DRAFT REVISED MONOGRAPH FOR COMMENTS

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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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Infectious Bursal disease, Live

Definition

Infectious Bursal Disease Vaccine, Live is a freeze dried preparation of attenuated strain of infectious bursal disease (IBD) virus. This monograph applies to vaccines intended for administration to chickens for active immunization against Infectious bursal disease.

Production

Substrate for virus propagation

The vaccine virus is grown in embryonated eggs obtained from SPF flocks or in cell culture derived from SPF eggs (2.7.7) or susceptible cell lines.

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*). or susceptible cell line

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).

Choice of vaccine virus

The vaccine virus shall be shown to be satisfactory with respect to safety (2.7.17) and efficacy (2.7.13) for the chickens for which it is intended. The following tests for safety, damage to the bursa of Fabricius, immune suppression, increase in virulence and immunogenicity may be used during the demonstration of safety and efficacy.

Safety

Damage to the bursa of Fabricius

Carry out the test for the route to be recommended for vaccination likely to be the least safe using chickens not older than the minimum age to be recommended for vaccination. Use 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 20 chickens from an SPF flock (2.7.7). Administer to each chicken a quantity of the vaccine virus equivalent to 10 times the maximum titre likely to be contained in a dose of the vaccine. On each of days 7, 14, 21 and 28 after administration of the vaccine virus, euthanise not fewer than 5 chickens and prepare a section from the site with the greatest diameters of the bursa of Fabricius of each chicken. Carry out histological examination of the section and score the degree of bursal damage using the following scale.

0.No lesion, normal bursa.

1. 1 per cent to 25 per cent of the follicles show lymphoid depletion (i.e., less than 50 per cent depletion in 1 affected follicle); influx of heterophils in lesions.
2. 26 per cent to 50 per cent of the follicles show nearly complete lymphoid depletion (i.e., more than 75 per cent depletion in 1 affected follicle), affected follicles show necrosis and severe influx of heterophils may be detected.
3. 51 per cent to 75 per cent of the follicles show lymphoid depletion; affected follicles show necrosis and severe influx of heterophils is detected.
4. 76 per cent to 100 per cent of the follicles show nearly complete lymphoid depletion, hyperplasia and cyst structures are detected; affected follicles show necrosis and severe influx of heterophils is detected.
5. 100 per cent of the follicles show nearly complete lymphoid depletion; complete loss of follicular structure, thickened and folded epithelium, fibrosis of bursal tissue.

Calculate the average score for each group of chickens. The vaccine virus complies with the test if:
– no chicken shows notable clinical signs of disease or dies from causes attributable to the vaccine virus;
– the average score for bursal damage 21 days after administration of the vaccine virus is less than or equal to 2.0 and 28 days after administration is less than or equal to 0.6;
– during the 21 days after administration a notable repopulation of the bursae by lymphocytes has taken place.

Immunosuppression

Carry out the tests for the route to be recommended for vaccination likely to be the least safe using 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 30 chickens from an SPF flock (2.7.7). Divide them randomly into 3 groups each of not fewer than 10 and maintain the groups separately. Administer to each chicken of 1 group a quantity of the vaccine virus equivalent to not less than the maximum titre likely to be contained in 1 dose of the vaccine. At the time after administration when maximal bursal damage is likely to be present, as judged from the results obtained in the test for damage to the bursa of Fabricius administer by eye-drop to each vaccinated chicken and to each chicken of another group 1 dose of Hitchner B1 strain Newcastle disease vaccine (live). Determine the sero-response of each chicken of the 2 groups to the Newcastle disease virus 14 days after administration. Challenge each chicken of the 3 groups by the intramuscular route with not less than 10^5 EID_{50} of virulent Newcastle disease virus and note the degree of protection in the 2 groups vaccinated with Hitchner B1 strain Newcastle vaccine compared with the non-vaccinated group. The test is not valid if 1 or more of the non-vaccinated chickens does not die within 7 days of challenge. The degree of immune suppression is estimated from the comparative sero responses and protection rates of the 2 Hitchner B1 vaccinated groups.

The vaccine complies with the test if there is no significant difference between the 2 groups.

Increase in virulence. Carry out the test according to general chapter (2.7.17) using chickens from an SPF flock and not older than the minimum age to be 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. Administer to each chicken of the 1st group by eye-drop a quantity of the vaccine virus that will allow recovery of virus for the passages described below. Prepare 3 to 4 days after administration a suspension from the bursa of Fabricius 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 damage to the bursa of Fabricius using the material used for the 1st passage and the virus at the final passage. Administer the virus by the route to be recommended for vaccination likely to be the least safe.
The vaccine virus complies with the test if no indication of increasing 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 chickens and a subsequent repeat passage in 10 chickens, the vaccine virus also complies with the test.

Immunogenicity
A test is carried out for each route and method of administration to be recommended using in each case chickens not older than the minimum age to be recommended for vaccination. The quantity of 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. 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 10 chickens. Maintain not fewer than 10 chickens as controls. Challenge each chicken after 14 days by eye-drop with a sufficient quantity of virulent avian infectious bursal disease virus. Observe the chickens at least daily for 10 days after challenge. Record the deaths due to infectious bursal disease and the surviving chickens that show clinical signs of disease. At the end of the observation period, euthanise all the surviving chickens and carry out histological examination for lesions of the bursa of Fabricius.

The test is not valid if one or more of the following applies:
– during the observation period following challenge, fewer than 50 per cent of the control chickens show characteristic signs of avian infectious bursal disease;
– 1 or more of the surviving control chickens does not show degree 3 lesions of the bursa of Fabricius;
– during the period between the 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 disease nor degree 3 lesions of the bursa of Fabricius.

Batch test
Identification
When mixed with monospecific infectious bursal disease virus antiserum the vaccine no longer infects susceptible cell culture derived from SPF eggs (2.7.7) or embryonated hen eggs, 9 to 11 days old.
Duly validated molecular biology (NAT) technique can also be applied for identification of vaccine virus

Sterility (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.

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

Safety
Use not less than ten SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, of recommended age. According to the type of viral vaccine strain incorporated in the product - Invasive - Moderately invasive- it may be necessary to conduct the safety test on chicks possessing moderate level of maternal antibodies. Administer by eye drop to each chicken ten doses of the vaccine reconstituted so as to obtain a concentration suitable for the test. Observe the chickens for 21 days. If during the period of observation more than 2 chickens die from causes not attributable to the vaccine, repeat the test. The vaccine complies with the test if none of the chickens shows signs of the disease, if no chicken dies from causes attributable to the vaccine and if 21 days after inoculation of the vaccine, no chicken shows lesions of the bursa of fabricius.

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

Virus titre
Infectious Bursal Disease Vaccine, Live (using IBD Intermediate strain): Not less than $10^{3.0}$ $TCID_{50}/EID_{50}$ of the IBD virus titre per dose;
Infectious Bursal Disease Vaccine, Live (using IBD Intermediate plus Strain): Not less than $10^{2.0}$ $TCID_{50}/EID_{50}$ of the IBD virus titre per dose.
Determining the titre in cell cultures derived from SPF embryo or onto the chorio – allantoic membrane of SPF embryonated hen eggs between 9 to 11 days old.

Potency
The vaccine complies with the requirements of the test prescribed under Immunogenicity when administered by a recommended route and method. If potency test has been performed with satisfactory results on a representative batch of the vaccine, 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.