Food and Agriculture Organization of the United Nations

WORLD ORGANISATION FOR ANIMAL HEALTH
Protecting animals, preserving our future

CRITERIA FOR RINDERPEST VACCINE MANUFACTURERS

These Criteria are applicable to facilities that wish to be part of the FAO-OIE roster of eligible rinderpest vaccine manufacturers. The mechanism to be followed by FAO and the OIE in assessing these facilities is described below.

The Good Manufacturing Practices (GMP) chosen as a reference standard for this document are those provided by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) [1]as it derives from the WHO GMP Guide and are also equivalent to the regulations in use in the European Union's GMP Guide and, currently, these documents are updated in parallel.

The Criteria provides a set of *Requirements* (conditions that are mandatory to be eligible) and *Recommendations* (aspects that are not mandatory but preferable).

There are two reasons for undertaking manufacture of rinderpest vaccine:

A. To expand or replenish vaccine stockpiles for improving preparedness

B. To produce vaccine supplies for immediate use in an ongoing, confirmed rinderpest emergency

A - CRITERIA FOR RINDERPEST VACCINE MANUFACTURERS (EXPANSION AND REPLENISHMENT OF ESTABLISHED RESERVES)

1. Facility, equipment and operation

REQUIRED

a. Good manufacturing practices (GMP) – the manufacturer must be in compliance with the standards of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) including the Guide to Good Manufacturing Practice for Medicinal Products and Annex 5 Manufacture of immunological veterinary medicinal products[2], as well as with the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual)[3] chapters pertaining to manufacturing and quality control of veterinary vaccines.

b. The facility must meet the international biosafety and biosecurity standards, as per the OIE Terrestrial Manual Chapters on Biosafety and biosecurity: Standard for managing

[1] https://www.picscheme.org/en/publications?tri=gmp
[2] https://www.picscheme.org/layout/document.php?id=1407
[3] http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/

biological risk in the veterinary laboratory and animal facilities, Principles of veterinary vaccine production, Rinderpest (infection with rinderpest virus), and Recommendations for the manufacture of vaccines as well as the PIC/S GMP Guide Annex 5.

c. The National Competent Authority should issue a pre-authorization for the production site-facility and the necessary regulatory approval for the vaccine, to allow the manufacturer to start production in case of an emergency – such as a fast track procedure.
d. Having a biosecure facility that can be committed to conduct Quality Control (QC) for in-batch and final batch testing, preferably on site.

   If not, there should be a procedure in place to safely transfer the vaccine to another location for the testing - in case of subcontracting the QC and batch release activities, it is important to have a contract in place between the two companies setting out the relevant roles and responsibilities. The facility in charge of QC should also be licensed or approved by the National Authority.

   The finished vaccine should be QC tested by an independent QC laboratory centre - the independent retest should be carried out in parallel with the company's batch release in order to save time in case of emergency.
e. The manufacturer should provide all the necessary information and contingency production plans to demonstrate its capacity to rapidly and safely switch production to begin manufacturing and testing rinderpest vaccine and scale up production in case of emergency.
f. Applying a 3-day personal quarantine of all involved technical staff members from contact with susceptible species during and immediately after the vaccine production campaign.
g. Having adequate cold chain storage capacity for quarantine and for released batches, dedicated to hold rinderpest vaccine prior to its shipment, with restricted access and controlled environmental conditions.
h. Having a dedicated space, equipment, and staff solely for vaccine production during the vaccine production campaign.

RECOMMENDED

a. Scale of production capacity should not be less than 5 million doses per week.
b. In production for replenishment of the reserve stock - having a BSL-3 animal facility to conduct the safety and efficacy testing in cattle, if testing in cattle is required for regulatory purposes, and with approval of FAO and OIE. In the case of emergency production, if the production and testing are taking place in the same country where the outbreak is happening, BSL-3 should not be required.
c. Manufacturers that produced rinderpest vaccine (in the past), have been or currently producing other morbilliviruses vaccine, i.e. PPR vaccine. Having experience in producing live virus vaccines in mammalian cell culture systems is an asset.

2. Personnel

REQUIRED

a. Having trained and qualified staff to provide oversight in charge of the vaccine production campaign. The manufacturer should keep training records for the staff responsible for production and quality control

3. Documentation

REQUIRED

a. Providing batch record of viral vaccine production. (bulk)
b. Provide a detailed procedure/plan for rinderpest vaccine production. (finished product)
   A dossier should be submitted to the FAO-OIE secretariat to describe the production process, quality control methods and quality assurance system containing the SOPs, batch production protocols, description of the areas and equipment to be used, validation procedures, and clinical, safety and efficacy evidence to be produced (or historical data).
c. The manufacturer should have validated procedures for packaging and shipping, following international standards.
d. Approval from the National Veterinary Authority must be granted and presented to the FAO-OIE Rinderpest Secretariat before undertaking measures to start production.
e. The country where the manufacturing facility is located should have an approved National Contingency Plan for rinderpest.
f. Manufacturers should send in advance information on all the pathogens they store or manipulate within the facility, and their GMP certificate, ISO accreditation, biosafety/security manual and any other relevant authorizations. A Site Master File (SMF) should be in place.

RECOMMENDED

a. The documentation that accompanies the vaccine packages (insert) should be provided in English. Capacity to produce inserts in other languages is an asset.

4. Seed

REQUIRED

a. A master seed for vaccine production, identified and made available by the FAO for each of the 2 strains, should be used as a reference. Master seeds are kept by the RHFs and sent to the manufacturing facility.

b. Passages from the master seed are limited to what is required in the OIE Terrestrial Manual Chapter *Rinderpest (infection with rinderpest virus)*[4].
c. Authorized strains are RBOK and LA-AKO (cf. OIE Terrestrial Manual chapter *Rinderpest (infection with rinderpest virus)*)

5. Cells and media

REQUIRED

a. For the purpose of this document, it is required to exclusively use Vero cell lines that are tested and designed for vaccine production, as referred by the OIE Terrestrial Manual, received from the FAO-OIE RHFs for vaccine production, in order to reduce the risk of contamination when using primary cells (cf. OIE Terrestrial Manual chapter *Rinderpest (infection with rinderpest virus*)). The Vero cell origin should be from an authorized master seed stock that is subject to standardised quality assessment and quality control (all certificates should be provided in the dossier).
b. Foetal and calf bovine sera and other ingredients of animal origin should be sourced from FMD-free, BSE-negligible risk countries, and tested for freedom from BVD virus and BVD viral antibodies, and any other adventitious viruses.

6. Final product

REQUIRED

a. The vaccine should be freeze-dried to maximize the shelf life of the vaccine
b. The vaccine should be tested for identity, purity and potency (*in vitro*) according to requirement described in the OIE Manual chapter *Rinderpest (infection with rinderpest virus)*.
c. The vaccine should have, at least, two years of initial shelf-life and should be tested for stability throughout this period by the RHF Category B that is holding it. After this period, the vaccine can be tested and its shelf life extended, if still meets the quality standard for potency and sterility. Such extension must be authorized by FAO and the OIE, and this procedure should be done by the RHF- Category B that is holding the vaccine.
d. The vaccine should be supplied with the appropriate diluent, produced or recommended by the manufacturer

[4] http://www.oie.int/fileadmin/Home/eng/Health_standards/tahc/current/chapitre_rinderpest.pdf

MECHANISM FOR SELECTION OF A MANUFACTURING FACILITY

1. Rinderpest Holding Facilities that are interested in augmenting their vaccine stocks would initiate a call for proposals.
2. Manufacturers can apply by filling in the FAO-OIE application form and submitting a dossier to the Selection Committee of which the RHF and the FAO-OIE Rinderpest Secretariat are a part of.
3. The applications will be evaluated against the criteria listed above by a Selection Committee of which the RHF, and the FAO-OIE Rinderpest Secretariat are a part of.
4. On-site inspections will be performed to assess the most highly qualified candidates. National regulatory authorities should be aware of, and involved in, the inspection process.

   Expert team composition: GMP expert(s); viral vaccine production expert(s); biorisk expert; national regulatory authority.

B – CRITERIA FOR EMERGENCY PRODUCTION

In the event of a confirmed emergency, it may be necessary to rapidly increase vaccine production.

Countries and Intergovernmental Agencies may request additional manufacturers to begin production, and additional manufacturers may, independently, wish to begin production to meet the increased need. It will be necessary to accelerate the approval process for admission to the roster to facilitate additional manufacturers' efforts to help control what will be a rapidly evolving animal health emergency.

As in the Criteria for replenishment, facilities are expected to pay close attention to Requirements, and it is anticipated that most Requirements will be met. Applications will be reviewed by FAO and the OIE on a case-by-case basis. In addition, Recommendations will be adapted as described below.

It should be noted that, in an emergency situation, FAO and OIE may waive the requirement for third-party in-batch and final batch testing, in parallel with the manufacturer's batch release. However, prior to release, samples form batches should be kept for post-release quality testing by a third party. The master and production seed should have the documentation to prove having been extensively tested under standardised quality assessment and quality control. Third-party facilities performing quality control must be licensed or approved by their National Competent Authority.

If production process, quality control and quality assurance SOPs, and batch production protocols are to be adapted from existing documents for other vaccines, FAO may assist in this, if appropriate.

1. Facility, equipment and operation

REQUIRED

a. Good manufacturing practices (GMP) – the manufacturer should be in compliance with an internationally recognised GMP standard for medicinal or veterinary products, and with the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual)[3] chapters pertaining to manufacturing and quality control of veterinary vaccines.
b. The facility should meet the international biosafety and biosecurity standards, as per the OIE Terrestrial Manual Chapters on *Biosafety and biosecurity: Standard for managing biological risk in the veterinary laboratory and animal facilities*, *Principles of veterinary vaccine production*, *Rinderpest (infection with rinderpest virus)*, and *Recommendations for the manufacture of vaccines*.
c. The National Competent Authority should issue an authorization for the manufacturer to start production, regulatory authorization of the production site facility and the vaccine

d. Having the capacity, and appropriate technical experience and expertise, to rapidly and safely begin manufacturing rinderpest vaccine, demonstrated by previous or current production of live viral vaccines in the facility.
e. Applying a 3-day personal quarantine of all involved technical staff members from contact with susceptible species during and immediately after the vaccine production campaign.
f. Having space, equipment and staff that can be dedicated solely for rinderpest vaccine production during the vaccine production campaign.

2. Personnel

REQUIRED

a. Having trained and qualified staff to provide oversight in charge of the vaccine production campaign

3. Documentation

REQUIRED

a. Providing batch records of viral vaccine production.
b. Providing an outlined procedure/plan for rinderpest vaccine production. A dossier should be submitted to the FAO-OIE secretariat to describe the production process, quality control and quality assurance SOPs, batch production protocols, validation procedures, and description of the areas and equipment to be used; and clinical, safety and efficacy evidence that will be produced (or historical data).
c. The manufacturer should have validated procedures for international packaging and shipping or adopt third-party procedures in consultation with FAO.
d. Support from the National Competent Authority should be granted and presented to the FAO-OIE secretariat before undertaking measures to start production.
e. The country where the manufacturing facility is located should have an approved National Contingency Plan for exotic animal diseases.
f. Manufacturers should send information on all the pathogens they store or manipulate in the facility, and their GMP certificate, ISO accreditation, biosafety/security manual and any other relevant authorizations. A Site Master File (SMF) must be in place.

4. Seed

REQUIRED

a. A FAO approved master seed will provided by a FAO-OIE RHF from which the manufacturer will make the working seeds.
b. Passages from the master seed are limited to what is referenced in the OIE Terrestrial Manual Chapter on infection with rinderpest virus.

c. Authorized strains are RBOK and LA-AKO (cf. OIE Terrestrial Manual chapter *Rinderpest (infection with rinderpest virus)*). Only working seeds made from a master seed provided by a FAO-OIE RHF can be used for vaccine production.

5. Cells and media

REQUIRED

a. It is required to exclusively use Vero cell lines, as referred by the OIE Terrestrial Manual, sourced from an FAO-OIE approved master seed stock. Primary cells must not be used, to reduce the risk of contamination (cf. OIE Terrestrial Manual chapter *Rinderpest (infection with rinderpest virus)*).
b. Foetal and calf bovine sera and other ingredients of animal origin should be sourced from FMD-free, BSE-negligible risk countries, and tested for freedom from BVD virus and BVD viral antibodies, and any other adventitious viruses.

6. Final product

REQUIRED

a. The vaccine should be freeze-dried.
b. The vaccine should be tested for identity, purity and potency (*in vitro*) according to what is described on the OIE Manual chapter *Rinderpest (infection with rinderpest virus)*.
c. The vaccine should be expected to have at least two years of initial shelf-life.
d. The vaccine should be supplied with the appropriate diluent.

MECHANISM FOR EMERGENCY PRODUCTION

1. Upon an emergency caused by rinderpest reoccurrence, FAO and/or the affected country may release a call for emergency vaccine production.
2. Any vaccine manufacturer that is not part of the established roster can apply by following the instructions in the FAO-OIE Emergency Rinderpest Vaccine Manufacture application form and submitting a dossier application to the FAO-OIE Rinderpest Secretariat. In an emergency situation, inability to initially meet some requirements should not present a barrier to admission to the roster. Each application will be reviewed on its own merit.
3. If some documents (e.g. approval from the National Competent Authority) are pending, the dossier should be submitted with a note that the document is pending, to avoid delays in starting the process.
4. The dossier will be evaluated by the FAO-OIE Rinderpest Secretariat and/or their appointed advisor(s) according the criteria listed above. A fast-track inspection may be organized by FAO and OIE. The inspection team will be appointed by the Rinderpest

Secretariat. In some circumstances (e.g. FAO/OIE familiarity with the facility and its environ) the inspection may be waived at FAO and OIE discretion.