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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Classical Swine Fever Vaccine, Live

Classical Swine Fever Vaccine, Live is a freeze dried preparation of a modified strain of classical swine fever virus, which is devoid of pathogenicity for the pig by adaptation either to cell cultures or to the rabbit. It is prepared immediately before use by reconstitution from the freeze dried vaccine with suitable diluents.

Production

Preparation of Vaccine

For vaccine prepared in rabbits, the seed-lot (or the vaccine) is prepared from the homogenised spleen and lymph nodes of rabbits sacrificed at the peak of temperature rise (104 to l06° F) following intravenous inoculation of the virus. The vaccine is freeze dried.
For cell culture vaccine, the virus is propagated in suitable cell culture. The viral suspension is harvested, titrated and mixed with a suitable stabilizing agent. The vaccine is then freeze dried. Cell cultures comply with the requirements for cell cultures for the production of vaccines for veterinary use (2.7.13)

Master seed lot

Choice of vaccine strain. A reference strain obtained from an authentic source shall be used for the vaccine production. Only a virus strain shown to be satisfactory with respect to identification, safety, test for extraneous pathogens, test for mycoplasma and potency may be used in the preparation of the vaccine.

Test for extraneous agent (2.7.19). Use method A or B.

A. The vaccine mixed with a mono specific antiserum does not cause cytopathic effects in susceptible cultures. The cells also show no evidence of the presence of haemadsorbing agents and the cell-culture fluids are free of haemagglutinating agents when tested with chicken erythrocytes.
B. Inject intracerebrally 30 µl of the vaccine, reconstituted in a manner that 1.0 ml contains one dose, into each of ten mice, weighing between 11 g and 15g. Observe the mice for 21 days. If more than two mice die within the first 48 hours, repeat the test. The mice show no abnormalities attributable to the vaccine within the third and twenty-first days after the injection.

Safety. Inject intramuscularly 10 times the minimum does stated on the label into each of 8 healthy piglets, between 10 and 12 weeks old, free from swine fever virus antibodies. Observe the animals for 21 days. Temperature curve should be normal and animals remain in apparent good health and display normal growth.

Test for reversion to virulence. If the source organization has carried out the test for reversion to virulence of vaccine strain it may be omitted. Otherwise carry out the following test.
Carry out the test, using piglets 6-10 weeks old that do not have antibodies against pestivirus (as determined by ELISA/ FAVN). 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 piglet of the 1st group by a route to be recommended a quantity of the vaccine virus equivalent to not less than the maximum virus titre likely to be contained in 1 dose of the vaccine. Collect an appropriate quantity of blood from each piglet daily between day 2 and day 7 after administration of the vaccine virus, and pool the samples taken on the same day. Administer 2 ml of the pooled blood with the highest virus titre by a route to be recommended to each

piglet of the next group. Carry out this passage operation not fewer than 4 times, verifying the presence of the virus at each passage. If no virus is found, repeat the test once. If virus is found, carry out a 2nd series of passages by administering 2 ml of positive blood by a route to be recommended to each piglet of a group of 10 animals. If the 5th group of animals 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 8 animals 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 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 2 animals and a subsequent repeat passage in 10 animals, the vaccine virus also complies with the test.

Immunogenicity. All the animals are healthy and must have had no contact with swine fever virus and serologically must be free from CSF and BVDV antibodies. Use 4 healthy piglets, 10 to 12 weeks old, for each of the 1/40 and 1/160 dilutions of a single dose of the vaccine prepared in a suitable diluents or buffer. Inject intramuscularly 1 ml of these dilutions into each of the piglets in respective groups. Use 2 healthy susceptible piglets of the same stock and age as control animal group.

After 28 days, inoculate intramuscularly with a sufficient quantity of the challenge virus in each vaccinated piglet and in each of the 2 unvaccinated control animals so that at least 1 of the two unvaccinated control animals dies within 7 to 14 days. Observe the vaccinated animals for 14 days. Calculate the number of PD_{50} contained in the vaccine by standard statistical methods from the number of animals, which survive without showing any signs of swine fever. The vaccine shall contains not less than 100 PD_{50} per dose. The test is not valid unless the control animals die within 7 to 14 days after inoculation. PD_{50} correlation studies with virus titres can replace the potency test on routine basis.

Batch tests

Identification

Lapinised vaccine. Administer 0.5 ml intravenously into one or more non-immunised rabbits, immunized either with an identical dose of a vaccine of the same type injected by the same route between 10 and 60 days before hand or with a sufficient dose of antiserum administered a few hours before the injection of the vaccine. 24 hours after the injection, start recording the temperature of the rabbits in the mornings and the evenings until the 5^{th} day after the injection. The immunised rabbits do not exhibit a rise in temperature of more than 1.5°. The test is not valid unless the non-immunised rabbits exhibit a rise in temperature of not less than 1.5°.

Cell culture vaccine. For non lapinised vaccines prepared in cell cultures, on administration to pigs immunised with the vaccine, specific neutralizing antibodies develop. Alternatively, a suitable method based on molecular or immunochemical techniques is also acceptable.

Bacterial and Fungal contamination (2.2.11). Complies with the test for sterility. Any diluents supplied with the vaccine complies with test for sterility.

Mycoplasmas (2.7.8). The vaccine complies with the test for mycoplasmas.

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

Virus titre. Not less than $10^{3.0}$ $TCID_{50}$ per dose (in Fluorescent Antibody test using CSFV monoclonal antibody).

Safety. The vaccine complies with the test for safety mentioned under seed lot.

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

Potency. The vaccine complies with the requirements of the test mentioned under Immunogenicity when administered according to the recommended schedule by a recommended route and method.

Cell culture vaccines can be alternatively tested for potency by virus neutralization in PK-15 cells by Fluorescent Antibody Test using following method.

As an alternate to determine the 100 PD_{50} content in each vaccine dose by challenge method, Fluorescent Antibody Virus Neutralization (FAVN) method can be used in which vaccinated animals are not to be challenged and instead 28 days post vaccinated sera to be used. Sera collected from both the vaccinated groups ($1/40^{th}$ dose and $1/160^{th}$ dose) and control are tested by FAVN in PK-

15 cells to measure virus neutralizing antibodies. Each vaccinated pig is considered to be protected if FAVN titre is greater than or equal to 10 and accordingly PD50 may be determined as per the calculations in challenge method. FAVN should be performed with PK-15 adapted virus**.** A vaccine passes the potency if it contains 100 PD_{50} which is equivalent to a virus titre of at least $10^{3.0}$ $TCID_{50}$ per dose

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. If 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 and, the virus titre is considered for a routine batch release

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 "the freeze dried vaccine shall be reconstituted with the diluent supplied" (4) the animal species for which the vaccine is intended; (5) storage temperatures; (6) Batch Number, Manufacturing date and expiry date; (7) Precautions in pregnant animals (If applicable); (8) Total volume or number of doses; (9) Minimum virus titre per dose of vaccine; (10) Dose of vaccine