms detected in the vaccine; the vaccine does not contain pathogenic micro-organisms and contains not more than 1 non-pathogenic micro-organism per dose. Any diluent supplied for reconstitution of the vaccine complies with the test for sterility prescribed in the monograph 2.2.11

Mycoplasmas (2.7.9). The vaccine complies with the test for mycoplasmas

Water (2.3.43). Not more than 3 percent.

Extraneous agents (2.7.11).The vaccine is free from extraneous agents.

Safety. The vaccine complies with the test for safety as mentioned under production tests.

Note: General Requirements shall be referred regarding omission of the batch safety test.

Virus titre. Titrate the vaccine virus by inoculation into embryonated hens' eggs (9 to 11 days old) from an SPF flock (*2.7.7)* or into suitable cell cultures (*2.7.13*). The vaccine complies with the test if 1 dose contains not less than 106 TCID50/EID50 of the virus per dose.

Potency

The vaccine complies with the requirements of the test prescribed under Immunogenicity when administered according to the recommended schedule by a recommended route and method. One out of every ten batches shall be tested as per the immunogenicity test described for master seed lot.

Labelling

The label must state that (1) the vaccine is for veterinary use only; (2) the recommended routes of administration; (3) the instructions for use, such as – "reconstituted with the diluent supplied for reconstitution where

applicable”(4) the animal species for which the vaccine is intended; (5) storage temperatures; (6) Batch Number, Manufacturing date and expiry date; (7) Total volume or number of doses; (8) Minimum virus titre9) Dose of vaccine

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