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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Infectious Chicken Anaemia, Live

Definition

Infectious chicken Anaemia Vaccine, Live is a preparation of a suitable strain of chicken anaemia virus. This monograph applies to vaccine intended for administration to breeder chicken for active immunization, to prevent excretion of virus, to prevent or reduce transmission through eggs and to protect passively their future progeny

Production

Preparation of vaccine

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

Substrate for virus propagation

Embryonated hen's 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*)*. Suitable cell line can also be used for virus propagation

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 is 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 safety, increase in virulence and immunogenicity may be used during the demonstration of safety and efficacy.

Safety

Carry out the test for each route and method of administration to be recommended for vaccination in chickens not older than the minimum age to be recommended for vaccination and from an SPF flock (2.7.7). Use vaccine virus at the least attenuated passage level that will be present in a batch of the vaccine.

General safety

For each test, use not fewer than 10 chickens. Administer to each chicken 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. 14 days after vaccination, collect blood samples from half of the chickens and determine the haematocrit value. Euthanise these chickens and carry out post-mortem examination. Note any pathological changes attributable to chicken anaemia virus, such as thymic atrophy and specific bone-marrow lesions. Observe the remaining chickens at least daily, for at least 21 days after vaccination. The

test is not valid if non-specific mortality occurs. The vaccine virus complies with the test if during the observation period no chicken shows abnormal signs of disease or dies from causes attributable to the vaccine virus.

Safety for young chickens

Use not fewer than twenty 1-day-old chickens from an SPF flock (2.7.7). Administer to each chicken by the oculo-nasal route a quantity of the vaccine virus equivalent to not less than the maximum titre likely to be contained in 1 dose of the vaccine. Observe the chickens at least daily. Record the incidence of any signs attributable to the vaccine virus, such as depression, and any deaths 14 days after vaccination, collect blood samples from half of the chickens and determine the haematocrit value. Euthanise these chickens and carry out post-mortem examination. Note any pathological changes attributable to chicken anaemia virus, such as thymic atrophy and specific bone marrow lesions. Observe the remaining chickens at least daily, for at least 21 days after vaccination. Assess the extent to which the vaccine strain is pathogenic for 1-day-old susceptible chickens from the results of the clinical observations and mortality rates and the proportion of chickens examined at 14 days that show anaemia (haematocrit value less than 27 per cent) and signs of infectious chicken anaemia on post-mortem examination. The results are used to formulate the label statement on safety for young chickens.

Increase in virulence

Carry out the test according to general chapter using 1-day-old chickens from an SPF flock (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 1st group by the intramuscular route a quantity of the vaccine virus that will allow recovery of virus for the passages described below. Prepare 7-9 days after administration a suspension from the liver of each chicken and pool these samples. Depending on the tropism of the virus, other tissues such as spleen or bone marrow may be used. Administer 0.1 ml of the pooled samples by the intramuscular route to each chicken of the next group. Carry out this passage operation not fewer than4 times; verify the presence of the virus at each passage. Ifthe virus is not found at a passage level, repeat the passage by administration to a group of 10 chickens. If the 5^{th}group of chickens shows no evidence of an increase in virulence indicative of reversion during the observation period, further testing is not required. Otherwise, carry out an additional safety test and compare the clinical signs and any relevant parameters in a group of at least 10 chickens receiving the material used for the 1st passage and another similar group receiving the virus at the final passage level. The vaccine virus complies with the test if no indication of increased virulence of the virus at the final passage level 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 for vaccination using chickens not older than the minimum age to be recommended for vaccination and from an SPF flock (2.7.7). The test for prevention of virus excretion is intended to demonstrate reduction of virus transmission to the egg through viraemia and virus excretion in the faeces. The quantity of the vaccine virus to be 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 vaccine.

Passive immunisation of chicken

Vaccinate according to the schedule to be recommended not fewer than 10 breeder chickens not older than the minimum age to be recommended for vaccination and from an SPF flock (2.7.7) keep not fewer than 10 unvaccinated breeder chickens of the same origin and from an SPF flock (2.7.7)as controls that have no contact with the vaccinated chickens. At a suitable time, after excretion of vaccine virus has ceased, collect fertilized eggs from the vaccinated and control breeder chickens and incubate them. Challenge at least 30 one -day-old chickens from each of the vaccinated and control groups by intramuscular administration of a sufficient quantity of virulent chicken anaemia virus. Observe the chickens at least daily for 14 days after challenge. Record the deaths and the surviving chickens that show signs of disease. At the end of the observation period determine the haematocrit value of each surviving chicken. Euthanise these chickens and carry out post-mortem examination. Note any pathological signs attributable to chicken anaemia virus, such as thymic atrophy and specific bone-marrow lesions.

The test is not valid if:

– the laying rate in the vaccinated and control breeder chickens is significantly different;

– during the observation period after challenge fewer than 90 per cent of the chickens of the control breeder chickens die or show severe signs of infectious chicken anaemia, including haematocrit value under 27 per cent, and/or notable macroscopic lesions of the bone marrow and thymus;

– and/or during the period between vaccination and egg collection more than 10 per cent of vaccinated or control breeder chickens show notable signs of disease or die from causes not attributable to the vaccine.

The vaccine complies with the test if during the observation period after challenge not fewer than 90 per cent of the chickens of the vaccinated breeder chickens survive and show no notable signs of disease and/or macroscopic lesions of the bone marrow and thymus.

Prevention of virus excretion

Vaccinate, according to the schedule to be recommended, not fewer than 10 chickens not older than the minimum age to be recommended for vaccination and from an SPF flock ((2.7.7) Maintain not fewer than 10 chickens of the same age and origin as controls that have no contact with the vaccinated chickens. At a suitable time after excretion of vaccine virus has ceased, challenge all the chickens by intramuscular administration of a sufficient quantity of virulent chicken anaemia virus. Collect blood samples from the chickens on days 3, 5 and 7 after challenge and faecal samples from the chickens on days 7, 14 and 21after challenge and carry out a test for presence of virus to determine whether or not the chickens are viraemic and are excreting the virus.

The test is not valid if:

– fewer than 70 per cent of the control chickens are viremic and excrete the virus at one or more times of sampling and/or during the period between vaccination and challenge more than 10 per cent of control or vaccinated chickens show abnormal clinical signs or die from causes not attributable to the vaccine.

The vaccine complies with the test if not fewer than 90 percent of the vaccinated chickens do not develop viremia or excrete the virus.

Batch tests

Identification
The vaccine, diluted if necessary and mixed with a monospecific chicken anaemia virus antiserum, no longer infects susceptible cell culture derived from SPF eggs (2.7.7) or egg from SPF flock (2.7.7) into which it is inoculated.
Duly validated molecular biology (NAT) technique can also be applied for identification of vaccine virus

Sterility/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 prescribed (2.2.11) Frozen or freeze-dried vaccines produced in embryonated eggs and not intended for administration by injection either comply 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 10 SPF chickens (2.7.7, Table 3) or healthy susceptible chickens, not older than the minimum age recommended for vaccination (2.7.7). Administer by a recommended route to each chicken 10 doses of the vaccine. Observe the chickens daily for 21 days. The test is not valid if more than 20 per cent of the chickens show abnormal clinical signs or die from causes not attributable to vaccine. The vaccine complies with the test if no chicken shows notable clinical signs of disease or dies from causes attributable to the vaccine

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

Virus titre. Titrate the vaccine virus by inoculating into suitable cell lines or eggs from SPF flocks (2.7.7) or in cell culture derived from SPF eggs (2.7.7). One dose vaccine contains not less than $10^{3.0}$ $TCID_{50}$; EID_{50} per dose.

Potency
The vaccine complies with the requirements of the tests 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.