DRAFT REGULATORY GUIDELINES FOR DEVELOPMENT OF VACCINES WITH SPECIAL CONSIDERATION FOR COVID-19 VACCINE

Central Drugs Standard Control Organization

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INDEX

1. Introduction

The main objective of development of vaccine is to generate adequate data on quality, safety, immunogenicity and /or efficacy to support application for marketing authorization.

As vaccines are heterogeneous class of medical products, much of the considerations for their development should be given on a product-specific basis.

Requirements may vary depending on the type of vaccine whether it is inactivated or live attenuated microorganisms based or antigen based which is extracted from pathogen or derived from r-DNA technology or by chemical synthesis, or a vaccine containing naked nucleic acid, including plasmids for expressing specific antigens or otherwise, it will also be dependent on manufacturing process, its mechanism of action and the nature of the disease to be prevented as well as target population.

This guidance provided in these documents will be applicable in general for CMC, nonclinical and clinical development of any vaccine including COVID-19 vaccines.

This document will provide guidance to the vaccine developers to ensure that-

--vaccines are well-characterized and manufactured consistently.

--Vaccines remain stable at the recommended storage conditions for the duration of clinical trial during clinical development stage and throughout its shelf life post approval.

--adequate toxicity data as well as immunogenicity in respect of humoral and/or cell-mediated immune response are generated in nonclinical studies in relevant animal models.

--challenge studies in relevant animal species and non-human primates may be conducted concurrently with clinical trial.

--adequate clinical data to establish safety and humoral, cell-mediated immunogenicity are generated.

--Post Marketing Surveillance including assessment of Adverse Events Following Immunization (AEFI) and Adverse Events of Special Interest (AESI) is carried out to assess vaccine safety in post market scenario.

2. Background

Import or manufacture for sale of drugs including vaccines are regulated under Drugs and Cosmetics Act, 1940 and Drugs & cosmetics Rules, 1945 and New Drugs and Clinical Trials Rules, 2019. Detailed requirements and guidelines for conduct of nonclinical and clinical studies and approval of new drug which includes vaccine are specified in SECOND SCHEDULE of New Drugs and Clinical Trials Rules, 2019.

As per the rules, products like vaccines, r-DNA derived products, LMO, Stem cell derived products, gene therapeutic products, etc are always considered to be new drugs. For such products manufacturers are required to obtain manufacturing permission from CDSCO under the New Drugs and Clinical Trials Rules, 2019 before Licencing the product under the Drugs and Cosmetics Rules,1945

The manufacturing licence for such product is granted after joint evaluation and inspection by the concerned State Licencing Authority & CDSCO.

In general, all vaccines including the vaccines against CORONA virus infection manufactured / imported into the country are required to comply with the requirements and guidelines specified in the Drugs and Cosmetics Rules, 1945 & New Drugs and Clinical Trials Rules, 2019 and other applicable guidelines published by CDSCO form time to time in case of manufacturer r-DNA derived vaccines the requirements and guidelines prescribed by Department of Biotechnology are also required to be complied with. However, vaccines unlike chemical drugs are complex heterogeneous class of medical products, and hence specific consideration in respect of development of CMC data, non-clinical data, and clinical data will provide clear understanding of regulatory landscape for their development and approval in a scientific manner. Therefore, these documents have been prepared to provide detailed guidelines and regulatory pathways for CMC, nonclinical and clinical development of vaccines including COVID-19 vaccines.

3. Chemistry, manufacturing & controls

3.1 General Consideration

In general, all vaccines including the vaccines against CORONA virus infection manufactured / imported into the country are required to comply with the requirements and guidelines for CMC specified in the Drugs and Cosmetics Rules, 1945 & New Drugs and Clinical Trials Rules, 2019 and other applicable guidelines published by CDSCO from time to time.

All vaccines are required to be characterized and manufactured in compliance with the Good Manufacturing Practices (GMP) as prescribed in the Rules.

It is important that the manufacturing processes of every vaccine are validated, defined and controlled adequately to ensure batch to batch consistency

This Section of the documents specify the need for appropriate starting materials, including seed lot system and cell banks; strict adherence to established protocols; tests for identity, purity, potency, stability and safety at specific steps during production; and documentation of the records properly.

3.2 Manufacturing

The biological nature of the starting materials, the manufacturing process and the test methods needed to characterize batches of the product are important elements to be considered for vaccine production and interpretation of preclinical testing of vaccines.

Establishment of a seed-lot system is essential for vaccine production. The quality, safety and potency of vaccine are usually sensitive to changes in manufacturing conditions. Therefore, purity and quality of the starting material (raw materials and seeds), in-process control testing, testing for process additives and process intermediates and the development and establishment of lot release tests are required to be demonstrated.

Moreover, as the relationship between physical and chemical characteristics, and the immunogenicity and efficacy of these products is frequently not completely

understood, biological characterization through the use of biological assays should always complement the physical and chemical product characterization.

The development of appropriate laboratory methods to characterize a vaccine formulation with respect to its components, as well as its safety and potency, is a prerequisite to the clinical use of new or novel vaccines including vaccine against CORONA viruses.

Consistency of production is essential, and the demonstration that the product does not differ from vaccine lots that have been shown to be safe and adequately immunogenic and protective in clinical studies is a crucial component of vaccine evaluation, approval and batch release.

For this reason, manufacturers should make every effort to characterize these clinical lots and if possible to keep some of these lots for future reference.

Where no appropriate animal model exists for testing potency or where direct serological or immunological correlates of clinical protection are not available, as in the case of CORONA vaccine, the challenge is to ensure that each production batch has the same protective efficacy as those batches shown to be protective in clinical trials.

In such cases, emphasis should be given on assuring the consistency of production using modern physical, chemical and immunological methods that enable characterization of some products to a degree of precision.

The vaccine lots used in preclinical studies should be adequately representative of the formulation intended for use in the clinical trial and, ideally, preclinical testing should be done on the same lot as that proposed for the clinical trials. If this is not feasible, then the lots studied should be comparable with respect to physicochemical data, stability and formulation.

Any change proposed to the manufacturing process during vaccine development should be considered carefully to evaluate its impact on the quality, safety and efficacy of the vaccine and the possible need for additional nonclinical and clinical investigations.

Subsequent changes in production methods or scale-up following product approval will necessitate further product characterization to demonstrate comparability with the original lot(s) used to demonstrate safety and efficacy of the product.

The extent of comparability testing needed depends on the nature of the changes implemented. These changes should be documented and submitted to CDSCO for approval or notification depending on the nature of changes made.

For further guidance in this matter, the guidelines published by CDSCO for Post Approval Changes for biological should be referred.

3.3 Potency

Potency measurement is often used to verify the consistency of the manufacturing process. Classical challenge studies in animals immunized with the vaccine under consideration are developed for routine potency assays. Where no suitable animal

challenge model exists, potency is often based on measurement of immune responses, usually serological.

Recombinant DNA methodology and modern physicochemical techniques have resulted in the manufacture of highly purified products that can be better characterized than the classic biological. However, for these products, characterization using physicochemical parameters, such as amount of antigen, size of the antigen, protein content and others can be used as a measure of consistency, but not necessarily of the potency of a vaccine, as the ability to measure the “relevant” biological activity for such products may still be lacking

For live attenuated vaccines, the approach to potency measurement is generally different. The potency of live viral vaccines is usually based on titration of the minimum infective dose in cell culture or chicken embryos, which may be considered as a surrogate marker of potency, but not as a measure of potency itself.

For vaccines that express inserts encoding heterologous vaccine antigens (vaccines based on viral or bacterial vectors), it is not sufficient to determine the “biological activity” of the entire construct by measuring colony forming units (CFU) or infectious titre. For these vaccines, the use of other methods such as the quantitation of the expression of the insert, or the evaluation of the effective dose (ED50) of the vectored vaccine should be considered.

3.4 Stability

The evaluation of vaccine stability is complex, as they are very susceptible to inactivation by environmental factors. Potency should be measured as a part of the stability testing, except in those cases where potency testing based on biological activity is not possible.

Physical and chemical product characterization should be included in the stability evaluation.

For a product entering human clinical trials, sufficient data should be collected to support the stability of the product for the duration of the clinical trial.

In certain cases, accelerated stability data may be used to support preliminary data obtained at the normal storage temperature.

Stability data to support licensure should be obtained under the proposed storage conditions and should be based on long-term, real-time stability studies.

Finally, the stability of standards and reference materials also needs to be considered to ensure that the procedures used to measure relevant parameters are reliably standardized.

3.5 Batch release and independent laboratory evaluation

The potential variability of methods for the production of biologicals emphasizes to specify requirements to define procedures for assuring the quality of vaccines and for assessing consistency.

Licensed vaccines are subject to independent batch release through review, testing and authorizing release of a batch of vaccine by Central Drugs Laboratory, Kasauli before release into the market.

Validation and establishment of lot release tests and specifications are a process that continues throughout product development and should be finalized prior to licensing.

Samples of vaccine for clinical trials are also required to be manufactured under a License in Form-29 granted based on inspection jointly by the CDSCO and the concerned State Licensing Authority, as a part of the approval process for clinical trials.

4. Nonclinical Development Programme

4.1 General Considerations

Nonclinical studies in animal models are required to be conducted to identify potential vaccine related safety risks and assess immunogenicity. The safety studies are also important for determine the dose, dosing regimen, and route of administration to be used in clinical trial.

Nonclinical immunogenicity studies should assess the relevant immune response, e.g. humoral and/or cell-mediated immune response, and functional immune responses. The aspects of immunogenicity to be measured should be appropriate for the vaccine construct and its intended mechanism of action.

Depending on the immune response induced, immunogenicity studies may include an evaluation of seroconversion rates, geometric mean antibody titres, or cell-mediated immunity in vaccinated animals.

These studies may also be designed to address interference between antigens and/or live viruses.

If a vaccine consists of more than one defined antigen the response to each antigen should be evaluated.

The extent of nonclinical data required to support proceeding to first in human (FIH) clinical trials depends on the vaccine construct, the supportive data available for the construct and data from closely related vaccines.

Challenge studies with the corresponding infectious agent may be conducted to confirm the relevance of the animal models concurrently with phase I clinical trial.

4.2 Special consideration for COVID-19 vaccine

Data from studies in animal models administered certain vaccine constructs against other coronaviruses (SARS-CoV and MERS-CoV) have raised concerns of a theoretical risk for COVID-19 vaccine-associated Enhanced Respiratory Disease (ERD).

In these studies, animal models were administered vaccine constructs against other coronaviruses and subsequently challenged with the respective wild type virus.

These studies have shown evidence of immunopathologic lung reactions characteristic of a Th-2 type hypersensitivity similar to ERD described in infants and

animals that were administered formalin-inactivated respiratory syncytial virus (RSV) vaccine and that were subsequently challenged with RSV virus due to natural exposure or in the laboratory, respectively.

COVID vaccine candidates should be assessed in light of the above studies, as described below.

For a COVID-19 vaccine candidate consisting of a novel product type and for which no prior nonclinical and clinical data are available, nonclinical safety studies will be required prior to proceeding to FIH clinical trials.

The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design. The principles of the “3Rs,” to reduce, refine, and replace animal use in testing when feasible should be followed.

In some cases, it may not be necessary to perform nonclinical safety studies prior to FIH clinical trials because adequate information to characterize product safety may be available from other sources. For example, if the COVID-19 vaccine candidate is made using a platform technology utilized to manufacture an approved vaccine or other previously studied investigational vaccines and is sufficiently characterized, it may be possible to use toxicology data (e.g., data from repeat dose toxicity studies, biodistribution studies) and clinical data accrued with other products using the same platform to support FIH clinical trials for that COVID-19 vaccine candidate.

When needed to support proceeding to FIH clinical trials, nonclinical safety assessments including toxicity and local tolerance studies must be conducted under conditions of Good Laboratory Practices (GLP).

Such studies should be completed and analyzed prior to initiation of FIH clinical trials.

When toxicology studies do not adequately characterize risk, additional safety testing should be conducted as appropriate.

Use of COVID-19 preventive vaccines in pregnancy and in women of childbearing potential will be an important consideration for vaccination programs. Therefore, prior to enrolling pregnant women and women of childbearing potential who are not actively avoiding pregnancy in clinical trials; applicant is required to conduct developmental and reproductive toxicity (DART) studies with their respective COVID-19 vaccine candidate.

Alternatively, applicant may submit available data from DART studies with a similar product using comparable platform technology if, those data are scientifically sufficient.

Biodistribution studies in an animal species should be considered if the vaccine construct is novel in nature and there are no existing biodistribution data from the platform technology.

4.2.1 Characterization of the Immune Response in Animal Models for COVID vaccine

Immunogenicity studies in animal models responsive to the selected COVID-19 vaccine antigen should be conducted to evaluate the immunologic properties of the COVID-19 vaccine candidate and to support FIH clinical trials.

The aspects of immunogenicity to be measured should be appropriate for the vaccine construct and its intended mechanism of action.

Studies should include an evaluation of humoral, cellular, and functional immune responses, as appropriate to each of the included COVID-19 antigens. Use of antigen-specific enyzme linked immunosorbent assays (ELISA) should be considered to characterize the humoral response.

Evaluation of cellular reponses should include the examination of CD8+ and CD4+ T cell responses using sensitive and specific assays. The functional activity of immune responses should be evaluated in vitro in neutralization assays using either wild-type virus or pseudovirion virus. The assays used for immunogencity evaluation should be demonstrated to be suitable for their intended purpose.

4.2.2 Studies to Address the Potential for COVID Vaccine-associated Enhanced Respiratory Disease (ERD).

To support proceeding to FIH clinical trials, sponsors should conduct studies characterizing the vaccine-induced immune response in animal models evaluating immune markers of potential ERD outcomes.

These should include assessments of functional immune responses (e.g., neutralizing antibody) versus total antibody responses and Th1/Th2 balance in animals vaccinated with clinically relevant doses of the COVID-19 vaccine candidate.

COVID-19 vaccine candidates with immunogenicity data demonstrating high neutralizing antibody titers and Th1-type T cell polarization may be allowed to proceed to FIH trials without first completing post-vaccination challenge studies in appropriate animal models provided adequate risk mitigation strategies are put in place in the FIH trials.

In these situations, post-vaccination challenge studies are expected to be conducted in parallel with FIH trials to ensure the potential for vaccine-associated ERD is addressed prior to enrolling large numbers of human subjects into Phase 2 and 3 clinical trials.

For COVID-19 vaccine candidates for whom other data raise increased concerns about ERD, post-vaccination animal challenge data and/or animal immunopathology studies are critical to assess protection and/or ERD prior to advancing to FIH clinical trials.

The totality of data for a specific COVID-19 vaccine candidate, including data from post-vaccination challenge studies in small animal models and from FIH clinical trials characterizing the type of immune responses induced by the vaccine will be considered in determining whether Phase 3 studies can proceed in the absence of post-vaccination challenge data to address risk of ERD.

A primary concern in interpreting the data obtained from such studies should be to determine how closely the animal model resembles the disease and immune response in humans. It should be recognized that animal models frequently fail to predict immunogenicity and efficacy in humans.

4.3 Toxicity assessments

As the design of any toxicity study is product-specific and based on indications, modifications to the framework outlined below may be necessary in response to particular product features, availability of animal models, methodologies, etc.

Special toxicity assessments that may be required should be decided on a case-by-case basis.

4.3.1 Study design

The preclinical toxicity study should be adequate to identify and characterize potential toxic effects of a vaccine to allow investigators to conclude that it is reasonably safe to proceed to clinical investigation.

The parameters to be considered in designing animal toxicology studies are the relevant animal species and strain, dosing schedule and method of vaccine administration, as well as timing of evaluation of end-points (e.g. sampling for clinical chemistry, antibody evaluation and necropsy).

The route of administration should correspond to that intended for use in the clinical trials.When the vaccine is to be administered in human clinical trials using a particular device, the same device should be used in the animal study, where feasible (e.g. measles aerosol vaccine in the monkey model).

Potential toxic effects of the product should be evaluated with regard to target organs, dose, route(s) of exposure, duration and frequency of exposure, and potential reversibility.

The toxicity assessment of the vaccine formulation can be done either in dedicated-stand alone toxicity studies or in combination with studies of safety and activity that have toxicity endpoints incorporated into the design. The study should also include an assessment of local tolerance.

4.3.2 Special consideration for COVID-19 vaccine

Studies in animal models (e.g., rodents and non-human primates) are considered important to address the potential for COVID vaccine-associated ERD.

Post-vaccination animal challenge studies and the characterization of the type of the nonclinical and clinical immune response induced by the particular COVID-19 vaccine candidate can be used to evaluate the likelihood of the vaccine to induce vaccine-associated ERD in humans.

To support proceeding to FIH clinical trials, sponsors should conduct studies characterizing the vaccine-induced immune response in animal models evaluating immune markers of potential ERD outcomes.

These should include assessments of functional immune responses (e.g., neutralizing antibody) versus total antibody responses and Th1/Th2 balance in animals vaccinated with clinically relevant doses of the COVID-19 vaccine candidate.

COVID-19 vaccine candidates with immunogenicity data demonstrating high neutralizing antibody titers and Th1-type T cell polarization may be allowed to proceed to FIH trials without first completing post-vaccination challenge studies in appropriate animal models provided adequate risk mitigation strategies are put in place in the FIH trials.

In these situations, post-vaccination challenge studies are expected to be conducted in parallel with FIH trials to ensure the potential for vaccine-associated ERD is addressed prior to enrolling large numbers of human subjects into Phase 2 and 3 clinical trials.

For COVID-19 vaccine candidates for which other data raise increased concerns about ERD, post-vaccination animal challenge data and/or animal immune-pathology studies are critical to assess protection and/or ERD prior to advancing to FIH clinical trials.

The totality of data for a specific COVID-19 vaccine candidate, including data from post vaccination challenge studies in small animal models and from FIH clinical trials characterizing the type of immune responses induced by the vaccine are taken into consideration in determining whether Phase 3 studies can proceed in the absence of post-vaccination challenge data to address risk of ERD.

4.3.3 Animal species, sex, age and size of groups

Data to be recorded on the animals used for toxicity testing should include information on the source, species and animal husbandry procedures (e.g. housing, feeding, handling and care of animals).

Where possible, the safety profile of a product should be characterized in a species sensitive to the biological effects of the vaccine being studied.

Ideally, the species chosen should be sensitive to the pathogenic organism or toxin. The animal species used should develop an immune response to the vaccine antigen.

In general, one relevant animal species is sufficient for use in toxicity studies to support initiation of clinical trials. However, there may be situations in which two or more species may be necessary to characterize the product, for example where the mechanism of protection induced by the vaccine is not well understood (for example, intranasal influenza vaccine and intranasal measles vaccine).

In addition, when species-specific or strain-specific differences in the pharmacodynamics of the product are observed, it may be necessary to address the nonclinical safety of the product in more than one safety study and in more than one animal model.

The size of the treatment group depends on the animal model chosen. The number of animals used in studies using non-human primates would be expected to be less than that in studies that used rodents.

For small animal models, e.g. rats and mice, it is recommended that approximately 10 males + 10 females per group be studied.

In general, the approximate age at the start of the study for rodents is 6–8 weeks, and for rabbits, 3–4 months.

4.3.4 Dose, route of administration and control groups

The toxicity study should be performed using a dose that maximizes exposure of the animal to the candidate vaccine and the immune response induced, for example, peak antibody response.

In general, an evaluation of the dose–response is not required as part of the basic toxicity assessment and the lethal dose does not have to be determined.

However, pilot dose–response studies may be conducted to determine which dose induces the highest antibody production in the animal model. If feasible, the highest dose (in absolute terms) to be used in the proposed clinical trial should be evaluated in the animal model.

However, the dose is sometimes limited by the total volume that can be administered in a single injection, and guidelines on animal welfare should be followed.

In such cases, the total volume may be administered at more than one site using the same route of administration. Alternatively, a dose that exceeds the human dose on a mg/kg basis and that induces an immune response in the animal model may be used.

In such cases, the factor between human and animal dose should be justified. The number of doses administered to the test animals should be equal to or more than the number of doses proposed in humans.

To better simulate the proposed clinical usage, vaccine doses should be given at defined time intervals rather than as daily doses; the dosing interval used in the toxicity study may be shorter (e.g. an interval of 2–3 weeks) than the proposed interval in clinical trials in humans.

The dosing interval in nonclinical trials may be based on the kinetics of the primary and secondary antibody responses observed in the animal model.

A single-dose study may be performed in situations in which vaccine-induced antibodies are expected to neutralize a live viral vector, thus limiting the expression of the gene of interest (e.g. antiadenovirus immune response), or when immune responses induced in animals are expected to react with species-specific proteins present in the vaccine formulation (e.g. human recombinant cytokines used as adjuvants).

The route of administration should correspond to that intended for use in the human clinical trials. If toxic effects are observed in safety studies using a particular route of

administration (e.g. intranasal), further toxicity studies using a different route of administration (e.g. intravenous) may be helpful in understanding the full spectrum of toxicity of the product.

The study design should include a negative control group(s) to evaluate a baseline level of treatment. If appropriate, active control groups (e.g. vaccine formulation without antigen) may also be included in the study. The study should include an additional treatment group of animals to be killed and evaluated as described below at later timepoints after treatment, to investigate the reversibility of any adverse effects observed during the treatment period and to screen for possible delayed adverse effects.

4.3.5 Parameters Assessed

Toxicity studies should address the potential of the product for causing local inflammatory reactions, and possible effects on the draining lymph nodes, systemic toxicity and on the immune system. A broad spectrum of information should be obtained from the toxicity studies. Parameters to be monitored should include daily clinical observations, weekly body weights and weekly food consumption.

During the first week of administration frequent measurements of body weight and food consumption are recommended, if feasible, as these are sensitive parameters indicating “illness”.

Interim analysis of haematology and serum chemistry should be considered approximately 1–3 days following the administration of the first and last dose and at the end of the recovery period.

Haematology and serum chemistry analyses should include, at the minimum, an evaluation of relative and absolute differential white blood cell counts (lymphocytes, monocytes, granulocytes, abnormal cells) and albumin/globulin ratio, enzymes and electrolytes.

In some cases, it may also be useful to evaluate coagulation parameters, urine samples and serum immunoglobulin classes. Data should be collected not only during treatment, but also following the recovery phase (e.g. 2 weeks or more following the last dose) to determine persistence, and look at exacerbation and/or reversibility of potential adverse effects.

At study termination, final body weights (after a period of fasting) should be measured. Terminal blood samples should be collected and serum chemistry, haematology and immunological investigations should be done as described in the preceding paragraph.

The immune response induced by the candidate vaccine should be assessed in order to confirm that the relevant animal model has been selected. A complete gross necropsy should be conducted and tissues collected and preserved, gross lesions should be examined and organ weights recorded.

Histopathological examinations of tissues should be performed and special attention paid to the immune organs, i.e. lymph nodes (both local and distant from site of administration), thymus, spleen, bone marrow and Peyer’s patches or

bronchusassociated lymphoid tissue, as well as organs that may be expected to be affected as a result of the particular route of administration chosen.

Histopathological examinations should always include pivotal organs (e.g. brain, kidneys, liver and reproductive organs) and the site of vaccine administration.

The choice of tissues to be examined will depend on the vaccine in question, and the knowledge and experience obtained from previous nonclinical and clinical testing of the vaccine components.

For example, full tissue examination will be required in the case of novel vaccines for which no prior nonclinical and clinical data are available. Therefore, the list of tissues to be tested should be defined on a case by-case basis, following consultation with the relevant regulatory authority.

Data should be reported in full listing the original collection of values, and summarized.

4.3.6 Local tolerance

The evaluation of local tolerance should be conducted either as a part of the repeated dose toxicity study or as a stand-alone study. Tolerance should be determined at those sites that come into contact with the vaccine antigen as a result of the method of administration, and also at those sites inadvertently exposed (e.g. eye exposure during administration by aerosol) to the vaccine. More details have been published elsewhere. If abnormalities are observed in the basic toxicity study further studies may be necessary to evaluate the mechanism of the toxic effect.

4.4 Additional toxicity assessments

4.4.1 Special immunological investigations

In certain cases, the results from evaluations of immune response from nonclinical and clinical studies, or from data on natural disease, may indicate immunological aspects of toxicity, e.g. precipitation of immune complexes, humoral or cell-mediated immune response against antigenic determinants of the host itself as a consequence of molecular mimicry or exacerbation of the disease (e.g. inactivated measles vaccine). In such cases, additional studies to investigate the mechanism of the effect observed might be necessary. Great similarity of vaccine determinants and host molecules could cause autoimmune reactions induced by molecular mimicry.

Therefore, any vaccine antigen whose characteristics might mimic those of a host antigen should be treated with caution, even though it is recognized that molecular mimicry does not necessarily predispose to autoimmunity. Because considerable efforts may be required in selecting and developing relevant animal models to address the above issues, caution should be exercised and a strong rationale provided when developing vaccines for diseases associated with autoimmune pathology. If data suggest that the pathogen against which the vaccine is directed may cause autoimmune pathology, studies may be needed to address this concern on a case-by-case basis, if an appropriate animal model exists. It should be noted that observations of biological markers for autoimmune reactions are not necessarily linked to pathogenic consequences. For instance, the presence of autoimmune antibodies does not necessarily indicate the induction of autoimmune disease. When hypersensitivity

reactions induced by the antigen(s), adjuvants, excipients or preservatives are of concern, additional investigations may be warranted.

4.4.2 Developmental and Reproductivetoxicity studies

Use of COVID-19 preventive vaccines in pregnancy and in women of childbearing potential is an important consideration for vaccination programs.

Therefore, prior to enrolling pregnant women and women of childbearing potential who are not actively avoiding pregnancy in clinical trials, developmental and reproductive toxicity (DART) studies should be conducted with COVID-19 vaccine candidate unless a scientific and clinically sound argument is put forward by the manufacturer to show that conducting such studies is unnecessary.

For a preventive vaccine, reproductive toxicity assessments are generally restricted to prenatal and postnatal developmental studies, because the primary concern is any potential untoward effect on the developing embryo, fetus or newborn.

The need to conduct fertility and post-weaning assessments should be considered on a case-by-case basis. The animal model chosen should develop an immune response to the vaccine, which is usually determined by serum antibody measurements. In addition, it is important to evaluate maternal antibody transfer by measuring vaccine-induced antibody in cord or fetal blood to verify exposure of the embryo or fetus to maternal antibody.

The route of administration should mimic the clinical route of administration. Ideally, the maximal human dose should be administered to the test animal. If it is not possible to administer the full human dose, e.g. limitations on the total volume that can be administered, or if local toxicity is observed that may result in maternal stress, a dose that exceeds the human dose on a mg/kg basis and is able to induce an immune response in the animal should be used. To assess any potential adverse effects of the vaccine during the period of organogenesis, the gestating animal is usually exposed to the vaccine during the period from implantation until closure of the hard palate and end of gestation defined as stages C, D and E in the ICH S5a document.

Because of the relatively short gestation period of most animal models used, pre-mating treatment is frequently required to ensure maximal exposure of the embryo or fetus to the vaccine-induced immune response. For a preventive vaccine, the number of doses administered depends on the time of onset and duration of the response.

Booster immunizations may be necessary at certain times during the period of gestation to maintain a high level of antibody throughout the gestation period and to expose the developing embryo to the components of the vaccine formulation.

End-points include, but are not limited to, viability, resorptions, abortions, fetal body weight and morphology.

It is also recommended that a period of postnatal follow-up of pups from birth to weaning be incorporated in the study design to assess normality of growth, body weight gain, suckling activity and viability. Studies should therefore be designed so that test groups are divided into subgroups. Half of the animals should be delivered by

Caesarean section and the other half allowed to deliver their pups without surgical intervention.

4.4.3 Genotoxicity and carcinogenicity studies

Genotoxicity studies are normally not needed for the final vaccine formulation. However, they may be required for particular vaccine components such as novel adjuvants and additives. If needed, the in- vitro tests for mutations and chromosomal damage should be done prior to first human exposure. The full battery of tests for genotoxicity may be performed in parallel with clinical trials.

Carcinogenicity studies are not required for vaccine antigens. However, they may be required for particular vaccine components such as novel adjuvants and additives.

4.5 Safety pharmacology

The purpose of safety pharmacology is to investigate the effects of the candidate vaccine on vital functions. If data from nonclinical and/or human clinical studies suggest that the vaccine may affect physiological functions (e.g. central nervous system, respiratory, cardiovascular and renal functions) other than those of the immune system, safety pharmacology studies should be incorporated into the toxicity assessment.

4.5.1 Pharmacokinetic studies

Pharmacokinetic studies (e.g. for determining serum or tissue concentrations of vaccine components) are normally not needed. The need for specific studies should be considered on a case-by-case basis (e.g. when using novel adjuvants or alternative routes of administration) and may include local deposition studies that would assess the retention of the vaccine component at the site of injection and its further distribution (e.g. to the draining lymph nodes).

Distribution studies should be considered in the case of new formulations, novel adjuvants or when alternative routes of administration are intended to be used (e.g. oral or intranasal). 5 Special considerations

4.6 Adjuvants

Adjuvants may be included in vaccine formulations or co-administered with vaccines to enhance the immune responses to particular antigen(s), or to target a particular immune response.

It is important that the adjuvants used comply with pharmacopoeial requirements where they exist, and that they do not cause unacceptable toxicity. Adjuvant activity is a result of many factors and the immune response obtained with one particular antigen/adjuvant formulation cannot, as a rule, be extrapolated to another antigen.

Individual antigens vary in their physical and biological properties and antigens may interact differently with an adjuvant.

Adjuvants must be chosen according to the type of immune response desired and they must be formulated with the antigen in such a way that distribution of both is optimized to ensure availability to the relevant lymphatic tissues. The route of administration of

the vaccine is also an important factor influencing the efficacy and safety of an adjuvant.

The effect of the adjuvant should be demonstrated in preclinical immunogenicity studies. If no toxicological data exist for a new adjuvant, toxicity studies of the adjuvant alone should first be performed. In general, assessment of new or novel adjuvants should be undertaken as required for new chemical entity.

These data may be obtained by the vaccine manufacturer or by the producer of the adjuvant. In addition to assessing the safety of the adjuvant by itself it is also important to assess whether the combination of antigen and adjuvant exerts a synergistic adverse effect in the animal model. When species-specific proteins (e.g. cytokines) are used as novel adjuvants, the issue of species-specific response should be considered.

When evaluating the safety profile of the combination of adjuvant and vaccine, the formulation proposed for clinical use should be used. Compatibility of the adjuvant(s) (e.g. lack of immune interference) with all antigenic components present in the vaccine should be evaluated.

If applicable, adsorption of all antigenic components present in the vaccine should be shown to be consistent on a lot-to-lot basis. Potential desorption of antigen during the shelf-life of the product should be performed as a part of stability studies, the results reported and specifications set, as this may affect not only immunogenicity, but also the toxicity profile of the product. It should be noted that no adjuvant is licensed in its own right, but only as a component of a particular vaccine.

4.7 Additives (excipients and preservatives)

Where a new additive is to be used, for which no toxicological data exist, toxicity studies of the additive alone should first be performed and the results documented according to the guidelines for new chemical entities. The compatibility of a new additive with all vaccine antigens should be documented together with the toxicological profile of the final vaccine formulation under consideration in animal models.

4.8 Vaccine formulation and delivery device

The vaccine formulation (i.e. liquid form, capsules or powder), as well as the delivery device, may have an impact on the uptake of the vaccine, its effectiveness and safety. Ideally, the delivery device and vaccine formulation tested in an animal safety study should be identical to those intended to be used clinically.

However, animal models in which delivery devices intended for clinical use can be tested may not be available. In these instances, in order to develop an appropriate animal model, it may be necessary to conduct pilot studies to define and optimize the conditions for drug delivery in the animal model before it can be used to assess the preclinical safety of the product.

4.9 Alternative routes of administration

When using a vaccine formulation administered by alternative routes (e.g. intranasal, oral, intradermal, rectal and intravaginal routes), it can be assumed that their potency,

relevant immunogenicity, tolerability, toxicity, and long-term safety may differ from that of products delivered by the parenteral route. Thus, when different routes of administration are proposed, nonclinical safety studies may have to be conducted using vaccine formulation and/or adjuvant alone in a suitable animal model to address the specific safety concerns associated with vaccine administration by these routes. Particular issues relevant to vaccines administered using alternative routes that may need to be considered are discussed below.

4.9.1 Animal models

A special consideration for vaccines administered by alternative routes should be the anatomy and physiology of the site of vaccine administration of the particular animal model chosen and its accessibility for the administration of the vaccine.

For example, for intranasally administered products, the species chosen should ideally be receptive to spray administration of the product.

In general, rabbits and dogs are useful test models for use of spray devices; however, their olfactory bulbs are highly protected and special techniques would be required to ensure that the test product reached this organ.

Although mice and rats are useful models, intranasal administration to these species presents technical difficulties. Intranasal administration to non-human primates may be preferable, if they are susceptible to the infectious agent in question.

Depending on the level of concern regarding a particular route of administration or when there are species-specific differences between the animal models in their sensitivity to the candidate vaccine, it may be necessary to address the preclinical safety of the product in more than one safety study and in more than one animal model.

4.9.2 Dose

As the optimal dose derived from studies using the parenteral route of administration may differ from the dose used for alternative route(s) of administration, dose-finding studies may need to be conducted for a particular route of administration.

Also, consideration should be given to the total volume of the vaccine administered as it may affect the outcome of the safety study. For example, intranasal administration of more than 5ml of test preparation per nostril to a mouse would result in the test preparation being swallowed, rather than being adsorbed by the nasal mucosa.

4.9.3 End-points

The toxicity end-points would include those described in section 4 and may include additional outcome measures that would depend on the route of administration and specific concerns associated with the particular route and target organ.

For example, if there is concern about the potential passage of vaccine components to the brain following intranasal administration, immunohistology and “in situ” methods and/or neurological assays and examinations may be necessary.

For vaccines administered by inhalation, outcome measures may include pulmonary function tests and data on histopathology of the lungs. Considerable efforts may be required to develop appropriate methods to address potential safety concerns associated with the use of new routes of administration.

4.9.4 Immunogenicity assessment

The development of appropriate assays for measuring mucosal immune responses is critical for vaccines that are expected to function as mucosal immunogens because serological assays alone may not reflect the relevant immune response for a mucosal vaccine.

Thus, in addition to measuring serological responses, it may be necessary to evaluate T cell responses, antibody-secreting cells and cytokine production.

In addition, assays may need to be developed to assess the induction of local and systemic responses at sites distant from administration of the vaccine antigen.

5. Clinical development Programme

5.1. General Consideration

In general, the clinical development methodology and requirements as prescribed in First Schedule and Second Schedule of the New Drugs and Clinical Trials Rules, 2019 respectively are applicable for clinical development of any vaccine.

As per the rules, for new candidate vaccines discovered or developed in India, clinical trials are required to be carried out right from Phase I.

The clinical development for any new candidate vaccines should always start with a phase I clinical trial conducted in India or outside to explore the safety of different amounts of the antigen(s) in each dose of the vaccine. It is also usual that immune responses to the antigens are generated in the Phase I trial.

Permission to carry out these trials is generally given in stages, considering the data emerging from earlier phases. However, on case by case basis,clinical development programs may proceedthrough a seamless approach to expedite the development of a vaccine for which, there is an unmet medical need in the country.

Regardless of whether clinical development programs proceed in discrete phases with separate studies or via a seamless approach, adequate data should be generated to support marketing authorization application to ensure the safety and effectiveness of the vaccine.

Conducting clinical trials in the setting of a public health emergency like COVID-19 pandemic, presents operational challenges. CDSCO has issued brief guidelines providing general considerations to address challenges in conducting clinical trial in COVID pandemic situation in protecting the right, safety and well-being of trial subjects. The same should be followed for conducting the trial in present situation maintaining compliance with GCP and validity of the data generated.

In most cases the first clinical trial should be conducted in healthy adults, while, phase II trials should be conducted in subjects who are representative of the intended target population for the vaccine at the time of approval.

For vaccines intended for all age groups of population it may not be necessary in all instances to apply an age de-escalation approach generally followed for any new drug

development.If a vaccine has negligible potential benefit for older children it may be acceptable in some cases to proceed directly from trials in adults to trials in younger children, including infants and toddlers.

Phase III clinical trials may be designed to provide an estimate of vaccine efficacy or to provide an indication of the ability of the vaccine to prevent clinical disease on the basis of immunogenicity data.

On occasion, an assessment of a specific safety aspect may be the primary (or a co-primary) objective in a phase III trial.

In case, a vaccine has been developed and has undergone clinical trial development outside India and marketing authorization application for the same have been submitted to CDSCO, the clinical data generated will be considered for evaluation of overall safety and effectiveness of the vaccine. However, additional clinical trial may be required in local population to confirm the safety and effectiveness in Indian population. The extent of local clinical trial requirements will be decided on case by case basis considering the urgency, unmet need of the vaccine in the country.

5.2. Special consideration for COVID-19 Vaccine

Considering the urgent need of a safe and effective vaccine for prevention of COVID-19, clinical development programs of COVID-19 vaccine may proceed through adaptive and seamless approach. However, as applicable for any vaccine, regardless of whether clinical development programs proceed in discrete phases with separate studies or via a more seamless approach, an adequate data, including data to inform the potential risk of vaccine-associated Enhanced Respiratory Disease (ERD) will be needed.

5.3 Immunogenicity

5.3.1 General Consideration

Immunogenicity trials are conducted at all stages of clinical development of vaccines. The evaluation of immune responses relies upon the collection of adequate specimens at appropriate time intervals and the measurement of immune parameters most relevant to the vaccine.

5.3.2 Characterization of the immune response

Characterization of the immune response may depend on whether any information on immune responses to the same or similar antigenic components in approved vaccinesis available or otherwise.

Immunological parameters are measures that describe the humoral immune response (for example, antibody concentrations or antibody titres,) or the cell-mediated immune response (for example, percentages of sensitized T-cells).

For known microorganisms or antigens in a candidate vaccine the range of parameters to be measured in clinical trials is usually selected on the basis of prior experience and whether or not there is an established Immune Correlate of Protection (ICP),which is a type and amount of immunological response that correlates with vaccine-induced protection against an infectious disease and that might predict the clinical efficacy.

For microorganisms or antigens not previously included in human vaccines the selection of parameters to be measured should take into account what is known about natural immunity. For some infectious diseases the nature of the immune response to infection in animal models may also be useful for parameter selection.

5.3.3 Humoral immune response

The humoral immune response is assessed from the post-vaccination appearance of, or increase after vaccination in, antibody directed at specific microorganisms or antigens in the vaccine.

If data are available, most weight is usually placed on functional antibody responses – for example, serum bactericidal antibody (SBA), toxin- or virus-neutralizing antibody or opsonophagocytic antibody (OPA).

Alternatively, or in addition to the determination of functional antibody, the immune response may be assessed by measuring total antibody – for example, total immunoglobulin G (IgG) measured by ELISA. Only a proportion of the total antibody detected may be functional.

The following should be taken into consideration when deciding how to measure the humoral immune response:

- If a correlation has already been established between total and functional antibody responses to a specific microorganism or antigen, it may be acceptable to measure only total IgG in further trials. However, determination of functional immune responses might be important for specific age groups or target populations where it is known or suspected that the binding and functional capacity of the antibodies elicited differs.
- For antigens for which there is an established ICP it may suffice to measure only the relevant functional antibody (for example, SBA for meningococcal vaccines) or total IgG response.
- If the ICP is based on total IgG there may be instances where there is still merit in measuring functional antibody.
- If there is no ICP the functional antibody response should be measured if this is feasible.
- Occasionally there may be more than one immunological parameter that can measure functional antibody but one is considered to be a more definitive measure than the other. In this case the more definitive parameter may be determined, at least in a subset.
- For some vaccines against certain viruses there is a possibility that some of the total antibody detected has no protective effect but could enhance cellular infection by wild-type virus and result in an increased risk of severe disease after vaccination. To assess this possibility, the routine measurement of total antibody to assess the humoral immune response to vaccination should be supported by other detailed investigations.

5.3.4 Cell-mediated immune response

Assessment of the cell-mediated immune response may have a role to play in the assessment of the interaction between the vaccine and the human immune system for some type of infectious diseases. In other cases, evaluation of the cellular immune response may serve to support findings based on the humoral immune response.

The cell-mediated immune response is most commonly assessed by detecting and quantifying sensitized T-cells in blood from trial subjects. These investigations may also serve to characterize the predominant cytokines released and to detect differences in sensitization between T-cell subpopulations. Several methods may be

usedwhich are typically based on measuring the production of a range of cytokines following in-vitro stimulation of T-cells with individual or pooled antigens.
The results may provide useful comparisons between treatment groups within any one study. If there are marked discrepancies in the patterns of responses observed between cell-mediated and humoral responses the findings should be carefully considered.

5.3.5 Identification and use of Immune Correlates of Protection (ICP)

5.3.5.1 Immune correlates of protection and their uses

All established ICPs are based on humoral immune response parameters that measure functional or total IgG antibody.

In most cases established ICPs have been shown to correlate with prevention of clinically apparent infectious disease, but for some pathogens, the ICP correlates with prevention of documented infection.

5.3.5.2 Establishing an ICP

Documentation of the immune response to natural infection, the durationof protection after clinically apparent infection and the specificityof protection should be taken into consideration when attempting toestablish an ICP from clinical data.

To date, widely accepted clinical ICPs have been established on the basis of one or more of the following:

- Sero-surveillance and disease prevalence in specific populations;
- passive protection using antibody derived from immune humans or manufactured using recombinant technology;
- efficacy trials;
- effectiveness trials;
- Investigation of vaccine failure in immunosuppressed populations.

Wherever it is feasible, ICP should be determined from vaccine efficacy trial that is initiated pre-approval, often with long-term follow-up of subjects that isextended into the post-approvalperiod. Efficacy trial protocol should plan to collect sufficient information to allow for analyses of the relationship between immune parameters and protection against clinically apparent disease.

To investigate the predictive capacity of a putative ICP, protocols should predefine the assessments to be applied to all cases of the disease to be prevented that occur in the vaccinated and control groups. These assessments should include investigation of the immune status of subjects as well as microbiological studies with the infecting microorganisms whenever these have been recovered. For breakthrough cases from which both post-vaccination sera and organisms have been recovered, it is recommended that, whenever feasible, functional antibody (or, if not possible, total antibody) should be determined for individuals against their own pathogen. An exploration of vaccine-elicited cell-mediated responses in individuals against their own pathogen may also be useful and, for some types of infectious disease, may be very important for further understanding vaccine-associated protection. These data may be

very important for investigating the broad applicability of the ICP, depending on host and organism factors.

A single clinical ICP identified from a vaccine efficacy trial in a definedpopulation may not necessarily be applicable to other vaccine constructs or to other populations and disease settings intended to prevent the same infectious disease. Therefore,the reliance that is placed on a clinical ICP, should take into account details of the efficacy trials from whichit was derived.

If it is not possible to derive a clinical ICP, the interpretation of the human immune response data may take into account what is known about immunological parameters that correlate with protection in relevant animal models and any nonclinical ICPs that have been identified (for example, from trials that assess passive protection and active immunization). This approach may be the only option available for interpreting immune responses to some new candidate vaccines.

Nevertheless, ICPs derived wholly from nonclinical data should be viewed with caution and attempts should be made to obtain a clinical ICP whenever the opportunity arises (for example, when the vaccine is used in the context of an outbreak).

If conducted, human challenge trials may also provide preliminary evidence supporting an ICP. If a human challenge trial suggests a correlation between a specific immunological parameter and protection, this may be further investigated during the clinical development programme.

The detailed considerations for trial end-points and approach to analysis and interpretation of immunogenicity data in the presence or absence of an ICP have been elaborated in Section 5 of this document.

5.3.5.3 Using immunogenicity data to predict efficacy

5.3.5.3.1 Bridging to efficacy data

Immunogenicity data may be used to provide evidence of efficacy when:

- there is a well-established ICP that can be used to interpret the immune responses to a specific antigenic component;
- it is possible to use immune responses to bridge to estimates of vaccine efficacy obtained from prior well-designed clinical trials.

The following two main situations should be considered when using immunogenicity data to bridge to estimates of vaccine efficacy obtained in prior clinical trials.

i. Modifying the use of the vaccine for which efficacy has been estimated.
ii. Inferring the efficacy of a new candidate vaccine

In both cases comparative immunogenicity trials designed to demonstrate non-inferiority are recommended. The choice of comparator is a critical factor in the interpretation of the results.

In case of Inferring the efficacy of a new candidate vaccine**,** the main evidence of efficacy for approval comes from one or more bridging efficacy trials.

The trial design may involve a direct comparison between: (a) the new

posology and that used in the efficacy trial; or (b) the new intended populationand a control group consisting of subjects who are representative of the priorefficacy trial population. It may also be acceptable to make an indirect (crosstrial)comparison with the immunogenicity data that were obtained during theefficacy trial.

The vaccine formulation and assay used should be the same as those

used in the efficacy trial whenever possible.

If the new candidate vaccine contains additional subtypes of an organism compared to approved products and/or it contains subtypes of an organism that have not previously been included in any licensed vaccine then interpretation of the immune responses to the added or new subtypes is not straightforward.

Approaches that could be considered include comparing immune responses to each added or new subtype with the mean immune response to all subtypes or with the lowest immune response to any individual subtype included in a vaccine for which efficacy was demonstrated.

Although these approaches may provide a route to approval, the limitations of these comparisons in predicting efficacy should be taken into account considering the overall risk–benefit relationship for the new vaccine.

5.3.5.3.2 Other approaches

When there is no ICP and it is not possible to bridge to a prior demonstration of efficacy, the evidence that may be provided to support likely vaccine efficacy must be considered on a case-by-case basis.

In each case, the depth of evidence that may be provided should be weighed against the advantages of having a approved vaccine – one that has been subjected to a full review of quality and nonclinical data, and for which it is considered that there are adequate clinical safety and immunogenicity data – available for use when needed.

Potential approaches may include establishing a nonclinical model of efficacy that is thought to be relevant to the human infection and identifying which immunological parameter best correlates with protection and, if possible, a putative ICP.

5.3.5.4 Special consideration for COVID-19 vaccine

The Immune Correlate of Protection (ICP) is currently limited in case of SARS-CoV-2. The understanding of SARS-CoV-2 immunology is currently evolving. However, considering that there is an urgent need of COVID-19 vaccine, the predictive value of the immune response for short-term and/or longer-term protection from SARS-CoV-2 infection and/or disease may be investigated.

Subsequently, after approval of the vaccine, however, the direct evidence of vaccine efficacy in protection from SARS-CoV-2 infection and/or disease must be accessed through appropriate study in Post Marketing Scenario.

Clinical development programs for COVID-19 vaccines might be expedited by adaptive and/or seamless clinical trial designs that allow for selection between vaccine candidates and dosing regimens and for more rapid progression through the usual phases of clinical development.

5.3.6 Immunization of pregnant women

Whenever the target population for a vaccine includes women of childbearing age there is a need to consider the importance of generating data in pregnant women.

These considerations should take into account the nature of the vaccine construct (for example, whether the vaccine contains a live organism that is replication competent), whether pregnant women can reasonably avoid exposure to an infectious agent and whether they may have the same risk of exposure but a greater risk of experiencing severe disease compared to non-pregnant women of the same age.
However, in such case, the developmental and reproductive toxicity studies data are required to be generated in accordance with the SECOND SCHEDULE of the New Drugs and Clinical Trials Rules, 2019,prior to consideration of inclusion of pregnant women in clinical trial.

5.3.7 Measuring the immune response

5.3.7.1 Collection of specimens

Immune responses to vaccination are routinely measured in serum (humoral immune responses) and blood (cellular immune responses).
For some vaccines it may be of interest to explore immune responses in other body fluids relevant to the site at which the target microorganism infects and/or replicates (for example, in nasal washes or cervical mucus), especially if it is known or suspected that the systemic immune response does not show a strong correlation with protective efficacy for the type of vaccine under trial (for example, intranasal vaccination against influenza).
Pre-vaccination samples should be collected from all subjects in early preliminary immunogenicity trials, after which it may be justifiable to omit these samples or to obtain them from subsets (for example, if antibody is rarely detectable or quantifiable prior to vaccination in the target population).
Pre-vaccination sampling remains essential if it is expected that the target population will have some degree of pre-existing immunity due to natural exposure and/ or vaccination history, since the assessment of the immune response will need to take into account seroconversion rates and increments in geometric mean titres (GMTs) or geometric mean concentrations (GMCs) from pre- to post-vaccination.
Pre-vaccination sampling is also necessary if it is known or suspected that pre-existing immune status may have an impact on the magnitude of the immune response to vaccination that is positive (for example, because preexisting antibody reflects past priming) or negative (for example, due to maternal antibody interfering with primary vaccination with certain antigens in infants).
The timing of post-vaccination sampling should be based on what is already known about the peak immune response after the first and, if applicable, sequential doses (for example, for vaccines that elicit priming, the rise in antibody after a booster dose is usually much more rapid than the rise after earlier doses). For antigens not previously used in human vaccines, sampling times may be based on nonclinical data and then adjusted when data that are specific to the antigen(s) under trial have been generated. As information is accumulated, the number and volume of samples taken

from individual subjects may be reduced to the minimum considered necessary to meet the trial objectives.

5.3.7.2 Assays

Assays of functional or total antibody that are used to report immune responses to vaccination (whether to the candidate vaccine or to co-administered vaccines) in trials intended to support approval (that is, in pivotal trials) is acceptable.

They may be:

- commercially available assays specifically designed and intended for quantification of antibody (that is, assays that have undergone a robust regulatory review);
- assays that are not commercially available but have been shown to be comparable to a reference assay (for example, to an assay established in a WHO reference laboratory or to an assay that is established in a recognized public health laboratory and has been used previously to support clinical trials that were pivotal for licensure).

Clinical trial protocols should specify which assays will be used. Clinical trial reports should include a summary of the assay methodology and its commercial or other validation status. For assays that are not commercially available any available validation reports should be provided. The same assays should preferably be used in the same laboratories throughout the clinical development programme (including pre- and post-approval trials) for an individual vaccine.

5.4 Immunogenicity trials

5.4.1 Objectives

The objectives of immunogenicity trials include, but are not limited to, the following:

- to select vaccine formulations and posologies (including primary and booster doses) ;
- to compare immune responses documented in a specific population and, using one vaccine formulation and posology,
- to immune responses to the same vaccine when used in other settings or with a different vaccine intended to protect against the same infectious disease(s) ;
- to support co-administration with other vaccines;
- to support maternal immunization;
- to support major changes to the manufacturing process
- to assess lot-to-lot consistency.
- alternative posologies,

5.4.2 General considerations for trial design

Immunogenicity trials are almost without exception comparative trials.

For candidate vaccines containing antigens for which there are well-established ICPs that can be applied to interpret the results sponsors may sometimes question the value of including a comparative arm. Nevertheless, there is great value in conducting a randomized controlled trial.

For example, the inclusion of a control group that receives an approved vaccine provides assurance of the adequacy of the trial procedures and methods, including the assays, and facilitates interpretation of data in circumstances in which unexpected

results (for example, low immune response to one or more antigens, high rates of specific AEs or unexpected AEs) are observed.

Comparative trials include those in which all subjects receive the same vaccine formulation but there are differences between groups in terms of how or to whom the vaccine is administered (for example, using a different dose or dose interval, or administering the vaccine to different age groups) as well as trials in which one or more group(s) receive an alternative treatment, which may be placebo and/or another licensed vaccine.

The design of comparative immunogenicity trials is driven by the characteristics of the vaccine, the trial objectives, the stage of clinical development, the trial population, the availability and acceptability of suitable comparators, and what is known about immune parameters that correlate with protection (including whether or not there is an established ICP).

In comparative immunogenicity trials, subjects should be randomized to one of the trial groups at enrolment. This also applies to trials that enroll sequential cohorts of subjects (as in ascending dose trials in which at least some subjects are assigned to receive placebo or another vaccine).

In some cases it may be appropriate that subjects who meet certain criteria (for example, completed all assigned doses in the initial part of the trial) are re-randomized at a later stage of the trial to receive a further dose of a test or control treatment.

5.4.3 End-points

The trial protocol should predefine the primary, co-primary, secondary and any other end-points (which may be designated tertiary or exploratory).

Co-primary endpoints may be appropriate in some cases, namely:

- The vaccine is intended to protect against multiple subtypes of the same microorganism.
- The vaccine contains multiple microorganisms or multiple antigens.

The following should be taken into consideration when selecting the primary end-point(s) following primary vaccination:

- When an ICP has been established the primary end-point is usually the percentage of subjects that achieves an antibody level at or above the ICP, which is sometimes referred to as the sero-protection rate.
- When there is no established ICP the primary end-point or the co-primary end-points is/are usually based on a measure of the humoral immune response.
    - ✓ In some instances, there may be evidence to support the application of a threshold value (that is, the primary end-point may be the percentage of subjects that achieves antibody levels at or above the threshold value).
    - ✓ If there is no threshold value that can be applied it may be appropriate to base the primary end-point on the seroconversion rate or on some other definition of the magnitude of the immune response that differentiates responders from non-responders. Comparisons of post-vaccination seropositivity rates may also be informative if pre-vaccination rates are very low.

An anamnestic (memory) immune response is anticipated following administration of a vaccine to subjects who are already primed (by natural exposure or prior vaccination) against one or more microorganisms or antigens in the vaccine.
Thus the seroprotection, seroconversion (fold-rise from pre-boost to post-boost) and seropositivity rates after the booster dose are likely to be very high. In these cases, and in other situations in which post-vaccination seroprotection and/or seroconversion rates are expected to be very high (that is, the vaccine is very immunogenic) the most sensitive immunological parameter for detecting differences between groups may be the GMC or GMT.
After primary vaccination and after any additional doses the results for all measured immunological parameters should be presented in the clinical trial report.

5.4.4 Trials designed to demonstrate superiority

Trials may assess whether a specific candidate vaccine formulation elicits superior immune responses compared to no vaccination against the disease to be prevented. In some cases trials may also assess whether immune responses elicited by a specific formulation of a candidate vaccine are superior to those elicited by other formulations. An assessment of superiority may also be applicable when an adjuvant is proposed for inclusion in the vaccine (for example, to demonstrate that the immune response to at least one of the antigenic components in an adjuvanted formulation is superior to the response in the absence of the adjuvant).
Protocols should predefine the magnitude of the difference between vaccine groups or between vaccine and control groups that will be regarded as evidence of superiority. This difference should be defined in such a way that it provides some evidence of a potential clinical advantage.

5.4.5 Trials designed to demonstrate non-inferiority

Most comparative immunogenicity trials are intended to show that the test vaccinated groups achieve comparable immune responses to the selected reference groups. If these trials are intended to be pivotal they should be designed and powered to demonstrate non-inferiority using a predefined and justifiable non-inferiority margin.
Factors to consider with regard to the stringency of the non-inferiority margin include the clinical relevance of the end-point, seriousness of the disease to be prevented, vulnerability of the target population, availability of a well-established ICP and the performance characteristics of the assay(s). A more stringent margin may be appropriate when the vaccine is intended to prevent severe or life-threatening diseases and/or will be used in particularly vulnerable populations (for example, infants and pregnant women). A more stringent margin could also be considered when there is potential for a downward drift in immunogenicity such as that which could occur when a new candidate vaccine can be compared only with vaccines that were approved on the basis of non-inferiority trials. In contrast, if a new candidate vaccine is known to offer substantial benefits in terms of safety or improved coverage then margins that are less stringent may be considered. As a result of such considerations it is possible that different non-inferiority margins may be considered appropriate in different settings.
When it is proposed to demonstrate non-inferiority between vaccine groups based on GMT or GMC ratios for antibody titers or concentrations it is suggested that the lower

bound of the 95% confidence interval around the ratio (test versus reference vaccine) should not fall below 0.67. Under certain circumstances it may be considered to allow a lower bound (for example, 0.5) or alternative criteria. The selection of a criterion should take into account whether or not an ICP has been identified. In addition, any marked separations between the reverse cumulative distributions of antibody titres or concentrations should be discussed in terms of potential clinical implications, including those which occur at the lower or upper ends of the curves.

5.4.6 Analysis and interpretation

A statistical analysis plan should be finalized before closing the trial database and unblinking treatment assignments (if these were blinded). This should include any planned interim analyses, which should be adequately addressed in terms of purpose, timing and any statistical adjustments required.

The immunogenicity data from all subjects with at least one result for any immunological parameter measured in the trial should be included in the clinical trial report. The analysis of the immune response based on any one parameter is commonly restricted to all subjects with a re-vaccination measurement (if this is to be obtained from all subjects) and at least one post-vaccination measurement.

Protocols may also restrict the primary analysis population to subjects with pre- and post-vaccination results, or to those with post-vaccination results who received all the assigned doses within predefined windows of the intended schedule and had no other major protocol violations. Other analysis populations of interest may be predefined in accordance with the primary or secondary objectives. Whatever the predefined primary analysis population, all available immunogenicity data should be presented in the clinical trial report.

If a trial fails to meet the predefined criteria for superiority and/or non-inferiority with respect to any of the antigenic components, the possible reasons for the result and the clinical implications of it should be carefully considered before proceeding with clinical development or licensure. The considerations may take into account: (a) the basis for setting the predefined criteria (for example, does failure to meet the criteria strongly imply that lower efficacy may result?); (b) the comparisons made for all other immune parameters measured (for example, were criteria not met for only one or several of many antigenic components of the vaccine?); (c) any differences in composition between the test and comparator vaccines that could explain the result; (d) the severity of the disease(s) to be prevented; and (e) the overall anticipated benefits of the vaccine, including its safety profile .

5.5 Special consideration for COVID-19 Vaccine

5.5.1 Trial Populations

First In Human (FIH) and other early phase studies should first enroll healthy adult participants who are at low risk of severe COVID-19.

Exclusion of participants at higher risk of severe COVID-19 from early phase studies is necessary to mitigate potential risk of vaccine associated Enhanced Respiratory Disease (ERD).

As the understanding of COVID-19 pathogenesis continues to evolve, exclusion criteria should reflect the current understanding of risk factors for more severe COVID-19 risk.

Older adult participants (e.g., over 55 years of age) may be enrolled in FIH and other early phase studies so long as they do not have medical co-morbidities associated with an increased risk of severe COVID-19.
Some preliminary safety data in younger adults (e.g., 7 days after a single vaccination) should be available prior to enrolling older adult participants, especially for vaccine platforms without prior clinical experience.
If possible, early clinical studies should also exclude participants at high risk of SARS-CoV-2 exposure (e.g., healthcare workers).
At least preliminary clinical safety and immunogenicity data for each dose level and age group (e.g., younger versus older adults) should be there to support progression of clinical development to include larger numbers (e.g., hundreds) of participants and participants at higher risk of severe COVID-19.
Preliminary immunogenicity data from early phase development should include assessments of neutralizing vs. total antibody responses and Th1 vs. Th2 polarization.
Additional data to further inform potential risk of vaccine-associated ERD and to support progression of clinical development, if available, may include preliminary evaluation of COVID-19 disease outcomes from earlier clinical development of non-clinical studies evaluating protection and/or histopathological markers of vaccine-associated ERD following SARS-CoV-2 challenge.
Initiation of phase III trials should be preceded by adequate characterization of safety and immunogenicity for each vaccine candidate, dose level, and age group to be evaluated to support general safety, potential for vaccine efficacy, and low risk of vaccine associated ERD.
Establishing vaccine safety and efficacy in SARS-CoV-2 naïve individuals is critical.
Vaccine safety and COVID-19 outcomes in individuals with prior SARS-CoV-2 infection, which might have been asymptomatic, is also important to examine because pre-vaccination screening for prior infection may not be feasible in practice when the COVID-19 vaccine is approved and introduced in the market.
Therefore, subjects with history or laboratory evidence of prior COVID-19 infection should not be excluded from COVID-19 vaccine trial.
However, subjects with acute COVID-19 or other acute infectious illness should be excluded from such trials.
Consideration should be given for inclusion of diverse populations in all phases of vaccine clinical development to ensure that vaccines are safe and effective for everyone in the indicated populations.
Evaluation of vaccine safety and efficacy in phase III clinical trial in adults should include adequate representation of elderly individuals and individuals with co-morbidities.
Early consideration of data should be given in the development programs that might support inclusion of pregnant women and women of childbearing potential who are not actively avoiding pregnancy in clinical trials.
In such cases, the reproductive and developmental toxicity data should be there as per the requirements specified in the SECOND SCHEDULE of the New Drugs and Clinical Trials Rules, 2019 to support the inclusion of pregnant women and women of childbearing potential.

It is important for COVID-19 vaccines to plan for pediatric assessments of safety and effectiveness considering the pandemic in accordance with the requirements and guidelines specified in the Second Schedule of the New Drugs and Clinical Trials Rules, 2019.

5.5.2 Trial Design

Early phase trials often aim to down-select among multiple vaccine candidates and/or dosing regimens via randomization of participants to different treatment groups. While including a placebo control and blinding are not required for early phase studies, doing so may assist in interpretation of preliminary safety data.

Later phase trials, including efficacy trials, should be randomized, double-blinded, and placebo controlled.

An individually randomized controlled trial with 1:1 randomization between vaccine and placebo groups is usually the most efficient study design for demonstrating vaccine efficacy.

An efficacy trial that evaluates multiple vaccine candidates against a single placebo group may be an acceptable approach to further increase efficiency, provided that the trial is adequately designed with appropriate statistical methods to evaluate efficacy.

If the availability of a COVID-19 vaccine proven to be safe and effective precludes ethical inclusion of a placebo control group, that vaccine could serve as the control treatment in a study designed to evaluate efficacy with non-inferiority hypothesis testing.

Protocols for adaptive trials should include pre-specified criteria for adding or removing vaccine candidates or dosing regimens and protocols for seamless trials should include pre-specified criteria (e.g., safety and immunogenicity data) for advancing from one phase of the study to the next.

Follow-up of study participants for COVID-19 outcomes (in particular, for severe COVID-19 disease manifestations) should continue as long as feasible, ideally at least one to two years, to assess duration of protection and potential for vaccine associated ERD as immune responses to the vaccine wane.

Efficacy trials should include contingency plans for continued follow up and analysis of safety and effectiveness outcomes in the event that a safe and effective vaccine becomes available (e.g., as demonstrated in a planned interim analysis or as demonstrated in another clinical trial).

In that case, prior deliberation and examination with CDSCO in consultation with the SEC is necessary to address ethical arguments to break the blind and offer vaccine to placebo recipients.

In cases where statistical equivalency testing of vaccine immune responses in humans is required to support manufacturing consistency (clinical lot-to-lot consistency trial), this testing can be incorporated into the design of an efficacy trial and does not need to be conducted in a separate study.

5.6 Efficacy trial

If immunological data cannot be used to select a dose, formulation and schedule that can be predicted to provide satisfactory protection against the infectious disease(s) to be prevented a vaccine efficacy trial should be conducted whenever this is feasible.

Vaccine efficacy trials are usually required whenever a new candidate vaccine is

developed with intent to protect against an infectious disease and one or more of the following apply:

- There is no established ICP that could be used to predict the efficacy of the new candidate vaccine.
- There is no approved vaccine with documented efficacy against a specific infectious disease to allow for bridging to a new candidate vaccine.
- Use of immune responses to bridge the documented efficacy of an approved vaccine to a new candidate vaccine is not considered tobe possible.
- There are sound scientific reasons to expect that the efficacy of a vaccine cannot be assumed to be similar between the population(s) included in the prior efficacy trial(s) and one or more other populations.
- It cannot be assumed that the vaccine efficacy demonstrated against disease due to specific strains of a pathogen (for example, serotypes or subtypes) would apply to other strains.

If it is not feasible to perform vaccine efficacy trials and there is no ICP, itmay be possible to obtain evidence in support of vaccine efficacy and/or to derive an immunological marker of protection from one or more of the following:

- Nonclinical efficacy trials.
- Passive protection trials – that is, nonclinical or clinical trials which assess the effects of administering normal or hyper-immune humangamma globulin or convalescent sera. The results may point to the sufficiency of humoral immunity for the prevention of clinical disease and may suggest a minimum protective antibody level that could be used to interpret data obtained in clinical trials with candidate vaccines.
- Comparison of immunological responses with those seen in past trials of similar vaccines with proven protective efficacy even if the relationship between immune responses to one or more antigeniccomponents and efficacy remains unknown.
- Human challenge trials.

Considerationmay be needed for conducting more than one vaccine efficacy trial in case different subtypes of a pathogen are involved. In such cases, the efficacy trials may be required to be conducted in different regions where certain subtypes are known to predominate. Depending on the vaccine construct, nonclinical and/or other clinical evidence may also be used to support the likely consistency of efficacy across all subtypes.

For some infectious diseases, there may be good scientific reasons to anticipate that the protective efficacy demonstrated in a pivotal efficacy trial in one population in a specific age range may not be extrapolated to other populations with the same age range. For example, in some regions there may be multiple co-infections in populations and/or there may be considerable boosting of the immune response due to natural exposure that could have positive or negative effects on the estimate of vaccine efficacy. In these cases, it may be necessary to conduct a pivotal trial that enrolls representative samples of different populations or to conduct more than one trial in separate populations.

5.6.1 Efficacy trial design

The protective efficacy of a vaccine against a specific infectious disease is usually determined in randomized trials that compare the incidence of disease after vaccination relative to the incidence of disease in the control group that has not been vaccinated. Less frequently, vaccine efficacy may be determined in a prospective randomized trial which compares the incidence of disease after vaccination between the group that received the new candidate vaccine and a control group that received a licensed vaccine intended to prevent the same infectious disease.

The unit of randomization is most usually the individual. Alternatives include the household or the cluster under trial (for example, a school population or a local community). Randomization of groups or clusters, rather than individuals, may be preferred when it is logistically much easier to administer the vaccine to groups than to individuals and when estimates of the indirect effects of vaccination (for example, herd immunity) are of interest. When the trial aims to vaccinate pregnant women to protect the infant during the early months of life then the unit of randomization is the mother.

The simplest design involves randomization of equal numbers of subjects to the candidate vaccine and control groups (that is, 1:1). In trials that employ a control group that is not vaccinated against the disease to be prevented, but some clinical data are available to support the likely efficacy of the candidate vaccine, it may be appropriate (subject to statistical considerations and an assessment of the impact on the total trial sample size) to use unbalanced randomization (for example,2:1 or 3:1) to reduce the chance that individual subjects will be randomized to the control group, thus ensuring that the majority of trial subjects receive the candidate vaccine.

Trials may be planned to follow trial subjects for a fixed period after the last dose of the primary series. The time at which the primary analysis is conducted should take into account the anticipated rates of the disease understudy in each treatment group, including the unvaccinated control group if applicable. Other considerations regarding the timing of the primary analysis may include the possible importance of having some information on the duration of protection before approval of the vaccine, the feasibility of following up subjects for prolonged periods, and whether or not the vaccine could address a pressing unmet need (for example, in an outbreak situation where there is no approved vaccine to prevent the disease).

5.6.2 Clinical End Points

5.6.2.1 Primary End Points

In most cases the focus of vaccine efficacy trials is the prevention of clinically apparent infections that fit the primary case definition based on clinical and laboratory criteria. If an organism causes a range of disease manifestations the primary end-point in any one trial should be carefully selected in accordance with the proposed indication(s) for use. In case a candidate vaccine contains antigens derived from one or several types (serotypes, subtypes or genotypes) of the same organism and there may also be some potential for cross-protection against types not included in the vaccine, it is usual for the primary end-point to comprise cases due to any of the types included in the vaccine, and the trial is powered for this composite end-point. It is not usually possible

to power the trial to assess efficacy against individual types in the vaccine or to assess cross-protection against types not in the vaccine.
Alternative primary end-points may include:

- clinical manifestations of reactivated latent infection;
- established chronic infections that may be asymptomatic but predispose to infection-related disease later in;
- other markers that predict progression to clinically apparent disease.

5.6.2.2 Secondary End Points

As applicable to the individual candidate vaccine, other important end-points may include:

- cases that occur after each dose, when the vaccine schedule includes multiple doses and/or a booster;
- cases due to each of the individual types of the organism included in the vaccine;
- cases due to the organism, regardless of whether the cases are caused by types that are or are not included in the candidate vaccine;
- cases due to non-vaccine types;
- cases occurring in groups with host factors of interest (for example, age or region);
- cases meeting criteria for disease severity – if available, validated measures of criteria for severity should be used to facilitate interpretation of the results;
- duration and/or severity of the illness, which may include clinical measurements and laboratory measurements

Eradication of carriage and/or reduction in disease transmission that is not directly linked to, and/or accompanied by, a clinical benefit of vaccination to the individual are not usually considered to be sufficient to support licensure.

5.6.3 Special consideration for Efficacy of COVID -19 Vaccine

Either laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection is an acceptable primary endpoint for a COVID-19 vaccine efficacy trial. Acute cases of COVID-19 should be virologically confirmed.SARS-CoV-2 infection, including asymptomatic infection, can be monitored for and confirmed either by virologic methods or by serologic methods evaluating antibodies to SARS-CoV-2 antigens not included in the vaccine. Standardization of efficacy endpoints across clinical trials may facilitate comparative evaluation of vaccines for deployment programs, provided that such comparisons are not confounded by differences in trial design or study populations.
It is advised that either the primary endpoint or a secondary endpoint (with or without formal hypothesis testing) be defined as virologically confirmed SARS-CoV-2 infection with one or more of the following symptoms:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue or Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat

- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

As it is possible that a COVID-19 vaccine might be much more effective in preventing moderate to severe versus mild COVID-19, consideration should be given for powering efficacy trials for formal hypothesis testing on a severe COVID-19 endpoint. Regardless, moderate to severe COVID-19 should be evaluated as a secondary endpoint (with or without formal hypothesis testing) if not evaluated as a primary endpoint.

It is recommended that severe COVID-19 be defined as virologically confirmed SARSCoV-2 infection with any of the following:

- Clinical signs at rest indicative of moderate to severe systemic illness (respiratory rate ≥ 30 per minute, SpO2 ≤ 94 % on room air or PaO2/FiO2 < 300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
- Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction Contains
- Admission to an ICU
- Death

SARS-CoV-2 infection (whether or not symptomatic) should be evaluated as a secondary or exploratory endpoint, if not evaluated as a primary endpoint.

The above diagnostic criteria may need to be modified in certain populations; for example, in pediatric patients and those with respiratory co-morbidities. Sponsors should discuss their proposed case definitions with the Agency prior to initiating enrollment.

5.6.3.1 Statistical Considerations

To ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%.

The same statistical success criterion should be used for any interim analysis designed for early detection of efficacy.

A lower bound ≤30% but >0% may be acceptable as a statistical success criterion for a secondary efficacy endpoint, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.

For non-inferiority comparison to a COVID-19 vaccine already proven to be effective, the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary relative efficacy point estimate is >-10%.

For each vaccine candidate, appropriate statistical methods should be used to control type 1 error for hypothesis testing on multiple endpoints and/or interim efficacy analyses.

Late phase studies should include interim analyses to assess risk of vaccine associated ERD and futility. Study sample sizes and timing of interim analyses should be based on the statistical success criteria for primary and secondary (if applicable) efficacy analyses and realistic, data-driven estimates of vaccine efficacy and incidence of COVID-19 (or SARS-CoV-2 infection) for the populations and locales in which the trial will be conducted.

5.7 Safety Considerations

The size of the pre-approval safety database should be decided on a case by case basis. If a candidate vaccine contains new components not previously included in approved vaccines it would be usual to aim for a safety database that is sufficient to estimate the frequency of uncommon adverse events (occurring in between 1/100 and 1/1000 vaccinated persons). However, there may be cases where special concerns may be needed to be addressed and in such cases a much larger database would be required.

A smaller safety database may be acceptable, if a candidate vaccine combines antigens with or without adjuvant that are all included in approved vaccines or contains additional antigens compared to an approved vaccine but all are derived from the same pathogen and manufactured in a similar fashion.

The duration of safety follow-up after the last dose should be justified based on the candidate vaccine construct, the inclusion of a new adjuvant and prior data of relevance to any of the components of the vaccine under development.

Safety assessments throughout clinical development should include:

- Solicited local and systemic adverse events for at least 7 days after each study vaccination in an adequate number of study participants to characterize reactogenicity (including at least a subset of participants in late phase efficacy trials).
- Unsolicited adverse events in all study participants for at least 21–28 days after each study vaccination.
- Serious and other medically attended adverse events in all study participants for at least 6 months after completion of all study vaccinations. Longer safety monitoring may be warranted for certain vaccine platforms (e.g., those that include novel adjuvants).
- All pregnancies in study participants for which the date of conception is prior to vaccination or within 30 days after vaccination should be followed for pregnancy outcomes, including pregnancy loss, stillbirth, and congenital anomalies.
- The safety database through pre and post approval of clinical development for preventive new candidate vaccines for infectious diseases may consists of many thousand subjects.
- The general safety evaluation of COVID-19 vaccines, including the size of the safety database to support vaccine licensure, should be no different than for other preventive vaccines for infectious diseases
- It is anticipated that adequately powered efficacy trials for COVID-19 vaccines will be of sufficient size to provide an acceptable safety database for each of younger adult and elderly populations, provided that no significant safety

concerns arise during clinical development that would warrant further pre-licensure evaluation.

- COVID-19 vaccine trials should periodically monitor for unfavorable imbalances between vaccine and control groups in COVID-19 disease outcomes, in particular for cases of moderate to severe COVID-19 that may be a signal for vaccine-associated ERD.
- Studies should include pre-specified criteria for halting based on signals of potential vaccine-associated ERD.
- It is recommended to use of an independent data safety monitoring board (DSMB) for vaccine-associated ERD and other safety signal monitoring, especially during later stage development.

5.8 Post Marketing clinical evaluation

After approval of a vaccine, it is essential to monitor vaccine safety in routine use. Studies designed to address specific safety issues that were identified as potential concerns from pre-approval trials may need to be conducted. It may be appropriate to conduct studies specifically intended to estimate vaccine effectiveness.

Post Marketing Assessment of vaccines for safety and /or effectiveness of vaccines should be considered on case by case basis defending on the category, nature of vaccine and the quantum of data generated through the non-clinical and clinical development programme in accordance with the general guidelines specified in the FIFTH SCHEDULE of the New Drugs and Clinical Trials Rules, 2019.

Accordingly, to ensure the vaccine safety and effectiveness of marketed vaccine, post marketing assessment may be carried out through the following ways:

- Phase IV (Post Marketing Trial)
- Post Marketing Surveillance or observational or non-interventional study for active surveillance
- Post Marketing Surveillance including assessment of Adverse Events Following Immunization (AEFI) and Adverse Events of Special Interest (AESI).

6 References

1. Drugs and Cosmetics Rules,1945
2. New Drugs and Clinical Trials Rules,2019
3. WHO guidelines on nonclinical evaluation of vaccines. TRS 927; Annex1
4. Guidelines on clinical evaluation of vaccines: regulatory Expectation WHO TRS 1004, Annex 9
5. Guidelines on clinical evaluation of vaccines: regulatory expectations, WHO TRS. 924 Annex 1
6. Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19, USFDA, June 2020
7. Guideline on clinical evaluation of vaccines EMEA/CHMP/VWP/164653/05 Rev.

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