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 (Mesogenic Strain)

Ranikhet Disease Vaccine, Live (Mesogenic Strain) is a preparation of a suitable strain of Newcastle disease virus (naturally modified avian Paramyxovirus 1). This monograph applies to vaccines intended for administration to chickens for active immunization.

Production

Preparation of the vaccine

The vaccine virus is grown in embryonated SPF eggs derived from SPF flocks (2.7.7) or in cell cultures derived from SPF eggs (2.7.13).

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 (2.7.10).

Identification

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

Choice of the 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, test for reversion to virulence and immunogenicity may be used during the demonstration of safety and efficacy of the vaccine.

Safety. Administer 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of recommended age with a minimum10 doses and by the route stated on the label. Observe the chickens for 21 days. Master seed virus complies with the test if no bird shows notable clinical signs of Newcastle disease or dies from causes attributable to the vaccine virus. If more than two chickens die during the period of observation due to causes other than those attributable to the vaccine, repeat the test.

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 hen 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 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 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 1.5.

Test for Reversion to Virulence

Carry out the test according to general chapter (2.7.17) using birds not less than 6 weeks old at age recommended for vaccination. If the properties of the vaccine virus allow sequential passage through 5 groups via natural spreading, this method may be used, otherwise passage as described below is carried out. Carry out the test in a target species, using the chicken 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 Newcastle disease virus. Administer to each bird of the 1st group by intra-muscular route one dose of the vaccine, *i.e* $10^{5.0}$ EID_{50} in 0.05ml 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); pool the samples. Administer 0.05 mL of the pooled samples by intra-muscular 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 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 Newcastle disease.

The vaccine virus complies with the test if, in the above tests no indication of increase in virulence of the virus recovered for 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. Carry out potency test for each of the routes of administration stated on the label. For each of the stated routes, use not less than 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of the minimum age recommended for vaccination. Administer each chicken with a volume of the reconstituted vaccine containing a quantity of the virus equivalent to the minimum titre stated on the label. Use 10 chickens of the same flock and age as controls. After 14 to 21 days, challenge each chicken by intramuscular injection with 10^5 LD_{50} of a virulent strain of Newcastle disease virus. Observe the birds for 14 days. The vaccine complies with the test if not more than two of the vaccinated chickens die or show signs of disease. The test is valid only if all the control chickens die within 6 days of inoculation of the virulent challenge strain. If the potency test has been performed with satisfactory results on a representative batch of the vaccine from the seed lot, it may be omitted as a routine control test during production on other batches of the vaccine prepared from the same seed lot.

Batch test

Identification. The vaccine, diluted, if necessary and mixed with a monospecific Newcastle disease virus antiserum, no longer provokes haemagglutination of chicken red blood cells or infects embryonated hens' eggs from SPF flock (2.7.7) or susceptible cell culture derived from SPF eggs (2.7.7) into which it is inoculated.

Alternatively suitable validated immunochemical/ molecular biology methods can be used with the approval of competent authority.

Bacterial and fungal contamination (2.2.11). The vaccine, including where applicable the diluent supplied for reconstitution, complies with the test for sterility.

Mycoplasmas (2.7.9). Complies with the test for mycoplasmas.

Water (2.3.43). Not more than 3.0 per cent.

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

Safety. Administer 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, not less than 6 weeks old with a minimum 10 doses and by the route stated on the label. Observe the chickens for 21 days. The vaccine batch complies with the test if no bird shows notable clinical signs of Newcastle disease or dies from causes attributable to the vaccine virus. If more than two chickens die during the period of observation due to causes other than those attributable to the vaccine, repeat the test.

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

Virus titre. Not less than $10^{5.0}$ $TC1D_{50}/EID_{50}$ of the virus per dose, determining the titre in suitable cell culture derived from SPF eggs (2.7.7) or by inoculation into the allantoic cavity of SPF embryonated eggs (2.7.7), between 9 -11 days old:

Potency. The vaccine complies with the requirements of the test prescribed under Immunogenicity when administered by a recommended route and method. It is not necessary to carry out the potency test for each batch of the vaccine if it has been carried out on a representative batch using a vaccinating dose containing not more than the minimum virus titre stated on the label.

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; (8) Total volume or number of doses; (9) Minimum virus titre per dose of vaccine; (10) Dose of vaccine