Government of India
Ministry of Fisheries, Animal Husbandry and Dairying
Department of Animal Husbandry and Dairying

Krishi Bhawan, New Delhi
Dated 09th May 2023

Office Memorandum

Subject: Seeking Public Comments on the proposed draft for amendment in Guidelines for conducting clinical trial / field trial of Biologicals (vaccines) and Drugs for Veterinary use– reg.

Sir/Madam,

This Department (DAHD) invites comments/ suggestions on the draft amendment.

The comments/ suggestions may be sent at the following e-mail IDs – sharma.aruna@gov.in, sudam29ovc@gmail.com.

The comments/inputs/feedback may be submitted within 21 days from the date of publishing the draft.

Meeting of the subcommittee to develop the guidelines for field trial for veterinary drugs and vaccines

Guidelines for conductingclinical trial / field trial of Biologicals and Drugs for Veterinary use

Preamble

As per The Drugs Rules, 1945thereunder, 'New Drugs' are subjected to clinical trials before being licensed for marketing in India and the 'New Drugs' for veterinary use are also covered under the said Act & Rules. Therefore, the clinical Trial / field trial in target species ismandatoryto prove/ establish safety and efficacy of New Drugs/Biologicals for veterinary use before commercialization in India.

Objective of this document is to provide guidance on

1. Prerequisites for clinicalTrial / field trial of Veterinary biologicals and drugs and regulatoryprocess for the trial
2. Designing of study protocol and conducting field trials for veterinary biologicals and drugs in the target species.
3. Approval process of the clinical Trial / field trial for Veterinary biologicals and drugs.

The guideline is written in two volumes as under.

Volume 1 provides guidelinesfor conducting clinical trial/ Field trial of vaccines forVeterinary use.

Volume 2 provides guidelines for conducting clinical trial/Field trial of bio-therapeutics including recombinant monoclonal antibodies, non-recombinant polyclonal antibodies / serum for parenteral application, bio-similars for Veterinary use and pharmaceutical Drugs for Veterinary use.

Note: These guidelines are not exhaustive and may be modified further through additional guidelines or amendments, if considered necessary.

Volume 1

Guideline for conducting clinical trial / field trial of Vaccines for Veterinary use (D2)

Details	Version No.	Date
Draft submitted for stakeholder's consultation	D1	22.09.2022
Draft submitted for public consultation	D2	
Draft submitted to ECAH and CDSCO		
Approved by ECAH		
Approval by CDSCO		
Effective date		

CONTENTS

1. INTRODUCTION

Volume 1 of the guideline is pertaining to vaccines for Veterinary use. This document shall be adopted as guidance while performing clinical/ field trial for veterinary vaccines. This document replaces the field trial section (page No 87 to 92) of'Guidance for Industry Document for Veterinary Biologicals in India' while performing field/ clinical trial for Veterinary vaccines.The efficacy and safety of veterinary vaccines shall in the first instance normally be demonstrated by experiments under laboratory conditions. It is also stated that, only when efficacy cannot be demonstrated by laboratory trials, field efficacy trials may be appropriate, if it is scientifically justified and also accepted by the competent authorities. Deviations from these guidelines may be acceptable provided they are scientifically justified and accepted by the competent authorities. The guidance should be followed for veterinary vaccines intended for use in food-producing animals, equines, camels, companion animals and in avian species.

It is directed at all individuals and organizations involved in the design, conduct, monitoring, recording, auditing, analysis and reporting of clinical / field studies in target species to ensure that such studies are conducted and documented in accordance with the principles of Good Clinical Practice (GCP). GCP is intended to be an international ethical and scientific quality standard for designing, conducting, monitoring, recording, auditing, analyzing and documenting clinical studies for evaluating veterinary vaccines. Compliance with this standard provides public assurance about the integrity of the clinical trial data, and that due regard has been given to animal welfare and protection of the personnel involved in the study, one health aspects, the environment and the human and animal food chains.Currently, CDCSO does not have any system to give accreditation for animal trial centers for GCP. In the absence of any such system, the documentation, data storage and trial implementation shall be as per the suggestions as mentioned in 'principles of GCP' section of this document.

All the applicationsregarding vaccine licensing including clinical trial / field trialapplication are to be sent to Central Drugs Standard Control Organization (CDSCO). For vaccines involving New Strain/ Exotic Pathogen NOC from Department of Animal Husbandry and Dairying (DAHD) is to be obtained through CDSCO.

This document is meant for guidance of the stakeholders for developing field trial / clinical trial data, which is intended for regulatory submission, and obtaining approval as per the Drugs Rules, 1945.Subject Expert Committee (SEC) shall also use this guideline to evaluate the study protocol and study results.

2. SCOPE

This guidance is intended to assist applicants in finding out the pre-requisites for clinical trial / field trial, filling and submitting an 'Application for a Clinical trial/ Field Trial', conducting clinical trial/ field trial and to provide insight into approval process of clinical/ field trials for Veterinary Vaccines. Further, the scope of this guidance is to advise on performing field trials with veterinary vaccines, the criteria to be taken into account, besides what outcomes are expected and how the data shall be analyzed. Subject Expert Committee (SEC) shall also use this guideline to evaluate the study protocol and study results.

3. DEVELOPMENT PROCESS FLOW

The development process flow for Veterinary Vaccines shall follow the below mentioned steps.

I. Research And Development

1. Veterinary vaccine development begins with strain development, process development of Drug Substance(DS), process development of Drug Product(DP) and analytical testing development.
2. Immunogenicity/ Potency, Safety and non-reversal to virulence (wherever it is applicable) shall be performed in target species and / or in animal model as per the details mentioned in Indian Pharmacopoeia under the section production in each monograph.

   Indian Pharmacopoeia detailsquality standards and testing requirements of seed lots. Part of developmental testing includes target animal safety testing and potency testing. Industry shall follow the IP monographs for performing the target animal safety and potency testing.

   Similarly, Non-reversal to virulence testing for live attenuated or live modified vaccine shall be performed as mentioned in IP.

   For the Veterinary vaccines which do not have IP monograph, general monograph of IP on veterinary products or monographs from other pharmacopoeia such as BP or Ph. Eur. can be used as reference. If the specific IP monograph does not mention any 'target

animal safety testing' under the section 'production', the 'target animal safety testing' as mentioned in general monograph can be followed.

The target animal safety testing, if performed as mentioned in IP during development stage, sufficient information on the formulation safety is generated. Therefore, a separate pre-clinical toxicology (PCT) study is not a mandatory requirement in normal circumstances for any Veterinary vaccines (except for recombinant vaccines). However, subject expert committee can decide on the requirement of a separate PCT study in specific cases where the environmental safety or zoonotic risk is perceived or the safety data provided in the development dossier is not as per IP requirement.

3. The developmental safety and potency/ Immunogenicity test can preferably be done using a formulation manufactured from master seed lot.

II. Manufacturing Of Batches For Clinical Trial/ Field Trial Purpose

1. Three clinical trial batches shall be manufactured at a facility after obtaining Licensein **Form 29** to manufacture the veterinary vaccines for purposes of examination, test or analysisissued by the concerned State Licensing Authority. Clinical trial batches shall be manufactured following the cGMP guidelines.
2. The clinical trial batchesshallbe sent to the testing laboratory for testing and analysis of the veterinary vaccine. (Testing at the labs and application to conduct clinical/field trial shall be parallel activities if the applicant intends to expedite the development).

III. Application To Conduct Field/Clinical Trial Or To Obtain Permission To Import Or Manufacture a New Veterinary Vaccine In The Country

1. An application shall be submitted to CDSCO in **Form- 44** along with a requisite fee and documents as prescribed in Schedule Y of The Drugs Rules, 1945for grant of permission to import or manufacture a new veterinary vaccine or to undertake clinical trial/ field trial for the veterinary vaccine which is to be imported or manufactured first time in the country or to conduct field/clinical trial in the country.

   Note:

- The applicant, in case of commercial setting, may be the company and in case of academics setting may be the Principal Investigator (PI) or a Veterinarian who shall be overall responsible for the conduct of the Field trial/Clinical trial.
- Details of the proposed license holder (i.e. the name, address and contact details of the applicant) shall be mentioned in the application with whom CDSCO can correspond. If the trial is being undertaken by an investigator at the request of a sponsor, the name, address of the sponsor should be provided, together with the name, address and contact details of the trial director with overall responsibility for the conduct of the trial.
- Submission of physical application in hard copies and soft copies shall be submitted to CDSCO. CDSCO is also developing an online portal for trial application of veterinary products and the same will be notified as and when the portal becomes functional. Apart from providing all the required details in the **Form-44** of The Drugs Rules, 1945 below mentioned specific details shall be part of the application. If any of the data is not available, a proper justification shall be provided.
    1. Developmental safety and efficacy/ potency study results (in compliance with Indian Pharmacopeia)
    2. Qualification of analytical testing procedures of DS, DP and clinical trial samples
    3. Detailed study plan of clinical/ field trial containing all the details mentioned in this document.
    4. Field trial sites may be included as per the requirements of animal ethical committeeDAHD and CDSCO.

2. Application for field trial, approval from testing laboratories and animal ethical approval can be parallel activities.
3. The applicant should obtain NOC from RCGM for recombinant vaccines, before initiating the clinical/ field trials.
4. The application may be referred to Subject Expert Committee (SEC) of CDSCO or Department of Animal Husbandry and Dairying (DAHD),as applicable for detailed deliberation before grant of permission by DCG(I)/ CDSCO.

5. The permission is granted by DCG(I) for the conduct of clinical trial / field trial or to obtain permission to import (**Form-45**) or to manufacture (**Form 46**) of new veterinary vaccine in the country as the case may be.
6. A proforma of the Form 44, Form 45 and Form 46 is provided in Annexure-1, 2 & 3.
7. For import and conduct of clinical trialsof new veterinary vaccines, an overseas manufacturing site and the vaccines to be imported shall be registered with the CDSCO in **Form 41**. An application in **Form 40** shall be submitted by the Indian Agent authorized by the overseas manufacturer.
8. For import of Vaccines for the purpose of test and Analysis etc as well as conduct of clinical trials, the applicant may apply in Form 12 along with requisite fee and documents as prescribed in the Drugs Rules, 1945. to CDSCO. After satisfying the requirements, the CDSCO may consider the application for grant of Test Licence in Form 11 for the purpose of testing/study.
9. A proforma of the Form 40, Form 41 and Form 8, Form 10, Form 11 and Form 12 are provided in Annexure-4, 5, 6, 7, 8 and 9.

IV. Conducting Field/ Clinical Trial And Submitting The Data To CDSCO

1. The applicant shall conduct the field trial after obtaining permission from DCG(I) under the provisions of The Drugs Rules, 1945.
2. After completion of the study, the field trial results shall be submitted to CDSCO for further deliberation by SEC / standing ECAH sub-committee for veterinary biologicals, DAHD.The trial results may be submittedto CDSCO as per the format provided in Appendix II of Schedule Y of Drugs Rules, 1945.
3. The applicant may be invitedfor deliberation with SEC on the study results, etc.
4. The data of the clinical trial/ field trial may be consideredfor obtaining permission for import or manufactureof the veterinary products for marketing in the country as per procedure as laid down in the The Drugs Rules, 1945.

V. Import License Or Manufacturing License For Marketing Of New Veterinary Vaccine In The Country:

1. Initially, an applicant shall obtain permission from CDSCO in **Form 45** / **Form 46** to import or manufacture a New Veterinary Vaccine respectively in the country.

a. For import and marketing of new veterinary vaccine:

1. After obtaining permission to import new veterinary vaccine in **Form 45** from DCG(I), the authorized agent of the foreign manufacturer shall submit an application to CDSCO in **Form 40** along with requisite fee and data as prescribed in Schedule DI and Annexure C of Schedule DII of The Drugs Rules, 1945for registration of the foreign manufacturing site and their vaccine. The application shall be submitted to CDSCO.
2. After satisfactory review of data by CDSCO, Registration Certificate in **Form 41** is granted to the applicant for registration of the applied foreign manufacturing site and their vaccine.
3. Once, Registration Certificate in **Form 41** is issued by DCG(I), The importer shall submit application in Form 8 along with requisite fee and information as prescribed and obtain Import License in **Form 10** for import and marketing of the veterinary vaccine manufactured by the registered foreign manufacturer for import and marketing the products in the county. The application shall be submitted through online sugam portal viz. 'cdscoonline.gov.in'.
4. The first three batches of the veterinary vaccines shall be sent to testing laboratories for evaluation before marketing the product in the country.

b. For manufacturing and marketing of new veterinary vaccine:

1. After obtaining permission to manufacture new veterinary vaccine in **Form 46** from DCG(I), the manufacturer shall submit an application to the concerned State/ UT licensing Authority to obtain Manufacturing License in **Form 28 D** or Loan License in **Form 28 DA**.
2. For the said purpose, an application in **Form 27D** or **27DA** shall be submitted along with requisite fee and documents as perthe Drugs Rules, 1945. to the concerned State/ UT licensing Authoritywith a copy to respective CDSCO zonal office and HQ, New Delhi.

3. After satisfactory review of data by the Licensing Authority, an inspection has to be carried out at the manufacturing premises to verify the GMP compliance by way of joint inspection both by State Licensing Authority and CDSCO.
4. Based on the satisfactory report of inspection, the licensing authority shall prepare a Manufacturing License in **Form 28 D** or Loan License in **Form 28 DA** as the case may be and forward the same to CLAA i.e. DCG(I) for approval.
5. After CLAA approval by DCG(I), The concerned State licensing authority shall issue manufacturing License to the firm in **Form 28 D** or Loan License in **Form 28 DA** for marketing of the applied veterinary vaccine in the country.
6. The first three batches of the veterinary vaccines shall be sent to testing laboratories for evaluation before marketing the product in the country.

All the steps shall be covered if the product is developed indigenously. In some instances, the development can occur in more than one organization with technology transfer between the organizations.

4. Clinical trial requirements for imported Vaccines:

Wherever applications are made to CDSCO and are referred to DAHD,'Standing ECAH regulatory subcommittee on veterinary biological and drugs' in DAHD examines the application. Based on the committee's suggestions, DAHD provides CDSCO with appropriate recommendations. CDSCO will advise the applicant to conduct clinical / field trials based on the recommendation of the standing ECAH regulatory Subcommittee. The applicant shall import vaccines for testing based on the approval from CDSCO as mentioned in above development process flow and conduct clinical trial.

NOC from Review Committee on Genetic Manipulation (RCGM) shall be obtained for all recombinant vaccines including live recombinant vaccines. NOC from Genetic Engineering Appraisal committee (GEAC) shall also be obtained for live recombinant vaccines containing Genetically Modified Organisms (GMO).

CDSCO will refer the application to DAHD (and 'Standing ECAH regulatory subcommittee on veterinary biological and drugs') only when the imported vaccine contained new strain/ new manufacturing technology (live, Inactivated, Sub-unit, vectored vaccine, recombinant vaccine, etc) or it is an entirely new vaccine compared to already licensed vaccines in India.

5. **Laboratory immunogenicity / Potency studies**

These trials are performed during the product development stage and Indian Pharmacopoeia details quality standards and testing requirements of seed lots.Part of seed lot testing includes immunogenicity / potency testing.The applicant shallrefer the appropriate sections of Indian Pharmacopoeia for performing the Immunogenicity / Potency testing. The results shall be included in the clinical trial / field trial application dossier.

If the vaccine seed is obtained from atechnology provider, the manufacturer can utilize some of the seed characterization data of the technology provider.However, the vaccine developed by the technology provider shall be in compliance with the requirements as prescribed in the Drugs Rules, 1945. Industry might not have to repeat experiments such as Potency or Sero-conversion tests, if the data generated by the technology provider are as per IP monographs. However, industry need to do other characterizations such as sterility/ purity testing, Mycoplasma testing, extraneous virus testing, Identity testing, etc, (as applicable) which are to be performed on every lot of the virus/ bacterial / cell banks.

6. **Pre-clinical toxicology trials**

Indian Pharmacopeia detailsquality standards and testing requirements of seed lots.Part of seed lot testing includes target animal safety testing. The applicant shall refer the appropriate sections of Indian Pharmacopoeia for performing the target animal safety testing. The results shall be included in the clinical trial / field trial application dossier.

Similarly, Non-reversal to virulence testing for live attenuated or live modified vaccine shall be performed as mentioned in IP.

For the Veterinary vaccines which do not have IP monograph, general monograph of IP on veterinary products or monographs from other pharmacopoeia such as BP or Ph. Eur. can be used for reference. If the specific IP monograph does not mention any ‘target animal safety testing’ under the section ‘production’, the ‘target animal safety testing’ as mentioned in general monograph can be followed. The target animal safety testing, if performed as mentioned in IP during the development stage, sufficient information on the formulation safety is generated. This study can be considered as pre-clinical toxicology study for all the regulatory purpose. Therefore, a separate pre-clinical toxicology study is not a mandatory requirement in normal circumstances for any non-recombinant veterinary bio-pharmaceuticals. However, Subject expert

committee can decide the requirement of a separate PCT study in specific cases where the environmental safety or zoonotic risk is perceived or the safety data provided in the development dossier is not as per IP requirement.

If the vaccine seed is obtained from a technology provider, the manufacturer can utilize some of the seed characterization data of the technology provider. However, the vaccine developed by the technology provider shall be in compliance with the requirements as prescribed in the Drugs Rules, 1945. Industry might not have to repeat experiments such as Safety test and test for non-reversal to virulence, if the data generated by the technology provider are as per IP monographs. However, industry need to do other characterizations such as sterility/ purity testing, Mycoplasma testing, extraneous virus testing, Identity testing, etc(as applicable) which are to be performed on every lot of the virus/ bacterial / cell banks.

6.1.Recombinant vaccines:

Pre-clinical toxicology study for recombinant vaccines are performed as per the regulations of Review Committee for Genetic Manipulations (RCGM).

7. New drug definition and clinical trial/ field trial requirement

As per rule 122E of The Drugs Rules, 1945,

Definition of new drug.- For the purpose of this Part, new drug shall mean and include

a. A drug, as defined in the act including bulk drug substance [or phytopharmaceutical drug] which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labelling thereof and has not been recognized as effective and safe by the licensing authority mentioned under rule 21 for the proposed claims:Provided that the limited use, if any, has been with the permission of the licensing authority.
b. A drug already approved by the Licensing Authority mentioned in Rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration.
c. A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio,

or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz. indications, dosage, dosage form (including sustained release dosage form) and route of administration. (See items (b) and (c) of Appendix VI to Schedule Y.)

Explanation.- For the purpose of this rule–

(i) all vaccines and Recombinant DNA (r-DNA) derived drugs shall be new drugsunless certified otherwise by the Licensing Authority under Rule 21;

(ii) a new drug shall continue to be considered as new drug for a period of four years from the date of its first approval

Veterinary Vaccines are considered as New Drugs and clinical/ field trials can be conducted with the approval from CDSCO.

Clinical trial are generally required to be conducted for those veterinary vaccines which have not been tested or used for veterinary purpose, as per rules.If a vaccine using same strain and manufacturing technology (live, inactivated, sub-unit, vectored vaccine, recombinant vaccine, etc) was approved earlier by CDSCO for any company, the next company which is manufacturing the vaccine with same strain for same indication does not require to perform extensive clinical trial. An abbreviated study is sufficient in such cases. An abbreviated study shall address the safety and efficacy (or correlate of protection such as sero-conversion) of the vaccine in a single study using smaller number of animals (50 to 100 animals in total).The test group of animals shall be compared with reference group and/or placebo group of animals. Statistical significance or non-significance, as the case may be, shall be calculated at 90% confidence interval level using ANOVA or any other suitable method.

If the technology provider does the clinical/ field trial, the trial data of the technology provider can be used by the manufacturer for getting the product license. However, the trial should have been performed by the technology providerin compliance with the procedures as prescribed inThe Drugs Rules, 1945.

Academic field trial:However, no permission for the conduct of clinical/ field trial intended for academic purposes in respect of approved drug formulation shall be required for any new indication or new route of administration or new dose or new dosage form where, subject to the provisions of sub-rule 5, the data generated is not intended for submission to licensing authority.

A field trial of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a trial are intended to be used only for academic or research purposes and not for seeking approval of the Central Licencing Authority or regulatory authority of any country for marketing or commercial purpose.

(1) No permission for conducting an academic field trial shall be required for any drug from the CDSCO where,—

i. the field trial in respect of the permitted drug formulation is intended solely for academic research purposes for a new indication or new route of administration or new dose or new dosage form; and

ii. the field trial referred to in clause (i) has been initiated after prior approval by the Animal Ethics Committee for field trial; and

iii. the observations generated from such field trial are not required to be submitted to the CDSCO; and

iv. the observations of such field trial are not used for promotional purposes.

(2) In the event of a possible overlap between the academic field trial and field trial or a doubt on the nature of study, the animal Ethics Committee concerned shall inform the CDSCO in writing indicating its views within thirty working days from the receipt of application to that effect. The CDSCO shall, after receiving the communication from the Animal Ethics Committee referred to in sub-rule (2), examine it and issue necessary clarification, in writing, within thirty working days from the date of receipt of such communication: Provided that where the CDSCO does not send the required communication to such Animal Ethics Committee within thirty working days from the date of receipt of communication from the said Animal Ethics Committee, it shall be presumed that no permission from the CDSCO is required.

Academic research which is performed in clinical settings or farms using a licensed product does not require permission from CDSCO. For eg. Academic research to evaluate human BCG vaccine in cattle, dose titration experiments, checking the efficacy of vaccine in another species of animal, evaluating human drugs in animals (such as Cancer drugs / therapeutics), etc. The investigator can perform the trials using a licensed product with the approval of research committee of the institution, Animal Ethical Committee, Owner's consent and Bio-safety committee or any other statutory bodies as applicable. The trial shall be approved by the IAEC of the institution / CRO which is performing the trial. For

approval of experimentation on large animals (species above of rodents and Lagomorpha) eg. Dogs, Cat, Sheep, Goats, Cattle, Horse, Pony, Mule, Pig, Monkey, etc., the case is required to be forwarded to CCSEA in prescribed manner with recommendation of IAEC as per the provisions under the prevention of Cruelty to Animals (PCA) Act, 1960. The trial on poultry shall be approved by IAEC.

Though, non-recombinant oral veterinary formulations containing pre/probiotics organisms or native proteins/ extractsfrom milk, colostrum, egg, liver and blood (Eg, Albumin, Globulin, lecithin, collagen, liver extract,etc) can be considered as feed supplements, DAHD might in future expect the manufacturers to perform laboratory animal safety test at least from representative batches when the oral formulationis indicated for large animals and companion animals.

8. Manufacture of test batches for field trials /clinical trial

Testbatch shall be manufactured in a cGMP facility, which complies with the schedule M of The Drugs Rules, 1945. The field trial material can be produced in a pilot facility and in a smaller scale compared to the commercial batches.

The test batch shall be released for trial by the testing laboratory.

9. Application for field trial/ clinical trial

Field trial/ clinical trial part of the regulatory path starts with ‘application for field trial/ clinical trial’ in form 44 of CDSCO as mentioned above. In a commercial setting, the applicant may be the company with overall responsibility for the conduct of the trial. In an academic or practice setting, the applicant will usually be the principal investigator or veterinarian responsible for the conduct of the trial. Details of the proposed license holder (i.e. the name, address and contact details of the applicant with whom CDSCO shall correspond) shall be given. If the trial is being undertaken by an investigator at the request of a sponsor, the name, address of the sponsor should be provided, together with the name, address and contact details of the trial director with overall responsibility for the conduct of the trial.

Physical application in hard copies and soft copies in CD/Pendrive shall be submitted to CDSCO. CDSCO is also developing an online portal for trial application of veterinary products and the same will be notified as and when the portal is functional.

Application for field trial, approval from testing laboratories and animal ethical approval can be taken up asparallel activities, if the applicant wishes to expedite the process. In such circumstances, the applicant might get conditional approval from various agencies. However, the applicant shall initiate the trial after receiving all the approvals.

10. The study Personnel

10. 1. The Investigator / Study Director

- An investigator is the individual responsible for all aspects of the conduct of the study. These would include: the dispensing and the administration of the investigational and control veterinary vaccine, the implementation of the study protocol, the collection and reporting of the study data and the protection of the health and welfare of the personnel involved in the study and the animals during the study.
- The investigator should be familiar with the background and requirements of the study before taking receipt of the investigational veterinary vaccine.
- A brief curriculum vitae of the investigator / trial director responsible for the conduct of the trial should be provided. The purpose of this information is to ensure that the person concerned has the appropriate qualifications, knowledge and expertise to oversee the conduct of the trial and ensure compliance with any conditions attaching to the CDSCO license. The information is expected to assist the CDSCO in judging the feasibility of the proposed trial.

Qualifications of the investigator:

- Veterinarian with BVSc degree (BVSc & AH or BVSc recognized by Veterinary Council), preferably having MVSc, having good scientific knowledge and with minimum two years expertise in field trials/ clinical trial/ animal experimentations.Otherwise, the investigator's team should consist of qualified veterinarian with abovementioned experience.
- The investigator may be assisted by trained competent staff in collecting, recording and the subsequent processing of data. If a study is conducted by a group of

individuals, the investigator shall be the leader of the group.It should be the responsibility of the investigator to maintain record of brief curriculum vitae of all the study personnel involved in field trial/clinical trial.

- An individual should not serve as both the investigator and the monitor of any one study.
- If veterinarians, other than those already listed in study plan, are to be engaged to perform follow up actions in relation to any adverse reactions that might occur as a result of treatment with the test veterinary vaccine or in relation to the supervision of animal welfare during the conduct of a trial, their names, addresses and contact details should be provided. This information aids the SEC in following up on any pharmacovigilance matters relating to the conduct of the trial.
- If there is any change in the study team, the same shall be included as part of study plan amendment

Responsibilities of the investigator:Responsibilities of the investigator is defined in Schedule Y of The Drugs Rules, 1945. An undertaking as per APPENDIX VII of Schedule Y shall be submitted by Investigator.

The investigator is responsible for:

- Submit all documentsto the sponsor, before the study is initiated, an up-to-date personal curriculum vitae and other applicable credentials.
- Agree, by signature, to the study protocol with the sponsor that the study will be conducted according to the study protocol following the principles of Good Clinical Practices (GCP) and applicable regulatory requirements.
- Ensure that the study is conducted according to the study protocol, relevant SOPs, GCP and applicable regulatory requirements.
- Maintain in the study documentation a signed and dated copy of the study protocol which includes each study protocol amendment. Each study protocol amendment, whether prepared by the sponsor or investigator, should be signed and dated by the sponsor and investigator and should identify what has been changed or modified and the reasons for such change or modification.

- Record in a signed and dated statement, to be retained in the study documentation, any deviation from the study protocol and the reason for its occurrence (if identifiable).
- Notify the sponsor,DAHD,CDSCO and IAEC promptly of any study protocol deviation within 15 days.
- Provide sufficient qualified personnel, including (as appropriate) a veterinarian to attend to the study animals, for the timely and proper conduct of the study. Adequately inform and provide any necessary training to personnel involved with the study or the management of the study animals to ensure compliance with the study protocol and applicable regulatory requirements.
- Delegate any authority and work, including any subcontracted work, only to individuals qualified by training and experience to perform the assigned duties.
- Provide relevant materials and information obtained from the sponsor to the study personnel.
- Ensure that adequate and well-maintained facilities and equipment, whether owned or leased, are used to conduct the study.
- Utilize Standard Operating Procedures (SOPs) for practical applications as appropriate.
- Comply with applicable regulatory requirements governing the humane care of study animals.
- Obtain informed consent (in native language) from each owner, or owner's agent, before their animal(s) participate in the study. Each owner or owner's agent should receive relevant information regarding such participation from the investigator prior to giving their consent.
- Supervise the housing, feeding, and care of all study animals at the study site and inform owners of animals housed off-site of their obligations as stated in the study protocol.
- Document any veterinary care and procedures, changes in animal health, or significant environmental changes.
- Comply with the study protocol regarding the use of edible products derived from food-producing animals treated with an investigational and control veterinary vaccines.

- Promptly notify the sponsor of adverse events (AEs). Notify DAHD, IAEC and CDSCO of serious adverse events (SAEs) through the sponsor.
- Manage any code procedure and documentation (e.g. randomization envelopes, blinding information) with professional care and ensure that any treatment code is only broken in accordance with the study protocol and with the sponsor's knowledge and consent. Study personnel who cannot be or are not blinded (masked) should participate in the conduct of the study to the minimum extent necessary.
- Be responsible for the receipt, control, storage, distribution, and further mixing with subsequent assay (if any) of the investigational and control veterinary vaccines shipped or delivered to the investigator for the conduct of the study.
- Provide secure storage of and control the access to the investigational and control veterinary vaccines in accordance with the study protocol and label specifications.
- Maintain a full inventory of receipt, usage, assay results for the investigational and control veterinary vaccines in feed or water (if further mixing by the investigator is required) and any remaining stocks of unused investigational and control veterinary vaccines.
- Ensure that the investigational and control veterinary vaccines are dispensed and administered to study animals in accordance with the study protocol.
- Not redistribute the investigational and control veterinary vaccines to any individual not authorized to receive them.
- At the end of the study, reconcile delivery records of the investigational and control veterinary vaccines with those of usage and returns including accounting for any discrepancies.
- When the study is completed or discontinued, be responsible for and adequately document the safe and final disposal of the investigational and control veterinary vaccines, including animal feed or water containing the investigational or control veterinary vaccines. This may be achieved by return to the sponsor or other appropriate means of disposal.
- Collect and retain the study documentation.
- Document unanticipated events that may affect the quality and integrity of the study when they occur and any corrective action taken.

- Collect and record data, including unanticipated observations, in accordance with the study protocol and applicable regulatory requirements in an unbiased manner that accurately and completely reflects the observations of the study.
- Prepare and maintain an accurate and complete record of all contacts including all telephone calls, visits, letters, and other contacts with representatives of the sponsor, representatives of relevant regulatory authorities and other personnel (e.g., contract research organization personnel) concerning the design, conduct, documentation, and reporting of the study. A contact record should include: the date and time of the contact; the nature of the contact; the name and organizational affiliation of all individuals involved; a summary of the purpose of the contact and subject matter discussed with sufficient detail to describe the basis of any actions that may be taken by the investigator and/or the sponsor as a result of the contact.
- Ensure that all specimens required to be retained by the study protocol and any applicable regulatory requirements are identified in a manner that is complete, accurate, legible and precludes loss of identification from the specimen.
- Securely store, protected from deterioration, destruction, tampering, or vandalism, all study documentation or authenticated copies of study documentation required to be retained by the investigator for a period of five years after completion of such study/trial.
- Provide to the sponsor on request either the signed study documentation or an authenticated copy. When all or part of the study documentation is forwarded to the sponsor, an authenticated copy of the forwarded information should be retained by the investigator.
- Participate, when applicable, in the preparation of the final study report.
- Permit monitoring and quality auditing of a clinical trial.
- Permit the relevant regulatory authority to inspect the facilities used by the investigator for the study and to inspect and copy any or all of the study documentation made or kept by the investigator as part of or pertaining to the study for the purpose of verifying the validity of the data.

10. 2. The Sponsor

The sponsor can be a company, institution or organization orIndividual which takes responsibility for the initiation, management, and financing of a clinical trialfor the veterinary vaccine under investigation.

Responsibilities ofthe sponsor:Responsibilities of the sponsor is defined in Schedule Y of The Drugs Rules, 1945.

The sponsor is responsible for:

- Ascertain that sufficient scientifically valid information exists with respect to the effectiveness and safety of the investigational veterinary vaccines to justify conduct of the clinical trial/ field trial. The sponsor should also determine from this information that there are no environmental, welfare, ethical or scientific grounds which might preclude the conduct of a clinical trial.
- Ensure that notification or application relating to the conduct of the study has been submitted to the CDSCO / DAHD (In case of recombinant products the application should be accompanied by the NOC from RCGM)
- Select the investigator(s) and assure their qualifications, determine their availability for the entire duration of the study, confirm that they agree to undertake the study in accordance with an agreed study protocol, GCP principles and applicable regulatory requirements.
- Appoint appropriately qualified and trained monitor(s).
- Arrange, as necessary, for the preparation of SOPs for the procedural and technical elements of the study.
- Prepare a study protocol, in consultation with the investigator as appropriate, giving due regard to the above considerations and consistent with the principles for GCP.
- Sign, along with the investigator, the study protocol as an agreement that the clinical trialwill be conducted according to the study protocol. Any amendments to the study protocol should have the signed agreement of both sponsor and investigator.
- Ensure, for multicenter studies, that:
    - All investigators conduct the study in strict compliance with the study protocol agreed to by the sponsor and by the CDSCO / DAHD.
    - The data capture system is designed to capture the required data at all multicenter study sites. For those investigators who are collecting additional data requested by

the sponsor, supplemental data capture systems should be provided and designed to capture the additional data.

    - All investigators are given uniform instructions on following the study protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings and on capturing data.
    - Communication between investigators is facilitated.

- Inform the investigator of appropriate chemical, pharmaceutical, toxicological, safety, effectiveness and other relevant information as a prerequisite to conducting the study. The sponsor should also inform the investigator of any such pertinent information that becomes available during the study and when required, ensure that the relevant regulatory authority is also notified.
- Report all SAEs to CDSCO / DAHD and IAEC within 21 days.
- Ensure the proper disposal of all study animals and any edible products derived from them according to the applicable regulatory requirements.
- Ensure that the investigational and control veterinary vaccineshave been prepared, labeled and shipped according to requirements of the CDSCO / DAHD.
- Prepare and retain records of shipment of the investigational veterinary and control vaccines. When the study is completed or discontinued, ensure the proper and final disposal of all supplies of the investigational and control veterinary vaccinesand any animal feed containing the investigational or control veterinary vaccines.
- Maintain study documentation, protected from deterioration, destruction, tampering or vandalism, for as long as required to fulfill applicable regulatory requirements to support the registration of the investigational veterinary vaccines.
- In the event that an animal is treated with an investigational veterinary vaccine, arrange for a study report to be written whether or not the study has been completed as planned.
- Ensure the quality and integrity of data from clinical studies by implementing quality audit procedures that are consistent with well recognized and accepted principles of quality assurance.
- Comply with the Good Practices as per CCSEA governing the humane care of study animals.

10. 3. Selection and Delegations to a Clinical Research Organization (CRO)

- A sponsor may delegate any or all of the sponsor's study-related duties and functions to a CRO, but the ultimate quality and integrity of the study data is always theresponsibility of the sponsor.
- Any study-related duty or function that is delegated to a CRO should be specified in writing. The sponsor should notify the CRO of its responsibility to comply with applicable regulatory requirements.
- Any study-related duties or functions not specifically delegated to a CRO are retained by the sponsor.
- All references to a sponsor in this guidance also apply to a CRO to the extent that a CRO has assumed the study-related duties and functions of a sponsor.

Sponsor might also choose to conduct the clinical / field trial in a Veterinary institution, Private farm or private clinic. The sponsor shall have written qualification criteria for selecting the trial site and the trial site shall have qualified personnel, as mentioned in the Investigator/ study Director Sections.

10. 4. The Monitor

- An individual appointed by the sponsor to be responsible to the sponsor for monitoring and reporting on progress of the study, verifying the data and confirming that the clinical trialis conducted, recorded and reported in compliance with applicable regulatory requirements.
- The monitor should be a veterinarian with minimum BVSc (BVSc & AH or BVSc recognized by Veterinary Council), have scientific training and experience to oversee a particular study.
- The monitor should be trained in quality control techniques and data verification procedures. The monitor should understand all applicable protocol requirements and be able to determine whether the study was conducted in accordance with the protocol and relevant SOPs.
- An individual should not serve as both the monitor and investigator for any one study.
- The monitor is the principal communication link between the sponsor and the investigator.

Responsibilities of the monitor:

- Assist the sponsor to select the investigator when requested.
- Be reasonably available to the investigator for consultation in person, by telephone or by other means.
- Determine that the investigator and staff have sufficient time to devote to the study. Also, determine that the study site has adequate space, facilities, equipment and staff and that an adequate number of study animals is likely to be available for the duration of the study.
- Confirm that the study staff has been adequately informed about the details of the study.
- Ensure that the investigator accepts responsibility for conducting the study and in doing so understands: the investigational status of the veterinary vaccineunder evaluation; the nature and details of the study protocol; the applicable regulatory requirements governing the humane care of study animals; the conditions of any authorization for the use of edible products derived from food-producing animals treated with the investigational or control veterinary vaccine(s) and any other applicable restrictions on the disposal or subsequent use of study animals.
- Work according to the sponsor's requirements, visit the investigator with sufficient frequency before, during and after the study to control adherence to the study protocol and applicable regulatory requirements.
- Not, in any way, bias the data collection process or outcome of the study, other than to ensure that the current study protocol, relevant SOPs and applicable regulatory requirements are being followed.
- Ensure that informed consent is obtained and recorded from the owner(s) or owner's agents prior to their animals participating in the study.
- Ensure that all data are correctly and completely recorded.
- Ensure that illegible, missing or corrected study documentation is fully explained.
- Confirm that the storage, dispensing and documentation of the supply of the investigational and control veterinary vaccine(s) are safe and appropriate and ensure that any unused Veterinary vaccines are returned by the investigator to the sponsor or disposed of properly.

- Review the raw data and other study documentation necessary to determine that the study protocol is being followed and the information maintained or kept by the investigator is accurate and complete.
- Prepare and maintain an accurate and complete record of all contacts including all telephone calls, visits, letters and other contacts with the investigator, representatives of the sponsor, representatives of CDSCO/ DAHD and other personnel (e.g., CRO personnel) concerning the design, conduct, documentation, and reporting of the study.
- A contact record should include: the date and time of the contact; the nature of the contact; the name, and organizational affiliation of all individuals involved; a summary of the purpose of the contact and subject matter discussed with sufficient detail to describe the basis of any actions that may be taken by the investigator and/or the sponsor as a result of the contact.
- Confirm investigator compliance to the principles of GCP by providing a signed and dated summary report of the contacts, visits made and activities witnessed during the conduct of the study. The summary report should be submitted to the sponsor at the end of the study.

11. The Study Protocol

Appendix X of the Schedule Y of the Drugs Rules, 1945. prescribed contents of the proposed protocol for conducting trials.A study protocol is a document that states the objectives of the studyand defines the conditions under which the study is to be performedand managed.

- A well-designed study relies predominantly on a thoroughlyconsidered, well-structured and comprehensive protocol which shouldbe completed and approved by the sponsor and investigator beforethe study is initiated.
- A comprehensive study protocol that is easily understood by theinvestigator who is executing the study and by the relevant regulatoryauthority who is reviewing the protocol and study results may facilitate theregistration process for veterinary vaccines.

11. 1. Study Protocol Check List

The study protocol should contain the information given in the following list of items or this list should be considered whenever a study is contemplated. The list provided is not exhaustive nor is every item included applicable to all study protocols, but it is intended to give guidance:

1. **Title of the study:** The title of the field trial should be summarized, where the trial is being conducted to satisfy regulatory requirements.
2. **Identifier unique to the study:** A unique identifier consists of a study protocol number, the status of the study protocol (i.e., draft, final, amended) and the date of the version of the study protocol, all of which should be clearly located on the title page.
3. **Study contacts:** Study contacts include the investigator, monitor, representatives of the sponsor and all other participants responsible for major aspects of the study. List, for each contact, the title, qualifications, professional background, as well as the postal address telephone number and other communication means.
4. **Identity of the sites:** Provide the information on the location(s) where the trial is to be conducted. Where various qualifying practices or individual farms are to be used and their location is unknown at the time of application, the expected number of practices and farms and their geographical location should be stated (e.g. 10 companion animal veterinary practices in Delhi, or 5 dairy farms with >30 cows in Hisar).

   Qualification criteria / accreditation considered for selection of site / institute/ farm/ laboratory.
5. **Objective(s)/purpose of the study:**
6. **Justification:** Describe all information where relevant to the understanding of the objective of the study (pre-clinical or clinical data published or otherwise available) that justifies the conduct of the clinical trial.
7. **Consent of animal owners:** In the case that the animals being used in the trial are not the property of the applicant or sponsor, confirmation that the informed consent of the owners of the animals used in the trial will be obtained and documented.
8. **Schedule of events:** Schedule of key events occurring during the animal phase of the study including: the expected date and time of commencement of the animal phase, the period during which the investigational and control veterinary vaccine(s) are being administered, the post administration observation period, the withholding period (when applicable) and the termination date where known.

9. **Study design:**

a. The overall design of the study, including a description of the type of study e.g. multicenter, a placebo control clinical field effectiveness study or a randomized blocked design versus a positive control, with blinding. Detail of the specific treatment groups and number of study animals in each group and investigative site, animal identification number assignment, and the type, sequence and duration of study periods.

b. Where vaccination of whole herds is proposed the need for this shall be justified. In such cases, comparison with animals vaccinated with a comparator vaccine may be used when available. For modified live vaccines, whose vaccine agent(s) spread, it is necessary to separate vaccinates from controls. In such cases separate housing of these both groups is justified.

c. The environment in which the two groups of animals are housed shall be as equivalent as possible (i.e.same farm/ barn/batch) or at least as similar as possible (e.g. same farm/ different barn/same batch)

d. The exposure to natural infection shall be as similar as possible in the two groups of animals. This will not be the case if cohorts consist of exclusively vaccinated animals or controls. In this case, repetition of the trials under the same conditions is necessary, using truly randomized groups.

e. When investigating a combined vaccine, the control group may comprise animals vaccinated with a vaccine formulated to contain all the components of the vaccine except the component under study. Ideally, the trials shall be double blind, placebo controlled.

f. In some circumstances (e.g. enzootic diseases, bio-security reasons, during disease eradication programs, animal welfare aspect, etc.) inclusion of controls may be difficult. However, even when this is not possible, sufficient evidence shall be presented that the veterinary vaccine is having a demonstrable beneficial effect.

g. If a similar vaccine is available in the market for same indication, it can be used as comparator vaccine to evaluate the test vaccine. A non-inferiority trial or a suitable study design can be suggested with scientific justification in such cases.

h. Flow chart of the study.
i. The treatment, if any, in detail to be applied to control group(s) or for control period(s).
j. The randomization method, including the procedures to be adopted and practical arrangements to be followed to allocate animals to treatment groups and treatment groups to experimental units.
k. The experimental unit(s) and justify their selection.
l. The extent and methods of blinding (masking) and other bias reducing techniques to be used and state the provisions, including procedures and personnel, for access to treatment codes.

10. **Animal selection and identification:** Specification of the source, number, identity and type of study animal to be used, such as species, age, gender, breed, weight, physiological status and prognostic factors.

    Appropriate method of identification Ear tag/ micro chip

11. **Inclusion/exclusion and post-inclusion removal criteria:** Specify objective criteria for the exclusion from, inclusion in and removal subsequent to inclusion in the study.
12. **Animal management and housing:**
    a. The containment of the study animals e.g. pens, kennels, pastures
    b. If the trial is performed in clinical settings, the same shall be included
    c. Space allocation per animal (in comparison to standard management practices).
    d. The thermoregulation (heating/cooling) and ventilation of animal accommodation.
    e. Permissible and non-permissible concomitant veterinary care and therapy.
    f. The management of feed (including pasture management and the preparation and storage of mixed feeds) and water (including supply, availability and quality) and their presentation to the study animals.
13. **Animal feeds:** Authoritative reference sources may serve as useful guides in the determination of the nutritional requirements of the study animals and preparation of feeds to ensure that animal welfare requirements are met.
    a. Determine the nutrient needs of the study animals and prepare feeds meeting these needs.

b. Provide quantitative composition (e.g., feedstuffs, vitamins, minerals and, as appropriate, permissible feed additives) and calculated nutrient densities for all feeds used in the study.
c. Describe procedures for the sampling of the feed used in the study and subsequent analysis of these samples for selected nutrients.
d. Develop and follow objective criteria to determine whether feeds used in the study, based on actual laboratory nutrient analyses, meet the pre-determined calculated requirements.
e. Provide a feeding program (feeding schedule).
f. Collect records of the amount of feed offered and refused.
g. The feed should be of qood quality and devoid of fungal contamination and toxins. The feed should be free from Aflotoxin.

14. Investigational veterinary and control vaccine(s):

a. Clearly and precisely identify the investigational veterinary vaccine to readily permit an unambiguous determination of the specific formulation. Instructions for the further mixing (if any), packaging and storage of these vaccines should be stated.
b. Details of the product composition (e.g. certificate of product specification), and name of manufacturer.
c. If the investigational veterinary vaccine is administered in feed or water, describe the procedures for determining the concentration of the investigational veterinary vaccine in the feed or water, including the sampling methods and assay methodologies (e.g. laboratory used, analytical method, number of replicates, assay limits, permitted analytical variation) to be used.
d. Where relevant (i.e. in the case the veterinary vaccine is to be administered to a food-producing animal species), a statement as to whether the active substances in the test product(s) have an established maximum residue limit (MRL), and the proposed withdrawal period(s).
e. Identify control veterinary vaccine by generic or trade name; dosage form, formulation (ingredients); concentration; batch number; expiry date. Store and use these products according to label directions.

f. Statement as to whether the veterinary vaccine (s) contains a genetically modified organism (GMO).

g. Statement as to whether the veterinary vaccine (s) is free from extraneous agents.

15. **Treatments:** For the investigational and control veterinary vaccine (s):

a. Justify the dosing to be used.

b. Describe the dosing regimen (route, site of injection, dose, frequency and duration of administration) to be followed in administering the veterinary vaccines.

c. Specify objective criteria for the potential use of concomitant veterinary treatment.

d. Describe the methods and precautions to be taken to ensure the safety of study personnel handling these veterinary vaccines prior to and during administration.

e. Describe measures to ensure administration of these veterinary vaccine in compliance with the study protocol or its labeling.

16. Status of study animals at the end of trial, products of study animals and investigational and control veterinary vaccine(s):

a. Describe the proposed restocking/ re-introduction of the study animals to the farm or retaining the companion animal with the owner.

b. Describe the care to be given to animals removed from the study in accordance with pre-established criteria.

c. State the conditions for use of edible products from food producing animals as per the CCSEA guidelines.

d. Describe policy and procedure for handling unused investigational and control veterinary vaccine(s).

17. Assessment of effectiveness:

a. The parameters to be measured shall be clearly defined and justified in relation to the indications and specific claims for the veterinary vaccine (e.g. mortality, morbidity, lesions, weight gain, epizootiological impact and serological response).

b. Define the effects to be achieved and the clinical endpoint(s) to be reached before effectiveness can be claimed.

c. Describe how such effects and end-points are to be measured and recorded.

d. Specify the timing and frequency of study observations.

e. Describe the special analyses and/or tests to be performed including the time of sampling and the interval between sampling, storage of samples, and the analysis or testing.
f. Select and define any scoring system and measurements that are necessary to objectively measure the targeted response(s) of the study animal and evaluate the clinical response.
g. Define the methods for computing and calculating the effect of the investigational veterinary vaccine.

18. **Statistics/Biometrics:** Thoroughly describe the statistical methodologies to be used to evaluate the effectiveness of the investigational veterinary vaccine, including the hypotheses to be tested, the parameters to be estimated, the assumptions to be made and the level of significance, the experimental unit and the statistical model to be used. The planned sample size should be justified in terms of the target animal population, the power of the study and pertinent clinical considerations.
19. **Handling of records:** Specify procedures for recording, processing, handling, and retaining raw data and other study documentation required by the relevant regulatory authority.
20. **Adverse events (AE):** Describe procedures for:
    a. Observing study animals with sufficient frequency to detect AEs.
    b. Taking appropriate actions in response to observed AEs. Appropriate actions may involve, among other items, locating and breaking blinding codes so that appropriate medical treatment can be given.
    c. Recording of the AEs in the study documentation.
    d. Reporting AEs to the sponsor/ CDSCO/ DAHD.
21. **Supplements to be appended to the protocol**:
    a. List any study-specific SOPs that apply to the conduct, monitoring and reporting of the study.
    b. Attach a copy of all data capture and event record forms to be used during the study.
    c. Include any other relevant supplements, e.g. information to be provided to the owners of animals, instructions to study personnel.

22. **Changes to the study protocol:** Instructions for preparation of amendments and reporting of deviations to the study protocol should be provided.
23. **References:** Provide citations to relevant literature referenced in the study protocol.

12. Animal ethical approval

The clinical/field trial for Veterinary drugs are conducted in farms or clinical settings so that the drug effect can be evaluated in real life situation.However, the trials are required to be performed by CCSEA registered establishments only. Animal farms in Veterinary universities or colleges, private animal farms, Veterinary hospitals/ clinics of Veterinary Universities or colleges or animal husbandry departments and private veterinary clinics undertake the clinical trials. The trials are undertaken even in multiple small households having animals. In such cases, some of the trial sites (animal farms, private clinics, households with animals) may not have statutory IAEC of their own.

Therefore, the trial shall be approved by the statutory IAEC of the institution/CRO, which is performing the trial. For approval of experimentation on large animals (species above of rodents and Lagomorpha) eg. Dogs, Cat, Sheep, Goats, Cattle, Horse, Pony, Mule, Pig, Monkey, etc., the case is required to be forwarded to CPCSEA in prescribed manner with recommendation of IAEC as per the provisions under the prevention of Cruelty to Animals (PCA) Act, 1960. The trial on poultry shall be approved by IAEC.

The IAEC/ CCSEA shall approve the trial based on the trial protocol approval from CDSCO. IAEC/ CPCSEA shall also provide conditional approval if the applicant does parallel application to IAEC and CDSCO for saving time. Consent from animal owner or farm owner or the institution where the trial is performed shall be obtained in an appropriate format"

13. Design of field trial protocol

13. 1. Species and breed of animals:

The predominant (one or more) species for which the vaccine is intended to be used shall be included in the trial. If the vaccine is to be used for several species of animals (for eg. FMDV, Rabies), the clinical trial can cover one or two species for which the vaccine is to be used predominantly. Applicant can provide the justification for the selection of species based on the vaccine (For Example Dogs can be the species of choice for rabies vaccine; Cattle and Buffaloes can be the species of choice for FMD Vaccine). Animal study results, generated during the developmental stage shall be used to determine the dose requirement, safety and immune response for other indicated species.

It is not possible to perform the trial in all the available breeds in India and therefore, the trial can be performed in representative breeds in India. Cross-bred cattle shall be considered for cattle trials as they represent predominant cattle population in India.

13. 2. Age and sex of the animal:

Age of the animal shall be as per the recommended vaccine schedule (For eg. Vaccine trials in broiler birds). If the vaccine is indicated for all age, a cross section of age (Animals having age equal to or above the recommended age for vaccine) shall be used for the trial.

Both the sexes shall be used for the trial except for few specific instances such as vaccine trial in layer birds.

13. 3. Parameters to be assessed:

The major parameters to be assessed during clinical/field trials are related to the evaluation of efficacy and safety of the vaccines.

13. 3. 1. Assessment of efficacy under field conditions

Efficacy criteria: The efficacy criteria shall be clearly defined in the study protocol and justified in relation to the indications and specific claims for the vaccine.Conversely, justification shall be given for not measuring parameters that are usually related to the disease concerned.

Primary efficacy criteria are generally derived from main disease parameters: mortality, morbidity, clinical signs and/or lesions. Secondary efficacycriteria may for example include parameters related to production (e.g. weight gain, egg laying) or infection parameters (e.g. shedding, viraemia).

An indicator can be used as correlate of protectionalong with or instead of Primary / secondary efficacy criteria.For an indicator (for eg. Antibody titer, T-cell response, reduced load of pathogen, etc) to be acceptable as a correlate of efficacy, it shall be demonstrated that a sufficient correlation exists between the indicator measured and the claimed protection in the target species. An indicator of protection should be shown to play a substantial role in the immune response and relevant for protection of the target species against the disease concerned. Reference to literature may be used to support the role of the indicator in the protection but the publications may not be sometimes sufficient to define the level necessary to

guarantee efficacy of vaccination. In such circumstances, it must be demonstrated that the level of response obtained for the indicator in clinical trials is equal to the one observed in vaccinated animals at the time of challenge in laboratory trials and for which protection was demonstrated. If the disease is having an established protective titer, the same can be used to evaluate the efficacy (for eg.>0.5 IU RFFIT titer for Rabies, >80 HI units for Canine Parvovirus and serotype specific SN_{50} or Liquid phase blocking ELISA titer for FMD).

Wherever, Primary or secondary efficacy criteria is used as end point, it is necessary to consider the endemicity of the disease while selecting the site for field / clinical trials. For example, clinical trials with anthrax vaccine shall be conducted in areas where anthrax is endemic.

Wherever, Immunological indicator is used as correlate of protection(for eg. protective titer is assessed as efficacy criteria), endemicity of the disease is not relevant while selecting the site.

13. 3. 1. 1. Controls and study design

In general, clinical/ field efficacy trials should be multi-centered, randomized, blinded and controlled unless otherwise justified. The study population shall be well defined and representative of the target population.

The trial shall, unless justified, compare a group of vaccinated animals with an equivalent group of unvaccinated or placebo controls.

Where vaccination of whole herds is proposed, the need for this shall be justified. In such cases, comparison with animals vaccinated with a comparator product may be used when available and a non-inferiority trial or a suitable study design can be suggested with scientific justification.

For modified live vaccines, whose vaccine agent(s) spreads, it is necessary to separate vaccinated animals from controls. In such cases separate housing of vaccinated and control groups is justified.Control groups shall also be subjected to the similar husbandry conditions. When the trial is performed in multiple small households, controls shall be selected from the households located in the same village or nearby villages, with similar husbandry conditions.

The choice of controls shall be justified. It is necessary to define in the study protocol what purpose the control group serves. This may include:

- Evidence that exposure to infection took place.

- A group of animals against which the vaccinated animals can be compared in a valid manner.

  For such comparison to be valid:

  - The controls and vaccinated animals shall be investigated at the same time. Where this is not possible, justification should be provided.
  - The animals of both groups have to be randomized according to the experimental unit, unless justified.
  - The environment in which the two groups of animals are housed shall be equivalent (i.e. same farm and barn) or as similar as possible (e.g. different barn on the same farm or same or nearby village with similar set-up).
  - Natural exposure in the field, if any, shall be as similar as possible in the groups of animals. The dynamics of a field infection may not be similar if cohorts consist of exclusively vaccinated animals or negative controls. Therefore, where possible, vaccinated and control groups should be housed together.

    (Note: Natural exposure in the field is the natural infection of vaccinated and unvaccinated animals during field trial in the endemic regions. This gains particular importance when the primary / secondary efficacy criteria is assessed)
  - When the trial was performed in clinical settings (for eg. In pet clinics), the treatment and control groups (Placebo control and/ or comparator control) shall be randomized.

The use of historical data for control purposes is rarely acceptable but when historical data are used, they shall have been shown to be consistent over a representative length of time and well documented.

It is recognised that in some circumstances inclusion of placebo/non-vaccinated controls may be difficult for reasons of animal welfare, disease security, and during the implementation of eradication programs. However, even when the inclusion of negative controls is not possible, sufficient evidence shall be presented that the vaccine is having a demonstrable beneficial effect (for eg. Non-inferior to available vaccine in a comparator study, significantly higher than Protective titer, Fold increase in titer is significantly high, etc).

The trials shall be performed double blind. Where this is not possible, alternative blinding practices may be applied when justified. As a rule, but in particular if the parameter to be measured is subjective (e.g. coughing, scoring of lesions), any observer and anyone involved in the generation of data (e.g. pathologist, laboratory staff) must be blinded to the treatment.

The batch(es) used may be of standard or intermediate potency or titre whenever safety and efficacy measurements are combined in one clinical trial. In case of separate trials are performed to determine safety and efficacy in the field, the use of minimum titre/potency batches in the efficacy trials is acceptable. When the vaccine is being compared to a comparator product, the use of standard titre/potency batches is acceptable.

Assays which are recommended by WOAH shall be used for evaluating the sero-conversion. If WOAH guidelines are not available, a proper justification can be provided by the applicant for the selection of the assay. The assays shall be qualified and the qualification data can be included in the application.

13. 3. 1. 2. Comparator product

The comparator product should have similar indications and specific claims as those proposed for the vaccine under study.

A study involving a comparator product is usually be designed as a non-inferiority study. If any other study design is proposed, a scientifically valid explanation shall be provided. When the vaccine under study is being compared with a comparator product, a group of non-vaccinated or placebo controls shall still be included whenever possible in order to verify field exposure (which means natural exposure of the pathogen in the endemic regions). If this is not possible, sufficient evidence shall be presented that both products are having a demonstrable beneficial effectwhen primary efficacy criteria is assessed.

13. 3. 1. 3. Exposure to infection

Evidence that the vaccinated animals and controls have been exposed to the concerned pathogen(s) shall be given, wherever, the natural infection is expectedand primary/ secondary efficacy criteria is assessed. In principle, the study should be designed to allow for a similar level and timing of exposure to the pathogen(s) in both groups of animals. In principle, the agent(s) itself shall be detected and identified. In case of live vaccines, the isolated field strains

shall, whenever possible, be differentiated from the vaccine strains. Appropriate immunological/serological tests relevant for a particular disease performed on a statistically sufficient number of animals, may be a supportive measure to demonstrate exposure to the pathogen. The serological method(s) used shall be validated.

The causes of any deaths or unexpected signs of disease shall be determined using appropriate methods, where possible, unless justified. It is expected that necropsy is performed in such cases. In avian spp., standard procedures for diagnosis may be used to determine the cause of death.

If justified, some of the vaccinated animals may undergo an experimental challenge under laboratory conditions but shall be shown not to have been naturally infected prior to challenge.

13. 3. 1. 4. Inter-current infections

Infections with agents other than those under study that may influence the parameters being measured may affect the outcome of the trial. Such an influence on the trial can be reduced considerably if vaccinated and control animals are investigated in parallel and if randomization is applied for allocation to study groups.

13. 3. 1. 5. Pre-existing antibodies

Pre-existing antibodies against the agent(s) in the vaccine may be maternally derived, due to infection or due to prior vaccination.

If the indication or specific claims for the vaccine are related to efficacy in the presence of maternal antibodies (MDA) against the vaccine agent(s), and when the impact of MDA is not addressed in a laboratory study, the trial protocol shall include a group of animals with titres of these antibodies representative of those normally occurring in the field.

Where pre-existing antibodies due to previous exposure to the concerned or related agents are present, the trial can still be acceptable if the immunological status of the vaccinated animals and controls at the time of vaccination is known and a justification for their use is given, ensuring that the animals are still relevant for the purpose of the trial. Fold increase in titer can be assessed in such cases while correlate of protection such as antibody titers are assessed.

Clinical/ field trials shall not be carried out in animals that have been vaccinated with products containing the same active substances as the vaccine under study. Exceptions are possible,such as cases when a booster effect is investigated and the same to be justified.

Assays which are recommended by WOAH shall be used for evaluating the sero-conversion. If WOAH guidelines are not available, a proper justification can be provided by the applicant for the selection of the assay. The assays shall be qualified and the qualification data can be included in the application.

13. 3. 2. Clinical safety trials

The clinical safety trials are primarily performed to verify the safety of the vaccine under field conditions after administration of one dose of vaccine as well as after repeated administration(s) depending on the recommendations for use.

13. 3. 2. 1. Safety Parameters to be assessed

Clinical safety trials shall be designed to detect both local and systemic reactions to vaccination. In addition, clinical safety trials provide an opportunity to detect rarer adverse reactions that are unlikely to occur in laboratory studies in a small number of animals.

Parameters used to determine systemic effects of vaccination may include allergic reactions, mortality, anorexia, pyrexia, changes in behavior (such as depression), weight gain, feed conversion, carcass quality, milk/wool/fur production, egg production and hatchability of breeding eggs and male and female fertility. Additional or alternative parameters relevant for a specific pathogen may be used, where appropriate and justified.

In case of live vaccines, the behavior of the vaccine agent(s) in animal populations should be documented (e.g. spread, persistence in the environment), if deemed necessary following results obtained in controlled animal during development stage.

In terms of local reactions, the size, duration and nature of any reactions appearing at the site of injection shall be monitored and recorded.

13. 3. 2. 2. Controls and trial design

In general, clinical safety trials should be multicentred, randomised, blinded and controlled unless otherwise justified. The study population shall be well defined and representative of the target population.

The trial shall normally compare a group of vaccinated animals with an equivalent group of unvaccinated or placebo controls originating from the same target population.

The choice of the controls and numbers shall be justified. The control group shall comprise animals against which the vaccinated animals can be compared in a valid manner.

The batch(es) used in combined safety and efficacy studies may be of standard or intermediate potency. In case separate clinical safety trials are performed, batches used may contain the maximum titre of the vaccine agent(s) or batch potency to be stated on the label, if deemed necessary following results obtained in laboratory studies. For live vaccines, the vaccine agent(s) may be at the least attenuated passage level that will be present in a batch of the vaccine.

13. 3. Trial site and Number of geographical locations to be used:

Sponsor/ applicant might choose to conduct the clinical / field trial in a Veterinary institution, Private farm or private clinic or with a CRO.The trials can be undertaken even in multiple small households having animals. The sponsor shall have written qualification criteria for selecting the trial site and the trial site shall have qualified personnel, as mentioned in the Investigator/ study Director Section.

As such, many veterinary clinics are not familiar with conducting studies or the elements of Good Clinical Practices. Therefore, it is important that organization/ sponsors, Veterinary college, or veterinary contract research organizations select the appropriate sites in order to perform the veterinary study.

The site and the study personnel are critical components of performing veterinary research in an effective manner. Veterinary study sites should be evaluated for:

Existing patient population, site resources, equipment and overall clinical facilities, hours of operation,investigational product security and storage capabilities, and allocation of sufficient space to store veterinary clinical trialdocuments (regulatory binders, patient binders, etc.) for the stipulated period.Applicant shall write in detail on providing above logistics when the trial is conducted at a farm or multiple households (For eg.The documents related to the study shall be stored at the place of Sponsor, etc).

The information on the location(s) where the trial is to be conducted shall be provided in the application. Where various clinical practices or individual farms are to be used and their

locationsare unknown at the time of application, the expected number of practices and farms and their geographical location should be stated (e.g. 10 companion animal veterinary practices in Mumbai, or 10 dairy farms with > 50 cows in Punjab, etc).

The clinical/ field trial shall usually be conducted at least in two different geographical locations in India. The locations can be selected based on disease prevalence (study shall be conducted where the disease is highly prevalent)wherever the primary/ secondary efficacy criteria are assessed. Disease prevalence criteria is not applicable wherever immunological parameters such as protective titer is assessed as correlate of protection. If it is not possible to conclude the location based on prevalence (Eg. Disease is prevalent widespread in India, No official data on prevalence is available, etc), different agro-climatic regions can be selected. Alternatively, scientific justification can be provided for selecting the location.

13. 4. Statistics:

The statistical section of the protocol should include the principal features of the statistical analysis. These include, where relevant:

- Definition of the experimental unit and populations
- Methods and details of randomisation and allocation concealment
- Methods of blinding
- Definition of variables (incl. aggregated variables) and handling of missing data
- Hypothesis to be tested, and specification of the primary one(s)
- Justification of the use of one-sided tests
- Treatment effect(s) to be estimated
- Methods, assumptions on the data variability and the size of clinically relevant differences, choices of statistical power (1-ß) and significance levels as well as other assumptions used in sample size estimation
- Assumptions for using the statistical analysis (e.g. test for normal distribution when using an analysis of variance)
- Planned data transformations
- Statistical model, test(s) and construction of confidence intervals
- Alternative methods to be used in case of expected problems (heteroscedasticity, nonnormality, etc)

- Use of covariate(s), adjusted analyses, sensitivity analyses and planned subgroup analyses
- Significance thresholds
- Equivalence and non-inferiority margins
- Planned interim analyses; stopping rules
- Reporting of summary data
- Comparison of groups at baseline

14. Study Protocol Review

Review of the study protocol bythe SEC and/ or DAHD will be completed in 30 working days and it is expected that both the sponsor and the CDSCO/ DAHD would benefit from such a review, in terms of a mutualunderstanding of the regulatory requirements and the relevance of theobjective(s) of the study protocol.

15. Conducting the trial

15. 1. The principles of GCP

Currently, CDCSO does not have any system to give accreditation for animal trial centers for GCP. However, the regulatory mechanism will move towards this direction in future. In the absence of any such system, a proper documentation and data storage shall be followed during trial implementation.

- ✓ The purpose of the GCP is to establish guidance for the conduct of clinical studies that ensures the accuracy, integrity and correctness of data. Due regard should be given to the welfare of the study animals, the effects on the environment and the study personnel and to residues in the edible products derived from food-producing study animals.
- ✓ Pre-established systematic written procedures for the organization, conduct, data collection, documentation and verification of clinical studies are necessary to assure the validity of data and to ensure the ethical, scientific and technical quality of the studies. A detailed study plan containing all aspects of the study with signatures from the responsible persons at study site and sponsor should be available.
- ✓ Data collected from studies designed, conducted, monitored, recorded, audited, analyzed and reported in accordance with this guidance can be expected to facilitate the review

process since the regulatory authorities can have confidence in the integrity of studies which follow such pre-established written procedures.

- ✓ By following such pre-established written procedures, it is likely that sponsors can avoid unnecessary repetition of definitive studies.
- ✓ Each individual involved in conducting a clinical trialshould be qualified by education, training, and expertise to perform their respective task(s). These individuals should demonstrate, in a manner that is evident from the study documentation, the highest possible degree of professionalism in the recording and reporting of study observations.
- ✓ The relevant regulatory authority should provide procedures that independently assure that the study animals and the human and animal food chains are protected (For eg. IBSC/ RCGM approval is to be obtained for conducting trials using GMO products and additional approval from GEAC may be considered for the live recombinant products).
- ✓ The sponsor and trial site should assure that an informed consent has been obtained from the owner of the study animals.
- ✓ Investigational veterinary vaccine to be used for field trials should be prepared, handled and stored in accordance with the concepts of good manufacturing practice (GMP) of the relevant regulatory authorities. Details of preparation, handling and storage of investigational veterinary vaccine should be documented and the veterinary vaccines should be used in accordance with the study protocol.
- ✓ The assurance of quality of every aspect of the study is a fundamental component of sound scientific practices. The principles of GCP support the use of quality assurance (QA) procedures for clinical studies. It is perceived that the sponsor/ applicant would be the party responsible for the QA functions for these studies. All sites in clinical studies/ field trials are encouraged to adopt and adhere to generally recognized sound QA practices.
- ✓ The sponsor shall audit the trial site and approve the site before selecting the site for trial.

16. The final study report

- The final study report (FSR) is a complete and comprehensivedescription of the study written after its completion. It includes adescription of the materials and methods, a presentation andevaluation of the results, statistical analyses and a critical

clinical,scientific and statistical appraisal. The report should follow the formatof the study protocol.

- It is the responsibility of the sponsor to provide a FSR for any study inwhich an animal has been treated with an investigational veterinary vaccine whether or not the study has been completed as planned.

16. 1. Authorship:

- The preparation of this report can be accomplished as follows:
  - The sponsor may prepare the FSR;
  - The investigator may prepare the FSR for the sponsor; or
  - The sponsor and investigator may prepare the FSRthrough a collaborative effort.

- All individuals involved in the preparation of the FSR would beconsidered author(s).
- When an investigator relinquishes authorship of the FSR, theinvestigator should provide to the authors:
  - All necessary study documentation specific to the site atwhich the investigator conducted the study, and
  - A signed and dated document, to be included in the FSR,which adequately describes the study documentation providedto the author(s) and attests to the accuracy and completenessof the documentation provided.
- The authors of the FSR should sign and date the report. Authors ofthe FSR should be aware that the regulatory authorities view thesesignatures as an affirmation that all data were collected in compliancewith the study protocol, relevant SOPs, applicableregulatory requirements and that all statements are accurate andcomplete representations of study activities and results and are fullysupported by the study documentation. Therefore, the authors maywish to include in the report a brief statement describing theircontributions to the report.

16. 2. Content of Final Study Report (FSR):

The Appendix II of the Schedule Y of the Drugs Rules, 1945. provides structure, contents and format for clinical trial reports. However, the FSR should include relevantinformation from the

following list. The list provided is not exhaustive nor isevery item included applicable to all FSRs but it is intended to giveguidance. The study protocol section should be consulted for anexplanation of the items in this list.

- Title and identifier of the study.
- Objectives of the study.
- The titles, names, qualifications and roles of all people involvedin conducting key elements of the study.
- The identity of the site(s) at which the study was conducted.
- Key study dates.
- Materials and methods.
    - Study design.
    - Animal selection and identification.
    - Full details of study animals in each group, includingbut not limited to: numbers, breed, age, gender andphysiological status.
    - Disease history of the animals, where available andif appropriate, relevant to the condition underinvestigation, especially in the case of specific diseaseproblems associated with an animal unit.
    - Where appropriate, diagnosis of the condition beingtreated or prevented, including a description of the clinicalsigns or other diagnostic methods according toconventional criteria.
    - Detailed inclusion and exclusion criteria applied tothe selection of study animals.
    - Full information on any study animal removedsubsequent to inclusion in the study.
    - Animal management and housing.
    - Details of animal housing and management.
    - Composition of feed and the nature and quantity ofany additives in the feed.
    - Details of any concomitant treatment administeredduring the study, either prior to, during or after treatmentwith the investigational veterinary or control vaccine (s)and details of any interactions observed.
    - Animal disposal. A summary of the disposal of the studyanimals and their edible products.
    - Treatments.

- The identification of the study investigationalformulation used in the study including strength, purity,composition, quantity and batch or code mark.
- The dosage of the investigational veterinaryvaccine, method, route and frequency of administrationand precautions, if any, taken during administration.
- Details of the control veterinary vaccine (s) used with ajustification for their selection.
- The duration of treatment and observation periods.
- A summary of use and disposal of all investigationalveterinary vaccine and control product(s) shipped ordelivered to the investigator.
- Study procedures. A full description of the methodsused including, if applicable, assay methods used to determineinvestigational veterinary vaccine concentration in feed, water,body fluids and tissues.
- Statistical methods. A description of thetransformations, calculations or operations performed on theraw data and any statistical methods employed to analyze theraw data. Reasons should be given if the statistical methodsused differed from those proposed in the study protocol.

- Results and their evaluation. A full description of the results of thestudy, whether favorable or unfavorable, including tables of all datarecorded during the study.
- Conclusions based on each individual case or treatment groupas appropriate.
- Administrative and compliance items.
  - A description of the procedures used to record, process,handle and retain raw data and other study documentation.
  - A description of any protocol deviations and/oramendments and an assessment of their impact on theoutcome of the study.
  - A description of circumstances that could have affectedthe quality or integrity of the data, specifying the time frame andthe extent of their occurrence.
  - Details of any AEs occurring during the study and anymeasures taken in consequence. For all studies where no AEwas observed or recorded a statement to this effect should beincluded in the FSR.
  - The location of all study documentation.

- Additional information. Additional information such as thefollowing may be included in the body of the report or as an appendix:
    - Study protocol.
    - Dates of monitoring visits.
    - Audit certification by auditor, consisting of the dates of sitevisits, audits and when reports were provided to the sponsor.
    - Supplementary reports, e.g. analytical, statistical, etc.
    - Copies of study documentation supporting studyconclusions

16. 3. Report Amendments:

Any addition, deletion, or correction to the FSRshould be in the form of an amendment by the authors. The amendmentshould clearly identify that part of the FSR that is being added, deleted orcorrected and the reasons for the change(s) and should be signed anddated by the authors. Minor errors, e.g. typographical errors, noted afterfinalization of the report may be indicated directly on the FSR whenaccompanied by the signature or initials of the authors, the date of thechange and the reason for the change.

17. Study Documentation

Study documentation consists of those records that individually andcollectively permit evaluation of the conduct of the study and thequality of the data produced. Filing study documentation, orauthenticated copies thereof, at the investigator and sponsor sites ina timely manner can greatly assist in the successful management of astudy by the investigator and sponsor.

All study documentation should be retained for a period of fiveyears, required by CDSCO/ DAHD. Any or all of the studydocumentation described in this guidance is subject to, and should beavailable for monitoring on behalf of the sponsor / applicant. Studydocumentation should be audited by the sponsor's quality auditprocedures, consistent with well-recognized and accepted principlesof quality assurance. When a quality audit is conducted, the

auditorshould prepare a report for the sponsor which details the auditingprocess and which certifies that the audit has been conducted.

Any or all of the study documentation described in this guidance maybe inspected and audited as part of the process to confirm the validity of the study conduct andthe integrity of the data collected.

The requirements for the submission of study documentation shouldbe governed by CDSCO.

Validity period of permission to initiate a field trial/ clinical trial

The permission to initiate clinical trial/ field trial granted by CDSCO shall remain valid for a period of two years from the date of its issue unless extended by the CDSCO.

Categories of study documentation. Study documentation includes, butis not limited to:

Study protocol: This documentation consists of the original studyprotocol, all protocol amendments and records of all protocoldeviations.

Raw data: The raw data of a study generally covered under the classes given below.

Animal records: All pertinent data relating to the studyanimals, such as purchase records, documentation of animalexclusion from, inclusion in and removal subsequent toinclusion in the study, informed consent of the owner, treatmentassignment, all recorded observations (including analyticalassay results of biological samples), case report forms, adverseevents, animal health observations, composition and nutrientassay of animal feeds and final animal disposal.

Investigational and control veterinary vaccine records: Allpertinent records of the ordering, receipt, inventory, assay, useor administration (documenting the dosing regimen, e.g. dose,rate, route, and duration of administration), return, and/ordisposal of all the investigational and control veterinaryvaccine(s) including any animal feed containing theinvestigational or control veterinary vaccine.

Contact records: The monitor's and investigator's recordsof all contacts (e.g. visits, telephone, written and electronic)relating to the design, conduct, documentation, and reporting ofa study.

Facility and equipment records: As appropriate,descriptions of the study site, e.g. diagrams and photographs,equipment identification and specifications, equipmentcalibration and maintenance records, equipment failure andrepair records, meteorological records and environmentalobservations.

Reports: consist of-

Safety reports: Reports of adverse events.

Final study report.

Other reports. For example, statistical, analytical, andlaboratory reports.

Standard operating procedures and reference materials: Include any reference materials and SOPs related to key elements ofthe study.

18. Recording and handling study documentation:

Raw data, whether handwritten or electronic, should be attributable,original, accurate, contemporaneous and legible. Attributable meansthe raw data can be traced by signature (or initials) and date to theindividual who observed and recorded the data. If more than oneindividual observes or records the raw data, that fact should bereflected in the data entries. In automated data collection systems,the individual(s) responsible for direct data input should record theirname along with the date at the time of data input. Original andaccurate means the raw data are the firsthand observations.

Contemporaneous means the raw data are recorded at the time ofobservation. Legible means the raw data are readable and recordedin a permanent medium, e.g. ink for written records or electronicrecords that are unalterable.

Raw data should be maintained in an organized manner and, whereappropriate, should be recorded in a bound laboratory notebook or onpre-established forms designed specifically for recording particularobservation(s). Records should be diligently completed with all datapoints recorded as required in the study protocol. When additionalobservations are warranted, e.g. to provide additional information forpre-planned observations or observation of unanticipated events,such observations should also be recorded.

Units used to measure observations should always be stated andtransformation of units should always be indicated and documented.Values of laboratory analyses should always be recorded on a recordsheet or attached to it. If available, normal reference values for thelaboratory analyzing the specimens should be included.

If a portion of the raw data needs to be copied or transcribed forlegibility, an authenticated copy of that data should be made. Thereason for the copying or transcription should be explained in a datedmemorandum or in a dated notation on the transcribed record, signedby the individual(s)

making the copy or transcription. In such a casethe copied raw data, the copy or transcript of the raw data and thememorandum should be kept together in the study documentation.

Any correction in the hand-written study documentation should bemade by drawing one straight line through the original entry. Theoriginal entry should still be legible. The correction should be initialedand dated by the individual(s) making the correction at the time thecorrection is made and should describe the reason for the change.

Similarly, if data are entered directly into a computer system, theelectronic record is considered the raw data. A computerized systemshould ensure that the methods for record keeping and retention.

Maintenance of Records:All records shall be safely maintained after completion of the studyfor not less than five years from the date of completion of the study (both in hard copy and soft copy).

19. Glossary

Academic field trial: A field trial of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a trial are intended to be used only for academic or research purposes and not for seeking approval of the Central Licencing Authority or regulatory authority of any country for marketing or commercial purpose.

Adverse Event (AE): Any observation in animals during the study trial that is unfavorable and unintended and occurs after the use of a veterinary biological or other product or investigational veterinary product, whether or not considered to be product related.

Applicable Regulatory Requirement(s): Any law(s) and regulation(s) of the relevant regulatory authority addressing the conduct of studies using investigational veterinary products.

Audit: A systematic and independent examination of study related activities and documentation to determine whether the study being evaluated is or was properly conducted and whether the data are or were recorded, analyzed and accurately reported according to the study protocol, study related standard operating procedures (SOPs), GCP and the applicable regulatory requirements.

Authenticated Copy: A copy, which is a complete reflection of an original document, that bears or contains a statement, signed and dated by the individual(s) making the copy, certifying that such copy is complete and accurate.

Blinding (Masking): A procedure to reduce potential study bias in which designated study personnel are kept uninformed of the treatment assignment(s).

Clinical study: A single scientific experiment conducted in a target species to test at least one hypothesis relevant to the proposed effectiveness claim(s) or to in-use safety in the target animal for a veterinary product under investigation. .

Clinical trial: A study which aims to examine under field conditions the safety or efficacy of a Veterinary drug under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof. For the purpose of this guidance, the term Field trial or clinical study are synonymous to clinical trial.

Compliance (in relation to studies): Adherence to the study protocol, relevant SOPs, Good Clinical Practice, and the applicable regulatory requirements.

CDSCO: Central Drugs Standard Control Organisation

Contract Research Organization (CRO): An individual or organization contracted by the sponsor or investigator to perform one or more of the obligations of the sponsor or investigator.

CCSEA: Committee for Control and Supervision of Experiments on Animals

DAHD: Department of Animal Husbandry and Dairying

Disposal of Investigational Veterinary Products: The fate of investigational veterinary and control products during or following completion of the study. For example, the products may be returned to the sponsor, incinerated or disposed of by other approved methods. This procedure shall be documented and signed by authorized signatory.

Disposal of Study Animals: The fate of the study animals or their edible products during or following completion of the study. For example, animals may be slaughtered, returned to the herd, sold, returned to their owner, retained in the farm or retained with the pet owner. This procedure shall be documented and signed by authorized signatory.

ECAH: Empowered Committee for Animal Health

Final Study Report (FSR): A comprehensive description of a study of an investigational veterinary product that is written after the collection of all raw data is complete or the study is discontinued and that completely describes the objectives and experimental materials and methods (including statistical analyses), presents the study results and contains a critical evaluation of the study results.

GEAC: Genetic Engineering Approval Committee

Good Clinical Practice (GCP): A standard for the design, conduct, monitoring, recording, auditing, analysis, and reporting of clinical studies. Adherence to the standard provides assurance that the data and reported results are complete, correct and accurate, that the welfare of the study animals and the safety of the study personnel involved in the study are ensured, and that the environment and the human and animal food chains are protected.

Informed Consent: A documented process by which an owner, or owner's agent, voluntarily confirms the owner's willingness to allow their animal(s) to participate in a particular study, after having been informed of all aspects of the study that are relevant to the decision to participate.

IAEC: Institutional Animal Ethics Committee

Inspection: The act by a relevant regulatory authority of conducting, in accordance with its legal authority, an official review of study documentation, facilities, equipment, finished and unfinished materials (and associated documentation), labeling, and any other resources related to the registration of an investigational veterinary product and that may be located at any site related to the study.

Investigational Veterinary Product (IVP): For the purpose of field trial/ clinical trial, the IVP means Pharmaceutical formulation of an active ingredient or placebo being tested or used in a clinical trial.

Investigator:A person who is responsible for conducting clinical trial at the clinical trial site. If a study is conducted by a group of individuals at a study site, the investigator is the leader of the group.

Monitor: An individual responsible for overseeing a clinical trialand ensuring that it is conducted, recorded, and reported in accordance with the study protocol, SOPs, GCP and the applicable regulatory requirements.

Multicenter Study: A study conducted according to a single study protocol at more than one site.

PCT: Pre-clinical Toxicology Study

Quality Assurance (QA): A planned and systematic process established to ensure that a study is performed and the data are collected, documented (recorded) and reported in compliance with this guidance and the applicable regulatory requirements.

Quality Control (QC): The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled.

Randomization: The process of assigning study animals (or groups of study animals) to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Raw Data: Any original worksheets, calibration data, records, memoranda and notes of firsthand observations and activities of a study that are necessary for the reconstruction and

evaluation of the study. Raw data may include, but are not limited to, photographic materials, magnetic, electronic or optical media, information recorded from automated instruments, and hand recorded datasheets. Facsimile transmissions and transcribed data are not considered raw data.

RCGM: Review Committee on Genetic Manipulations

Regulatory Authorities: Bodies having the statutory power to regulate. In this guidance, the expression 'regulatory authorities' includes the authorities that review submitted clinical data and conduct inspections.

Report Forms/ Record Sheets Printed, optical, electronic, or magnetic documents specifically designed to record study protocol-required and other observations of study animals or laboratory results.

Serious Adverse Event (SAE):A Serious Adverse Event (SAE) is actually a special case of an adverse event where adverse outcomes are severe. It includes the following events:

- Death of any of the animals associated with a clinical trial
- An event that can lead to life-threatening complications or put the lives of animals at risk as a result of participation in a clinical trial.
- Events that result in such a condition where the animals may require immediate hospitalization or increase the duration of hospitalization.
- Any events that lead to a permanent or temporary physical disability in the body of the animals. Any sort of incapacity is also regarded as SAE.
- Any events where an investigator or team of investigators finds feel that it can lead to significant hazards.

Similar biologic:A biological product which is similar in terms of quality, safety and efficacy to reference biological product licensed or approved in India, or any innovator product approved in International Council of Harmonization (ICH)member countries

Sponsor: An individual, company, institution or organization which takes responsibility for the initiation, management, and financing of a clinical trialfor the veterinary product under investigation.

Standard Operating Procedure (SOP): A detailed, written instruction to facilitate consistency in the performance of a specific function.

Study Animal: Any animal that participates in a clinical trial, either as a recipient of the investigational veterinary product or as a control.

Study Protocol: A document containing the background, objective, rationale, design, methodology including matters concerning performance, management, conduct, analysis, adverse event reporting, withdrawal, statistical consideration and record keeping pertaining to clinical trial.

Study Protocol Amendment: A written change or modification of the study protocol effected prior to the implementation of the protocol or execution of the changed or modified task. Study protocol amendments should be signed and dated by the investigator and sponsor and incorporated into the study protocol.

Study Protocol Deviation: A departure from the procedures stated in the study protocol. Study protocol deviations should be recorded as a statement signed and dated by the investigator describing the deviation and the reason for its occurrence (if identifiable).

Target Animal: The specific animal by species, class and breed identified as the animal for which the investigational veterinary product is intended for use.

Annexure-1

FORM 44

(See rules 122A, 122B, 122D and 122 DA)

Application for grant of permission to import or manufacture a New Drug or to undertake clinical trial.

I/We*…… of M/s. ..... …….. (address) hereby apply for grant of permission for import of and/or clinical trial or for approval to manufacture a new drug or fixed dose combination or subsequent permission for already approved new drug. The necessary information / data is given below:

1. Particulars of new drug:

(1) Name of the drug.

(2) Dosage form.

(3) Composition of the formulation:

(4) Test specification.

(i) active ingredients.

(ii) inactive ingredients.

(5) Pharmacological classification of the drug.

(6) Indications for which proposed to be used.

(7) Manufacturer of the raw material (bulk drug substances).

2. Data submitted along with the application (as per Schedule Y with indexing and page numbers:)

A. Permission to market a new drug:

(1) Chemical and Pharmaceutical information.

(2) Animal Pharmacology.

(3) Animal Toxicology.

(4) Human / Clinical Pharmacology (Phase I).

(5) Exploratory Clinical Trials (Phase II).

(6) Confirmatory Clinical Trials (Phase III) (including published review articles)

(7) Bio-availability, dissolution and stability study data.

(8) Regulatory status in other countries.

(9) Marketing information:

(a) Proposed product monograph.

(b) Drafts of labels and cartons.

(10) Application for test license.

(11) New Chemical Entity and Global Clinical Trials-

(a) Assessment of Risk versus benefit to the patients.

(b) Innovation vis-avis existing therapeutic option.

(c) Unmet medical need in the country.

B. Subsequent approval / permission for manufacture of already approved new drug:

(a) Formulation:

(1) Bio-availability / bio-equivalence protocol.

(2) Name of the investigator/center.

(3) Source of raw material (bulk drug substances) and stability study data.

(b) Raw material (bulk drug substances):

(1) Manufacturing method.

(2) Quality control parameters and/or analytical specification, stability report.

(3) Animal toxicity data.

(C) Approval / Permission for fixed dose combination:

(1) Therapeutic Justification. (authentic literature in peer-reviewed journals/text books)

(2) Data on pharmacokinetics/pharmacodynamics combination.

(3) Any other data generated by the applicant on the safety and efficacy of the combination.

(D) Subsequent Approval or approval for new indication - new dosage form:

(1) Number and date of Approval / permission already granted.

(2) Therapeutic justification for new claim / modified dosage form

(3) Data generated on safety, efficacy and quality parameters.

A total fee of rupees ..... (in words) ..... has been credited to the Government under the Head of Account..... (Photocopy of receipt is enclosed).

Dated : .....

Signature……..

Designation…….

Note: *Delete whichever is not applicable.

Annexure-2

FORM 45

(Refer rules 122 A, 122 D and 122 DA)

Permission to import Finished Formulation of the New Drug.

Number of the permission and date of issue…….. M/s .....of……. (address) is hereby permitted to import the following new drug formulation under rule 122 A /122 D/122 DA of the Drugs and Cosmetics Rules, 1945.

(1) Name of the New Drug:

(2) Dosage form:

(3) Composition:

(4) Indications:

Dated: ..... Signature.....

Name and designation of Licensing Authority

Conditions for Grant of Approval / Permission.

(1) The formulation shall conform to the specifications approved by the Licensing Authority.

(2) The proper name of the drug shall be printed or written in indelible ink and shall appear in a more conspicuous manner than the trade name, if any, which shall be shown immediately after or under the proper name on the label of the innermost container of the drug or every other covering in which the container is packed.

(3) The label of the innermost container of the drug and every other covering in which the container is packed shall bear a conspicuous red vertical line on the left side running throughout the body of the label which shall not be less than 1 mm in width and without disturbing the other conditions printed on the label to depict it as prescription drug.

(4) The label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning:

"WARNING : To be sold by retail on the prescription of a ..... Only."

(5) Post marketing surveillance study shall be conducted during initial period of two 239 Drugs and Cosmetics Rules, 1945 years of marketing of the new drug formulation, after getting the protocol and the names of the investigator duly approved by the Licensing Authority.

(6) All reported adverse reactions related to the drug shall be intimated to the Drugs Controller, India and Licensing Authority and regulatory action resulting from their review should be complied with.

(7) No claims except those mentioned above shall be made for the drug without the prior approval of the Licensing Authority.

(8) Specimen of the carton, labels, package insert that will be adopted for marketing the drug in the country shall be got approved from the Licensing Authority before the drugs is marketed.

(9) Each consignment of imported drug shall be accompanied by a test/analysis report.

Annexure-3

FORM 46

(Refer rules 122 B, 122 D and 122 DA)

Permission / Approval for manufacture of new drug formulation

Number of permission and date of issue ..... M/s …… of ..... (address) is hereby granted Permission/Approval to manufacture following new drug formulation under rule 122B/122D/122DA of the Drugs and Cosmetics Rules, 1945, namely:-

(1) Name of the formulation:

(2) Dosage form:

(3) Composition:

(4) Indications:

Dated ……. Signature ..... ……

Name and designation of Licensing Authority

Conditions for Grant of Approval / Permission.

(1) The formulation shall conform to the specifications approved by the Licensing Authority.

(2) The proper name of the drug shall be printed or written in indelible ink and shall appear in a more conspicuous manner than the trade name, if any, which shall be shown immediately after or under the proper name on the label of he innermost container of the drug or every other covering in which the container is packed.

(3) The label of the innermost container of the drug and every other covering in which the container is packed shall bear a conspicuous red vertical line on the left side running throughout the body of the label which shall not be less than 1 mm in width and without disturbing the other conditions printed on the label to depict it as prescription drug.

(4) The label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning:

"WARNING : To be sold by retail on the prescription of a .....only."

(5) Post marketing surveillance study shall be conducted during initial period of two years of marketing of the new drug formulation, after getting the protocol and the names of the investigator duly approved by the Licensing Authority.

(6) All reported adverse reactions related to the drug shall be intimated to the Drugs Controller, India and Licensing Authority and regulatory action resulting from their review should be complied with.

(7) No claims except those mentioned above shall be made for the drug without the prior approval of the Licensing Authority.

(8) Specimen of the carton, labels, package insert that will be adopted for marketing the drug in the country shall be got approved from the Licensing Authority before the drug is marketed.

Annexure-4

[FORM 40]
(See rule 24-A)
Application for issue of Registration Certificate for import of drugs into India under the Drugs and Cosmetics Rules 1945

I/We* ..... (Name and full address) hereby apply for the grant of Registration Certificate for the manufacturer, M/s..... (full address with telephone, fax and E-mail address of the foreign manufacturer) for his premises, and manufactured drugs meant for import into India.

1. Names of drugs for registration.

2. I/We enclose herewith the information and undertakings specified in ScheduleD (1) and Schedule D(II) duly signed by the manufacturer forgrant of Registration Certificate for the premises stated below.

3. A fee of_____for registration of premises, the particularsof which are given below, of the manufacturer has been credited to theGovernment under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines‖ under the Drugs and Cosmetics Rules, 1945-Central videChallan No._____ dated_____(attached in original).

4. A fee of_____for registration of the drugs forimport as specified at Serial No. 2 above has been credited to the Governmentunder the Head of Account "0210-Medical and PublicHealth, 04-Public Health,104-Fees and Fines" under the Drugs and Cosmetics Rules, 1945-Central vide
Challan No._____, dated_____. (attached in original).

5. Particulars of premises to be registered where manufacture iscarried on:

Address (es).....
Telephone No.....
Fax.....
E-mail.....

I/We* undertake to comply with all terms and conditions required toobtain Registration Certificate and to keep it valid during its validity period.

Place: Name

Date: Designation _____

Signature Seal/Stamp of manufacturer or his authorised Agentin India.

(Note: In case the applicant is an authorised agent of the manufacturer in India, the Power of Attorney is to be enclosed).

*Delete whichever is not applicable.

Annexure-5

[FORM 41]
(See rule 27 A)
RegistrationCertificate
Registration Certificate to be issued for import of drugs into India under Drugs and Cosmetics Rules, 1945

Registration Certificate No..... Date.....

M/s _____ (Name and full address of registered office) having factory premises at.....(full address) has been registered under rule 27-A as a manufacturer and is hereby issued this Registration Certificate.

2. Name (s) of drugs which may be imported under this Registration Certificate.

3. This Registration Certificate shall be in force from _____ to unless it is sooner suspended or cancelled under the rules.

4. This Registration Certificate is issued through the office of the manufacturer or his authorised agent in India M/s (name and full address)_____ who will be responsible for the business activities of the manufacturer, in India in all respects.

5. This Registration Certificate is subject to the conditions, stated below and to such other conditions as may be specified in the Act and the rules, from time to time.

Place..... LicensingAuthority
Date..... Seal/Stamp

Conditions of the Registration Certificate.

1. The Registration Certificate shall be displayed at a prominent place by the authorised agent.
2. No drug shall be registered unless it has a free sale approval in the country of origin, and/or in other major countries.
3. The manufacturer or his authorised agent in India shall comply with the conditions of the import licence issued under the Drugs and Cosmetics Rules, 1945.
4. The manufacturer or his authorised agent in India shall inform the licensing authority forthwith in the event of any administrative action taken due to adverse reaction, viz. market withdrawal, regulatory restrictions, or cancellation of authorization, and/or not of standard quality report of any drug pertaining to this Registration Certificate declared by the Regulatory Authority of the

country of origin or by any Regulatory Authority of any other country, where the drug is marketed/sold or distributed.
The dispatch and marketing of the drug in such cases shall be stopped immediately, and the licensing authority shall be informed immediately. Further action in respect of such stopped marketing of drug shall be followed as per the direction of the licensing authority. In such cases, action equivalent to that taken with reference to the concerned drug in the country of origin or in the country of marketing shall be followed in India also, in consultation with the licensing authority. The licensing authority may, however, direct any further modification to this course of action, including the withdrawal of the drug from Indian market within 48 hours time period.
5. The manufacturer or his authorised agent in India shall inform the licensing authority within 30 days in writing in the event of any change in manufacturing process, or in packaging, or in labelling or in testing, or in documentation of any of the drugs pertaining to this Registration Certificate.
In such cases, where there shall be any major change/modification in manufacturing, or in processing or in testing, or in documentation as the case may be, at the discretion of the licensing authority, the manufacturer or his authorised agent inIndia shall obtain necessary approval within 30 days by submitting a separate application along with the registration fee, as specified in clause (ii) of sub-rule (3) of rule 24-A.
6. The manufacturer or his authorised agent in India shall inform the licensing authority immediately in writing in the event of any change in the constitution of the firm and / or address of the registered office / factory premises operating under this Registration Certificate. Where any such change in the constitution of the firm and/or address takes place, the current Registration Certificate shall be deemed to be valid for a maximum period of three months from the date on which the change has taken place unless, in the meantime, a fresh Registration Certificate has been taken from the licensing authority in the name of the firm with the changed constitution of the firm and/or changed address of the registered office or factory premises.]

Annexure-6

[FORM 8]
(See rule 24)
Application for licence to import drugs (excluding those specified in Schedule X) to the Drugs and Cosmetics Rules, 1945

I/We* ..... (full address with telephone number, faxnumber and e-mail address) hereby apply for a licence to import drugs specified belowmanufactured by M/s ..... (full address with telephone no, fax ande- mail no.).
2. Names of the drugs to be imported:
(1)
(2)
(3)
3. I/We* ..... enclose herewith an undertaking in Form 9dated .....signed by the manufacturer as required by rule 24 of the Drugs and CosmeticsRules, 1945.
4. I/We* ..... enclose herewith a copy of RegistrationCertificate concerning the drugs to be imported in India, issued under Form 41 of the rules,vide Registration Certificate No .....dated ..... issued through M/s..... (name and full address) .....valid up to .....
5 I/W e * .....hold a valid wholesale licence for sale ordistribution of drugs or valid licence to manufacture drugs, under the provisions of the Act andrules made thereunder. A copy of the said licence is enclosed.
6. A fee of .....has been credited to Government under the Head of Account "0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines" under the Drugs andCosmetics Rules, 1945 - Central vide Challan No ..... dated .....(attached inoriginal)

Signature .....
Name.....
Designation .....
Seal/Stamp of Manufacturer's agent in India.

Place: .....
Date: .....

*Delete whichever is not applicable.]

Annexure-7

[FORM 10]
(See rules 23 and 27)
Licence to import drugs (excluding those specified in Schedule X) to the Drugs and Cosmetic Rules, 1945

Licence Number ..... Date ... .

..... (Name and full address of the importer) is hereby licensed to import into India during the period for which the licence is inforce, the drugs specified below, manufactured by M/s .....(name and full address) and any other drugs manufactured by the said manufacturer as mayfrom time to time be endorsed on this licence.

2. This licence shall be in force from ..... to ..... unless it is soonersuspended or cancelled under the said rules.

3.Names of drugs to be imported.

Place : .....
Date : .....

Licensing Authority
Seal/S t amp

Conditions of Licence.

1. A photocopy of licence shall be displayed in a prominent place in a part of the premises, and the original licence shall be produced, whenever required.

2. Each batch of drug imported into India shall be accompanied with a detailed batch test report and a batch release certificate, duly signed and authenticated by the manufacturer with date of testing, date of release and the date of forwarding such reports. The imported batch of each drug shall be subjected to examination and testing as the licensing authority deems fit prior to its marketing.

3. The licensee shall be responsible for the business activities of the manufacturer in India along with the registration holder and his authorised agent.

4. The licensee shall inform the licensing authority forthwith in writing in the event of any change in the constitution of the firm operating under the licence. Where any change in the constitution of the firm takes place, the current licence shall be deemed to be valid for a maximum period of three months from the date on which the change takes place unless, in the meantime, a fresh licence has been taken from the licensing authority in the name of the firm with the changed constitution.]

Annexure -8

FORM 11

(See rule 33)

Licence to import drugs for the purposes of examination, test or analysis

I ……of ..... is hereby licensed to import from ..... the drugs specified below for the purposes of examination, test or analysis at .....or in such other places as the licensing authority may from time to time authorise.

1. This licence is subject to the conditions prescribed in the Rules under the Drugs and Cosmetics Act, 1940.
2. This licence shall, unless previously suspended or revoked, be in force for a period of one year from the date specified below:-

Name of drugs	Quantities which may be imported

Date……

Licensing Authority

Annexure -9

FORM 12

(See rule 34)

Application for licence to import drugs for purpose of examination, test or analysis

I,……resident of ……. Byoccupation……. hereby apply for a licence to import the drugs specified below for the purposesof examination, test or analysis at ..... from .....and I undertake to comply withthe conditions applicable to the licence.

[A fee of rupees ..... has been credited to Government under the head of Account —0210-Medical and Public Health, 04-Public Health, 104-Fees and Fines‖ under the Drugs and Cosmetics Rules,1945-Central vide Challan No…….dated……(attached in original).]

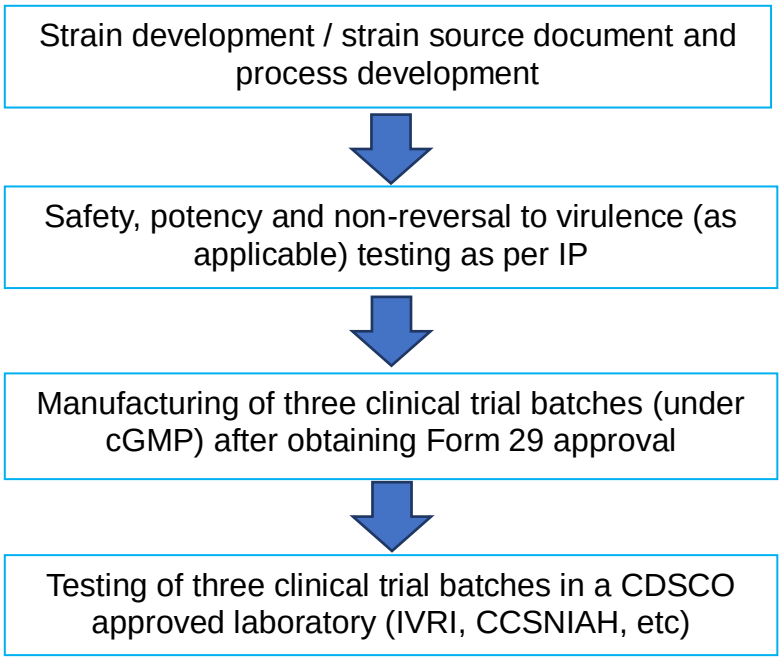
Name of drugs	Quantities which may be imported

Date……

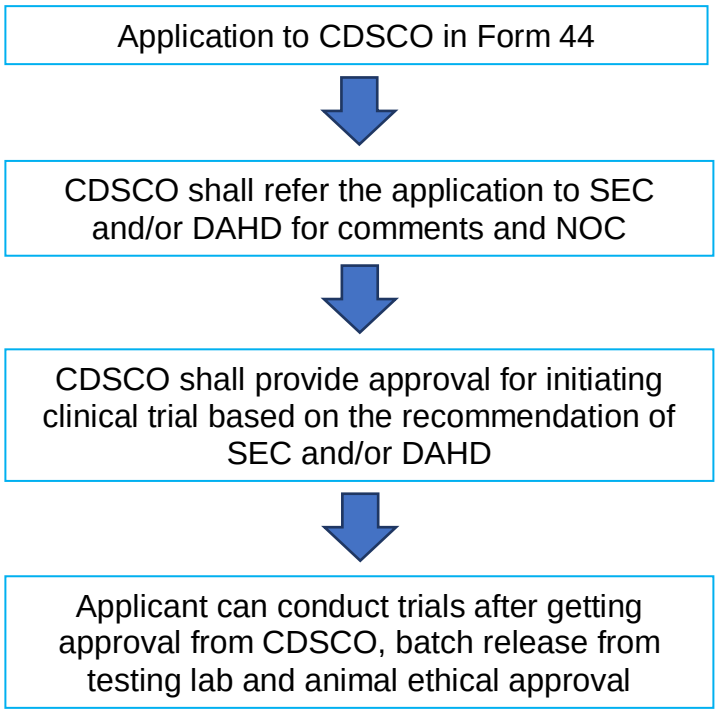
Signature……

Indigenous development ofVaccines

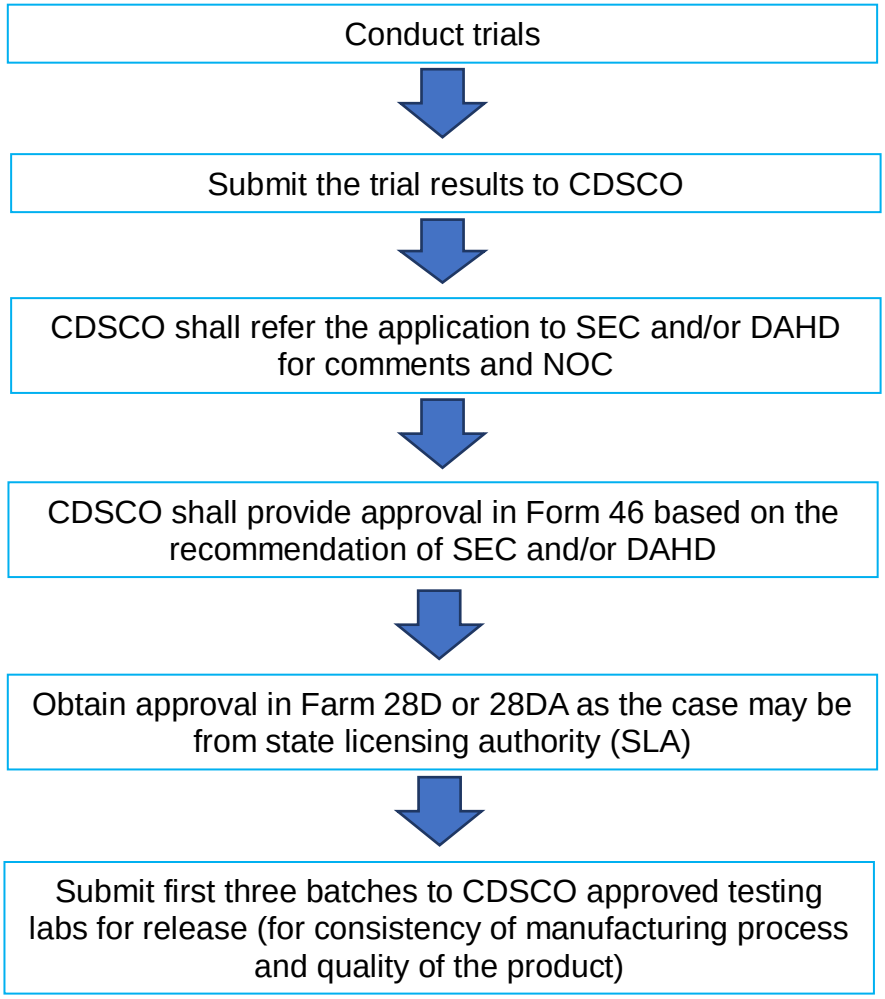
Product development and clinical trial batch manufacturing



Clinical trial / field trial approval



Conducting Clinical/ field trial and obtaining product license



Import and marketing of Vaccines

Import of vaccine for clinical trial purpose

Overseas manufacturing site and the vaccines to be imported shall be registered with the CDSCO in **Form 41**

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For import of Vaccines for the purpose of test, Analysis and conduct of clinical trials, the applicant may apply in Form 12 to CDSCO

↓

CDSCO shall refer the application to SEC and/ or DAHD for comments and NOC

↓

CDSCO shall provide approval for import in Farm 11 based on the recommendation of SEC and/ or DAHD

↓

Import of vaccine for clinical trial purpose and Testing of three trial batches (or commercial batches if the vaccine is under marketing in other countries) in a CDSCO approved laboratory (IVRI, CCSNIAH, etc)

Approval for Clinical trial/ field trial

Application to CDSCO in Form 44

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CDSCO shall refer the application to SEC and/or DAHD for comments and NOC

↓

CDSCO shall provide approval for initiating clinical trial based on the recommendation of SEC and/or DAHD

↓

Applicant can conduct trials after getting approval from CDSCO, batch release from testing lab and animal ethical approval

Conducting Clinical/ field trial and obtaining product license