الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Clinical Considerations for Vaccines

Version 2

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Drug Sector

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

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List of Abbreviations

AEs	**Adverse Events**
EIA	Enzyme Immunoassay
ELISA	Enzyme-Linked Immunosorbent Assay
FAMA	Fluorescent-Antibody-to-Membrane-Antigen
GMT	Geometric Mean Titers
gpELISA	Glycoprotein Enzyme-Linked Immunosorbent Assay
HAI	Hemagglutination Inhibition
ICP	Immune Correlate of Protection
IgG	Immunoglobulin G
LNI	Log10 Neutralization Index
MIT	Micrometabolic Inhibition Test
Nab	Neutralizing antibody
NF50	Neutralization Factor 50
NT	Neutralization Assay
TBE	Tick-Borne Encephalitis
TNA	Toxin Neutralization Activity
RFFIT	Rapid Fluorescent Focus Inhibition Test
RMP	Risk Minimization Plan
PA	Protective Antigen
PIL	Patient Information Leaflet
PRP	Polyribosylribitol Phosphate
SAEs	Serious Adverse Events
SBA	Serum Bactericidal Assay
SPC	Summary of Product Characteristics

1. Introduction

Vaccines are important and cost-effective interventions that protect public health. All submitted vaccines marketing applications as well as applications for variations of marketed vaccines, undergo clinical assessments by the Saudi Food and Drug Authority (SFDA). The benefit-risk assessment of vaccines depends on the type of submission and the components of the vaccine. In order to harmonize the clinical requirements across different types of submissions and vaccine platforms, this guideline was developed to facilitate the submission, evaluation, and marketing authorization of vaccines.

2. Scope

This guidance covers the regulatory expectations of vaccines from a clinical evaluation point of view. It provides recommendations on the clinical data requirements for safety, immunogenicity and efficacy of submitted marketing authorization applications of vaccines for infectious diseases. In addition, this guidance applies to major variations: type II variations which have a significant impact on the safety or efficacy of a SFDA marketed vaccine that require prior approvals before implementation. Therapeutic vaccines not targeting infectious diseases (e.g. Cancer therapeutic vaccines) are excluded from the scope of this document. This guidance should be read in conjunction with related SFDA guidelines for drug registration.

2.1. Related guidelines

- Regulatory Framework for Drugs Approvals
- The GCC Data Requirements for Human Drugs Submission
- Guidelines for Production and Quality Control of Vaccines
- Clinical Considerations for Efficacy and Safety Assessment
- Guidelines for Good Clinical Practice (GCP)
- Guidelines for Variation Requirements
- International Council for Harmonization (ICH) guidelines:
    - ICH E3: Structure and content of clinical study reports
    - ICH E4: Dose-response information to support drug registration
    - ICH E6: Good clinical practice
    - ICH E8: General considerations for clinical studies
    - ICH E9: Statistical principles for clinical trials

- ICH E10: Choice of control group and related issues in clinical trials
- ICH E11: Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population
- ICH E17: General principles for planning and design of multi-regional clinical trials

3. Definitions

- **Vaccine:** Preparations containing antigenic substances capable of inducing a specific and active immunity against the infecting agent or the toxin or the antigen produced by it.
- **Immunological correlate of protection (ICP):** An ICP is most commonly defined as a type and amount of immunological response that correlates with vaccine-induced protection against a clinically apparent infectious disease and that is considered predictive of clinical efficacy. In other words, ICP is the type of immune response (antibody, antitoxin antibody or other immune response), and specific level required to provide an immune protection against a specific pathogen.
- **Clinically significant endpoints:** Some vaccines do not have a well-established ICP. Therefore, the vaccine should provide a clinically significant endpoint relating to the vaccine preventable disease. They are commonly evolve around measuring meaningful benefit to the patient's health such as improve survival rates, reduce hospitalization or severe cases, or relieve symptoms.
- **Human challenge study:** It is a type of study where participants are intentionally challenged with an infectious disease organism. Such studies, are conducted in the early phase during vaccines development and in some cases to demonstrate vaccine efficacy.
- **Immunogenicity:** The capacity of a vaccine to elicit a measurable immune response.
- **Novel Vaccine:** A vaccine containing new antigenic/adjuvant components that were not used in previously licensed vaccines.
- **Stringent Regulatory Authority (SRA):** USFDA, EMA, MHRA (UK), Swissmedic, Health Canada, TGA (Australia) and PMDA (Japan).
- **Vaccine antigen:** The active ingredient in a vaccine (or generated by a vaccine) against which a specific immune response is elicited.
- **Vaccine adjuvants:** A substances or combinations of substances that are used in conjunction with a vaccine antigen to improve immune response and clinical effectiveness of the vaccine.

4. Clinical Considerations per Submission Type

4.1. New Drug Applications (NDA)

4.1.1. Novel Vaccines (new antigen)

For novel vaccines containing a new antigen, the clinical development program must demonstrate safety, immunogenicity, and efficacy through multiple trials (phase I, II and III). Safety monitoring, including adverse event reporting, should be integrated across all phases. The program typically includes Phase I trials to assess product safety and preliminary immunogenicity in healthy adults, this includes evaluating initial immune responses (e.g., antibody titers) to inform dose selection. Phase II trials are dose-ranging studies that identify the optimal dose and regimen by comparing different doses, while assessing immunogenicity and preliminary efficacy signals in target populations.

Phase III trials should be a well-controlled, randomized, and preferably double-blind pivotal study to establish safety and efficacy, typically demonstrating superiority over placebo. The primary endpoint should either an appropriate clinical endpoint, such as the incidence of confirmed cases or prevention of disease or an endpoint that incorporates an established immune correlate of protection (ICP) (if available) with a predefined level of seroprotection, typically measured by neutralizing antibody (Nab) titers (refer to Section 6).

Secondary endpoints may include, but are not limited to: the proportion of subjects achieving a predefined fold increase in antibody concentrations/titers from pre- to post-vaccination, percentages of seronegative or seropositive subjects, both before and after vaccination; post-vaccination seroprotection and seroconversion rates reported separately for subjects who were seronegative or seropositive at baseline, geometric mean antibody concentrations (GMCs) or titers (GMTs) and pre-/post-vaccination ratios (GMRs), and pre- and post-vaccination numbers or percentages of subjects with antigen-specific T-cells.

The study should be appropriately powered, and sample size calculations should be based on anticipated effect size of the tested arm and the expected immune response or clinical

outcome in the control arm, and the desired statistical power (generally minimum accepted ≥80–90%), with adjustments made for anticipated dropouts, protocol deviations, and any planned subgroup analyses. The trial design should incorporate rigorous measures to minimize bias, including adequate randomization, allocation concealment, and blinding of participants, investigators, and laboratory staff wherever feasible. Moreover, the trial population characteristics should be representative of the intended target group like age groups, risk factors, and geographical regions consistent with the proposed indication. Baseline characteristics should be balanced between treatment arms to minimize confounding and to support the generalizability of the findings to the broader population. Protocols must predefine clinically meaningful differences between vaccine and control groups as evidence of superiority. Furthermore, Immunogenicity should be measured using validated assays to detect vaccine induced antibodies against targeted antigens.

4.1.2. Vaccines with Known Components or Antigens Yet Developed by a New Manufacturer

For vaccines containing the same antigenic components as an already licensed product, but developed by a new manufacturer, the general principles for Phase I and Phase II trials must be applied as described in Section 4.1.1. A pivotal clinical evidence is required from a well-designed Phase III non-inferiority trial using a licensed comparator vaccine. The non-inferiority approach should demonstrate that the new vaccine preserves a clinically meaningful proportion of the established efficacy of the reference vaccine, while also providing comparative data on safety and immunogenicity.

The non-inferiority margin should be pre-specified in the study protocol and supported by a combination of statistical reasoning and clinical judgement which should be based on historical data from efficacy trials of the reference vaccine taking into account the variability in immune responses and the established threshold for protection (if applicable). The selected margin must ensure that the new vaccine retains a clinically meaningful proportion of the efficacy of the reference product. The study must be appropriately powered to detect differences within the pre-specified non-inferiority margin. Analysis populations, such as the per-protocol set and the full analysis set, must be pre-defined in

the study protocol, accompanied by a clear methodology for handling of missing data. Other methodological and statistical considerations described in Section 4.1.1 must also be implemented.

It is mandatory for the selected active comparator in the pivotal study to be registered either by the SFDA or by one of the stringent regulatory authorities recognized by SFDA with a well-established efficacy and safety profile.

4.1.3. Combination Vaccines

Combining antigens that protect against multiple types of infections could result in a negative effect on the immune response due to the possibility of interactions between the vaccine components or a negative immune interference effect toward some antigenic component. However, several combination vaccines have been established to be safe and effective providing an advantage for the recipient by combining more than one vaccine.

For new candidate vaccines Containing known – and one or more new – antigenic components or combining several known antigenic component that has not been combined before in the same vaccine, it is suggested to provide a non- inferiority preliminary trial of immune response to each known antigenic components in the new formulation versus separate administrations of known and new antigenic components. It could be useful if a control group received co-administration of known and new antigenic components. The exact design depends on the availability of a single licensed vaccine that contains the known antigenic components and whether more than one licensed vaccine has to be given. The trial should aim to assess the safety and immunogenicity of the new combination versus approved separate vaccines.

For combination vaccine application similar to an approved combination vaccine, a non-inferiority approach must be followed to ensure that all considerations detailed in Section 4.1.2 are fulfilled.

4.2. Variation Applications (Type II)

- Any modifications to previously approved therapeutic indication, primary vaccination dosing schedule, booster dosing, or any other significant clinical changes must be supported by well-conducted clinical evidence to prove the safety and efficacy of the proposed modification. In case of age group modification in a vaccine use, usually, a bridging trial is required in Type II variations of a new indication submission. The trial design may include in addition to safety assessment, comparison of the immune response between the new claimed age group population versus the representative population in the previous efficacy trial.
- For applications to update seasonal influenza strains, the variation type is categorized under quality variations since no changes to the clinical use of the vaccine are proposed (replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza). The variation should typically include an updated product information documents (SPC and PIL) with the new introduced strains according to the WHO recommendations on the composition of influenza virus vaccines in the northern hemisphere without any changes in the clinical particulars section. However, if there is a significant change introduced that affects the use of the newly submitted seasonal influenza vaccine from a clinical point of view, an appropriate clinical type II variation should be submitted.
- Authorized COVID-19 vaccine requires continuous update of composition to accommodate the continuous change in circulating variants. According to the current global regulatory practices, variation requests to update the composition of previously approved COVID-19 vaccines to reflect the local circulating variant can be based on manufacturing/quality and non-clinical data only given that previously established immunogenicity, efficacy and safety of the vaccine is assumed unaffected. However, additional clinical data might be required on a case by case basis if the clinical particulars are affected by the introduced change.

4.3. General Safety Considerations

Safety monitoring must be a core objective across all phases in the clinical development program of any vaccine. This requires the standardized collection of adverse events (AEs)

including solicited, unsolicited, serious AEs [SAEs], and reactogenicity. The sufficient sample size required for safety assessment is determined on case by case basis. Preclinical data, included antigens and other factors may affect the required database for safety assessment. However, it is generally accepted that a minimum of 3000 subjects receiving the vaccine across the clinical development program is sufficient to detect AEs accruing at a rate of 1 in 1000 (95% probability). Risk management plans (RMPs) especially for novel platforms should be part of the post marketing management of the vaccine. In case of vaccines intended for use in infants and children, where co-administration with other vaccines is anticipated, appropriate clinical evidence should be provided to demonstrate the absence of clinically relevant vaccine–vaccine interactions as described in Section 5.

5. Additional Considerations

- Clinical studies included in the clinical development program and submitted as supportive evidence must be designed and conducted in accordance with Good Clinical Practice (GCP). All relevant certificates and reports supporting this GCP claim should be included in the submission.
- If the vaccine is to be co-administered with other vaccines (e.g., to be co-administered in the same time point according to vaccines listed in the national immunization schedule), it is advised to compare concomitant vs. separate administration to assess interference in immune responses or safety.
- In rare cases (given that ethically justified), human challenge studies can be used as an efficacy-indicating study or to demonstrate a "proof of concept" during the clinical development of vaccines. Consultations with the authority should be carried out depending on the objectives, and the design of the study.
- The submission of a new vaccine for registration or a major type two variation is expected to have a dossier that adheres to the GCC data requirements for human drugs submission guidance. All relevant reports of clinical studies are essential component of the clinical evaluation process. Missing documents may affect the validity of data produced by such clinical study.

6. Correlates of Protection

For some vaccines with known antigenic components, there is an established immune correlate of Protection (ICP). The following table lists vaccines, analytical tests and the required level of immune response. Different assays that assess ICP could be used. However, they need to be validated and justified by the applicant.

No.	Vaccine	Test	Level required
1	Anthrax	Toxin Neutralization Activity (TNA)	TNA NF50 threshold of 0.56
		Antibody dilution titer (TNA), Protective antigen (PA) specific IgG	1/3000, 10 µg/ml
2	Diphtheria	Toxin neutralization	0.01–0.1 IU/ml
3	Hepatitis A	Enzyme-linked immunosorbent assay (ELISA)	≥ 10 mIU/ml
4	Hepatitis B	ELISA	≥ 10 mIU/ml
5	Hib polysaccharides	Anti- polyribosylribitol phosphate (PRP) IgG levels measured by ELISA	0.15 µg/ml (Short-term protection) 1 µg/ml (Long-term protection)
6	Hib conjugate		
7	Influenza	Hemagglutination inhibition (HAI) titers	1/40 dilution
8	Japanese encephalitis	Plaque reduction neutralization test ($PRNT_{50}$)	1/10 dilution
9	Lyme disease	ELISA	1,100 EIA U/ml1400 U/mL
10	Measles	Enzyme immunoassay (EIA)	≥ 120 mIU/ml ≥ 21.3 measles AB units (207.5 mIU/ml)

11	Meningococcal	Serum Bactericidal Assay (SBA)	≥ 1/4
12	Pneumococcus	ELISA	0.35 µg/ml
13	Polio, inactivated	Micrometabolic Inhibition Test (MIT)	≥ 1/8 dilution
14	Rabies	Rapid fluorescent focus inhibition test (RFFIT)	≥ 0.5 IU/ml
15	Rubella	ELISA	≥ 10 mIU/ml
16	Tetanus	ELISA	≥ 0.01 IU/ml (Short-term protection) ≥ 0.1 IU/ml (Long-term protection)
17	Tick-borne encephalitis	TBE virus neutralization test (NT)	≥ 10
18	Varicella	Fluorescent-antibody-to-membrane-antigen (FAMA)	≥ 1:4
		Glycoprotein enzyme-linked immunosorbent assay (gpELISA)	≥5 IU/ml 5 IU/ml (gp-ELISA)
19	Yellow fever	log10 neutralization index (LNI)	≥ 0.7

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