الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Clinical Considerations for Vaccines

Version 1

Date of issue	28 April 2020
Date of implementation	16 August 2021

Clinical Considerations for Vaccines

Version 1

Saudi Food & Drug Authority

Drug Sector

For Comments *Drug.Comments@sfda.gov.sa*

Please visit SFDA's website for the latest update

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

Version	Author	Date	Comments
Draft	Products Evaluation Executive Directorate	28 April 2020	-
Draft 2	Products Evaluation Executive Directorate	25 May 2021	-
Version 1	Products Evaluation Executive Directorate	16 August 2021	Final

Table of Content:

1. **Introduction** 6
2. **Definitions** 7
3. **Types of Submissions** 8
4. **Correlate of Protection** 12
5. **Vaccine Excipients** 13
6. **References** 16

1. INTRODUCTION

Vaccines are important and cost-effective interventions that protect public health. All submitted vaccines marketing applications and variations to the Saudi Food and Drug Authority (SFDA) undergo clinical assessments. To ensure efficiency and consistency of submissions, the SFDA issued this statement with the aim of presenting its point of view regarding clinical requirements for vaccines. This statement represents the current thinking of the SFDA regarding the appropriate level of evidence to support vaccines applications. This guidance should be read in conjunction with SFDA guidelines for drug registration, Guidelines for Production and Quality Control of Vaccines (version 2.1) and international vaccines relevant guidelines produced by the World Health Organisation (WHO).

1.1. Related guidelines

- Regulatory Framework for Drugs Approvals.
- The GCC Data Requirements for Human Drugs Submission.
- Guidelines for Production and Quality Control of Vaccines.

2. DEFINITIONS

- **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.
- **Human challenge study:** It is a type of study where the study participants intentionally challenged with an infectious disease organism. Such studies conducted in the early phase during vaccines development and in some cases to demonstrate the efficacy of the vaccine.
- **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.
- **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.

3. TYPES OF SUBMISSIONS

3.1. Novel Vaccines (new antigen):

Clinical requirements:

I. Phase I study that assess the product safety.

II. Phase II study: such study is concerned with finding the appropriate dose of the vaccine by comparing different doses (dose ranging study).

III. Phase III study: a well-controlled study to establish superiority (in case of new antigenic component) over placebo or appropriate control arm. Such study will usually be considered by the reviewer as pivotal study for approval.

Establishing efficacy profile should be the main objective of the study; appropriate consideration should be made to different aspects of the study such as power calculations, selection of appropriate endpoint (i.e. ICP or a clinical endpoint), selection of comparative arm, and ensuring means of reducing bias (e.g. randomization, blinding).

Immunogenicity of the product should be measured appropriately by the use of appropriate assays for detecting correlate of protection against targeted antigen/s. The Protocols should predefine the magnitude of the difference between vaccine groups or vaccine and control group that will be regarded as evidence of superiority. The difference should be selected in such a way that it provides some evidence of a potential clinical advantage.

If the vaccine will/might be given simultaneously with other vaccines, appropriate clinical evidence should be provided to ensure absence of vaccines interaction.

IV. Lot-to-Lot Consistency Study using different batches of the vaccine to provide an assessment of manufacturing consistency. In addition to the information provided on the manufacturing process. Whether or not a clinical lot-to-lot consistency trial is conducted, the consistency of manufacturing to the vaccine lots used in clinical trials should be both demonstrated and well documented. The lots used in clinical trials should be adequately representative of the formulation intended for marketing.

3.2. Vaccines with known components or antigens yet developed by a new manufacturer:

Clinical requirements:

I. Phase I study that assess the vaccine safety.

II. Phase II study: such study is concerned with finding the appropriate dose of the vaccine by comparing different doses (dose ranging study). Robust phase II design with strong statistical analysis, outcome measures and appropriate control may in some cases be used as a proxy for phase III trials. In this instance, the applicant should consider discussing the application with the SFDA.

III. Well-designed Phase III, non-inferiority studies that assess the difference between the new manufactured vaccine and well-established vaccine may be required as pivotal evidence for approval. Such studies should be designed appropriately to allow the detection of differences in terms of safety and efficacy profile. The same consideration of study power, selection of appropriate clinical or ICP endpoint, selection of comparative arm, and ensuring means of reducing bias (e.g. randomization, blinding). In addition, scientifically justified non-inferiority margin should be identified prior starting the study.

IV. Lot-to-Lot Consistency Study using different batches of the vaccine.

3.3. Combination Vaccines

I. Combining antigens that protect against multiple types of infections could result in a negative effect on immune response due to the possibility of interactions between the vaccine components or a negative immune interference effect toward some antigenic component. To weigh the risk and benefits due to such combinations, the applicant should be able to provide justification by citing local or international guidelines and relevant clinical trials.

II. For new candidate vaccines that contain known – and one or more new – antigenic components, it is suggested the application may have a non- inferiority preliminary trials 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.

3.4. Major variations (Type II) requirements

I. Any changes in the product composition, e.g. use.

II. Requirements for applications to update seasonal influenza strain:
A TYPE II variation should be submitted, including the new introduced strains according to the WHO recommendations on the composition of influenza virus vaccines in the northern hemisphere.

III. Modifying the age group for already known vaccine
In case of age group modification in a vaccine use, bridging trial is required in variation of new indication submission. The trial design may include comparison between the new claimed age group populations versus the representative population in the previous efficacy trial.

NOTES:

- Selection of comparator arm registered by the SFDA is mandatory unless the comparator is registered by a stringent regulatory authority.
- In some cases, human challenge studies can be used as an efficacy-indicating study or to demonstrate a “proof of concept” during the clinical development of vaccines. Depending on the aim, the clinical phase and the study design will be determined.
- Other non-clinical and quality requirements for vaccine must be met.

4. CORRELATE OF PROTECTION

For some vaccines with known antigenic components, there is established ICP. The following table lists vaccines, analytical tests and the required level of immune response.

Vaccine	Test	Level required
Anthrax	Toxin neutralization	1,000 IU/ml
Diphtheria	Toxin neutralization	0.01–0.1 IU/ml
Hepatitis A	ELISA	10 mIU/ml
Hepatitis B	ELISA	10 mIU/ml
Hib polysaccharides	ELISA	1 _g/ml
Hib conjugate	ELISA	0.15 _g/ml
Human papillomavirus *	ELISA	ND
Influenza	HAI	1/40 dilution
Japanese encephalitis	Neutralization	1/10 dilution
Lyme disease	ELISA	1,100 EIA U/ml
Measles	Microneutralization	120 mIU/ml
Meningococcal	Bactericidal	1/4 (human complement)
Mumps *	Neutralization	ND
Pertussis*	ELISA (toxin)	5 units
Pneumococcus	ELISA; opsonophagocytosis	0.20–0.35 _g/ml (for children); 1/8 dilution
Polio	Neutralization	1/4–1/8 dilution
Rabies	Neutralization	0.5 IU/ml
Rubella	Immunoprecipitation	10–15 mIU/ml
Rotavirus *	Serum IgA	ND
Tetanus	Toxin neutralization	0.1 IU/ml
Smallpox	Neutralization	1/20
Tick-borne encephalitis	ELISA	125 IU/ml
Tuberculosis *	Interferon	ND
Varicella	FAMA gp ELISA	≥1/64 dilution; ≥5 IU/ml
Yellow fever	Neutralization	1/5

*has a clinically significant endpoint.

Different assays that assess ICP could be used. However, they need to be validated and justified by the applicant.

5. VACCINE EXCIPIENTS

For a variety of reasons, each vaccine requires unique composition of different types of excipients. However, an additional consideration should be taken into account for people known to have an allergy toward a specific vaccine component. Below are some types of vaccine excipients.

Types of excipients

- **Adjuvants:** added for enhance immune response to vaccine antigen, targeting the effector response better and conducting a long-term protection.
- **Preservative:** to prevent contamination.
- **Stabilizer**: to keep the stabilization of the vaccine during transportation and storage conditions such as heat, freeze-drying and breaking down from light exposure.
- **Inactivating Ingredients:** used to kill viruses or inactivate toxins.
- **Antibiotics:** used to prevent contamination by bacteria
- **Cell culture materials:** used to grow the vaccine antigens.
- **Emulsifiers** to hold other ingredients together
- **Buffers:** to keep the vaccine at the right PH (acid/alkaline level)
- **Diluent:** is a liquid used to dilute a vaccine to the proper concentration immediately prior to administration.
- **Solvent:** is a substance that dissolves another substance, creating a solution

Listed below are vaccines excipients included in SFDA reviewed vaccines submissions. This list is advisory only and manufacturers can use any excipients as long as they are scientifically justified.

Adjuvants	- Aluminium hydroxide - Aluminium hydroxide gel - Aluminium Phosphate Gel - alpha-Tocopheryl hydrogen succinate
Preservative*	- Thimerosal* - 2-Phenoxyethanol - Phenol - Ethanol anhydrous
Stabilizer	- Gelatin - Phenol red - Magnesium chloride hexahydrate - Monosodium L-Glutamate (Photosensitivity) - Medium 199 Hanks 10xC without phenol red - Octoxinol 10 - Sucrose - Urea
Inactivating Ingredients	- Formaldehyde - Formaldehyde solution
Antibiotics	- Kanamycin Acid Sulphate - Neomycin Sulphate
Cell culture materials	- Dulbecco's Modified Eagle's Medium
Emulsifiers	- Polysorbate 80
Buffers	- Dipotassium hydrogen Ortho phosphate - Disodium hydrogen phosphate - Disodium phosphate dehydrate - Disodium phosphate dodecahydrate - Histidine - Potassium chloride - Potassium Dihydrogen Ortho phosphate - Potassium dihydrogen phosphate - Potassium L-glutamate monohydrate - Potassium Phosphate Monobasic - Sodium chloride - Sodium dihydrogen phosphate - Sodium dihydrogen phosphate monohydrate - Sodium dihydrogen phosphate dehydrate - Sodium phosphate buffer

	- Sodium Phosphate Dibasic - Calcium chloride dehydrate - Dihydrated disodium hydrogen phosphate - Monohydrated sodium dihydrogen phosphate - PBS Solution
Diluent	- Water for injection - Concentrated dilution fluid
Solvent	- Magnesium sulphate heptahydrate

* Should be reserved to multidose vaccines vials only

6. REFERENCES

- World Health Organization. Biologicals. Vaccines Standardization. Available from: https://www.who.int/biologicals/vaccines/en/. Accessed: April, 2020.
- Plotkin, S. A. (2010). "Correlates of protection induced by vaccination." Clin Vaccine Immunol 17(7): 1055-1065.
- World Health Organization. Annex 9. Guidelines on clinical evaluation of vaccines: regulatory expectations. Available from: https://apps.who.int/medicinedocs/documents/s23328en/s23328en.pdf . Accessed: April, 2020.