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.**

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Avian Infectious Bronchitis Vaccine, Live

Infectious Bronchitis Vaccine, Live, Avian Infectious Bronchitis Vaccine Living

Avian Infectious Bronchitis Vaccine, Live is a preparation of one or more suitable strains of avian infectious bronchitis virus.This monograph applies to vaccines intended for administration to chickens for active immunization against respiratory disease caused by avian infectious bronchitis virus.

Production

Preparation of the Vaccine

The vaccine virus is grown in embryonated hens' eggs or in cell culture. derived from SPF eggs (2.7.7).

Embryonated hens' eggs. If the vaccine virus is grown in embryonated hens' eggs, they are obtained from flocks free from specified pathogens (SPF) (2.7.7).

Cell cultures. 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

Extraneous Agent. The master seed lot complies with the tests for extraneous agents (2.7.10).

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 chickens for which it is intended.

The following tests for identification, safety, test for reversion to virulence and immunogenicity may be used during the demonstration of safety and efficacy.

Identification.

Carry out either the test A or B.

A. Inoculate 0.2 ml undiluted seed in the allantoic sac of SPF embryonated eggs and incubate at 36° ± 1° for 5 to 6 days. Lesions typical of infectious bronchitis (IB) are observed in the embryo's and allantoic fluid does not agglutinate chicken erythrocytes.

B. Specific antiserum against the strain or each of the strains of the avian infectious bronchitis virus used in the vaccine should neutralize corresponding IB virus. When mixed with specific antiserum, the vaccine no longer infects 9-11 day old embryonated SPF eggs (2.7.7). Similar test can be performed using cell culture for the cell culture adapted virus.

Safety

Safety for the respiratory tract and kidneys. Carry out the test in chickens not older than the minimum age to be recommended for vaccination. Use vaccine virus at the least attenuated passage level that will be present between the master seed lot and a batch of the vaccine. Use not fewer than 15 chickens of the same origin and from an SPF flock (2.7.7). Administer to each chicken by the occulo-nasal route a quantity of the vaccine virus equivalent to not less than 10 times the maximum virus titre likely to be contained in 1 dose of the vaccine. On each of days 5, 7 and 10 after administration of the virus, euthanize not fewer than 5 of the chickens and take samples of trachea and kidney. Fix kidney samples for histological examination. Remove the tracheas and prepare 3 transverse sections from the upper part, 4 from the middle part and 3 from the lower part of the trachea of each chicken; examine all tracheal explants as soon as possible and at the latest 2 h after sampling by low-magnification microscopy for ciliary activity. Score for

ciliostasis on a scale from 0 (100 per cent ciliary activity) to 4 (no activity, complete ciliostasis); calculate the mean ciliostasis score (the maximum for each trachea being 40) for the 5 chickens euthanized on each of days 5, 7 and 10. The test is not valid if more than 10 per cent of the chickens die from causes not attributable to the vaccine virus.

The vaccine virus complies with the test if: no chicken shows notable clinical signs of avian infectious bronchitis or dies from causes attributable to the vaccine virus; any inflammatory lesions seen during the kidney histological examination are, at most, moderate. A risk/benefit analysis is carried out, taking into account the average ciliostasis scores obtained and the benefits expected from the use of the vaccine.

Safety for the reproductive tract. If the recommendations for use state or imply that the vaccine may be used in females less than 3 weeks old that are subsequently kept to sexual maturity, it shall be demonstrated that there is no damage to the development of the reproductive tract when the vaccine is given to chickens of the minimum age to be recommended for vaccination.

The following test may be carried out: use not fewer than 40 female chickens from an SPF flock (2.7.7) that are not older than the minimum age to be recommended for vaccination; use the vaccine virus at the least attenuated passage level that will be present between the master seed lot and a batch of the vaccine; administer to each chicken by a route to be recommended a quantity of virus equivalent to not less than the maximum titre likely to be present in 1 dose of vaccine; at least 10 weeks after administration of the vaccine virus and carry out a macroscopic examination of the oviducts. The vaccine virus complies with the test if abnormalities are present in not more than 5 per cent of the oviducts.

Test for Reversion to Virulence. Carry out the test according to general chapter using 2-week-old SPF chickens (2.7.7). 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.

Administer to each chicken of the 1 group by eye-drop a quantity of the vaccine virus that will allow recovery of virus for the passages described below. 2-4 days after administration of the vaccine virus, prepare a suspension from the mucosa of the trachea of each chicken and pool these samples. Administer 0.05 ml of the pooled samples by eye-drop to each chicken 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 chickens. Carry out the test for safety for the respiratory tract and kidneys and, where applicable, the test for safety for the reproductive tract using the material used for the 1 passage and the virus at the final passage level. Administer the virus by the route to be recommended for vaccination that is likely to be the least safe.

The vaccine virus complies with the test if no indication of an increase in virulence of the virus recovered for the final passage compared with the material used for the 1 passage is observed. If virus is not recovered after an initial passage in 5 chickens and a subsequent repeat passage in 10 chickens, the vaccine virus also complies with the test.

Immunogenicity. Immunogenicity is demonstrated for each strain of virus to be included in the vaccine. A test is carried out for each route and method of administration to be recommended using in each case chickens from an SPF flock (2.7.7) that are not older than the minimum age to be recommended for vaccination. The quantity of the vaccine virus administered to each chicken is not greater than the minimum virus 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.

Either or both of the tests below may be used during the demonstration of immunogenicity.

Ciliary activity of tracheal explants. Use not fewer than 25 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 5 chickens as controls. Challenge the vaccinated and control birds after 21 days by eye-drop with a sufficient quantity of virulent avian infectious bronchitis virus of the same type as the vaccine virus to be tested. Euthanise the chickens 4-7 days after challenge and prepare 3 transverse sections from the upper part, 4 from the middle part, and 3 from the lower part of the trachea of each chicken. Examine all tracheal explants as soon as possible and at the latest 2 h after sampling by low-magnification microscopy for ciliary activity. For a given tracheal section, ciliary activity is considered as normal when at least 50 per cent of the internal ring shows vigorous ciliary movement. A chicken is considered not affected if not fewer than 9 out of 10 rings show normal ciliary activity.

The test is not valid if:

–fewer than 80 per cent of the control chickens show cessation or extreme loss of vigour of ciliary activity;

–and/or during the period between the vaccination and challenge, more than 10 per cent of 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 not fewer than 80 per cent of the vaccinated chickens show normal ciliary activity.

Virus recovery from tracheal swabs. Use not fewer than 30 chickens of the same origin and from an SPF flock (2.7.7). Vaccinate by each route of administration recommended on the label and for each serotype against which protection is claimed and of the minimum age stated for vaccination. Administer to each of 20 SPF chickens, 3 to 4 weeks old, for each of the stated routes a volume of reconstituted vaccine containing a quantity of virus equivalent to the minimum titer stated on the label. Remaining 10 SPF chickens are used as unvaccinated controls. Three to four weeks later, administer by eye drop a virulent strain of bronchitis virus to all the vaccinated and control birds. Between 4^{th} and 7^{th} day after the challenge, take tracheal swabs from each of the vaccinated and control birds. Place each swab in a sterile test tube containing 3 ml of tryptose phosphate broth and antibiotics. Swirls the tube containing swabs thoroughly and store at -20° pending inoculating into eggs. For each tracheal swab, inoculate at least 5 chicken embryos, 9-11 days old with 0.2 ml of the broth from each tube into the allantoic cavity. All the embryos surviving on the third day after inoculation are used in the evaluation. A tracheal swab is considered positive for recovery of the virus if any of the embryos shows typical infectious bronchitis leisons such as stunting, curling, kidney urates, clubbing down or death between the 4^{th} and the 7^{th} day after inoculation. Alternatively, duly validated molecular biology (NAT) technique may be used to detect the challenge virus in the swabs.

The test is not valid if:

–the challenge virus is detected in less than 80 per cent of the control chickens

–and/or 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 the challenge virus is detected in not more than 20 per cent of the vaccinated chickens.

Batch tests

Identification

Vaccine complies with the test mentioned under Production.

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 complies with the test for sterility. 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

for bacterial 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 (2.2.11).

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

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

Safety . Inject 10 times the dose by the route stated on the label into each of 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens of minimum age recommended for vaccination. Observe the birds for 21 days. Not more than one of the vaccinated chickens shows symptoms of or dies from infectious bronchitis. If during the period of observation more than 2 of the vaccinated chickens die from causes not attributable to the vaccine, repeat the test.
Note: General Requirements shall be referred regarding omission of the batch safety test.

Virus titre. Titrate the vaccine in cell culture derived from SPF eggs (2.7.7) or by inoculating into the allantoic sac of SPF embryonated eggs, 9 to 11 days old. One dose of the vaccine contains not less than $10^{3.5}$ $TCID_{50}/EID_{50}$.

Potency. The vaccine complies with the requirements of one of the tests prescribed under Immunogenicity when administered according to the recommended schedule by a recommended route and method. Virus titer can replace in-vivo potency testing during batch test if a correlation of virus titer and potency is established.
If potency test has been performed with satisfactory results on a representative batch of the vaccine, using one vaccinating it may be omitted as a vaccine test during production on the other batches of vaccine prepared from the same 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 and number of doses; (8) Minimum virus titre; (9) Dose of vaccine