Pre-clinical And Regulatory Approach of Vaccines

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What are vaccines?

Vaccines are biological pharmaceutical products prescribed as preventive and curative remedies for infections and diseases. The desired pharmacodynamic action of vaccines is the induction of a persistent immunological response against the targeted pathogen.

Type of Vaccines	
Therapeutic	Autologous
	Allogeneic
Prophylactic	Whole pathogen (Live-attenuated and Inactivated)
	Subunit (Polysaccharide, Conjugate, Toxins, Recombinant protein)
	Nucleic acid (DNA plasmid, mRNA plasmid, Recombinant vector)
	Valance (Monovalent, Polyvalent, Combination)
Vaccines Content	
Antigens	Derived from the structure of disease-causing organisms
Adjuvants	Boost the immune response of antigens present in the vaccine
Stabilizers	Maintain vaccine's effectiveness during storage
Antibiotics	Prevent bacterial contamination of culture cells in which viruses or bacteria are grown
Preservatives	Prevent bacterial and fungal growth in the final formulation

Why is a non-clinical safety assessment of vaccines required?

Over many years, vaccination is generally considered a safe and well-tolerated procedure.

Vaccines were administered at most only a few times over the course of a life. However, recent advances in vaccine formulation, which includes both varieties of antigen sources and new adjuvant technologies lead to increase complexity and require to assess overall safety.

Source of Toxicity	
Reactogenicity (Local toxicity)	**Immune overdose (Systemic toxicity)**
Toxicity at the site of injection	Toxicities linked to pharmacodynamic action of the vaccine
Toxicity of constituent materials like adjuvants	Toxicity related to recombinant proteins, conjugated molecules, genetic constructs, and recombinant cells

Purpose of Safety Assessment
To assess pharmacological and toxicological effects of a new vaccine
For the establishment of relevant and potential immunogenicity efficacy and dose in humans
To provide evidence of proof of concept and safety to support the clinical development
To establish the vaccine is safe, pure, and potent for the application
For the registration and licensure for vaccines

What are the regulatory guidelines for **vaccine safety assessment?**

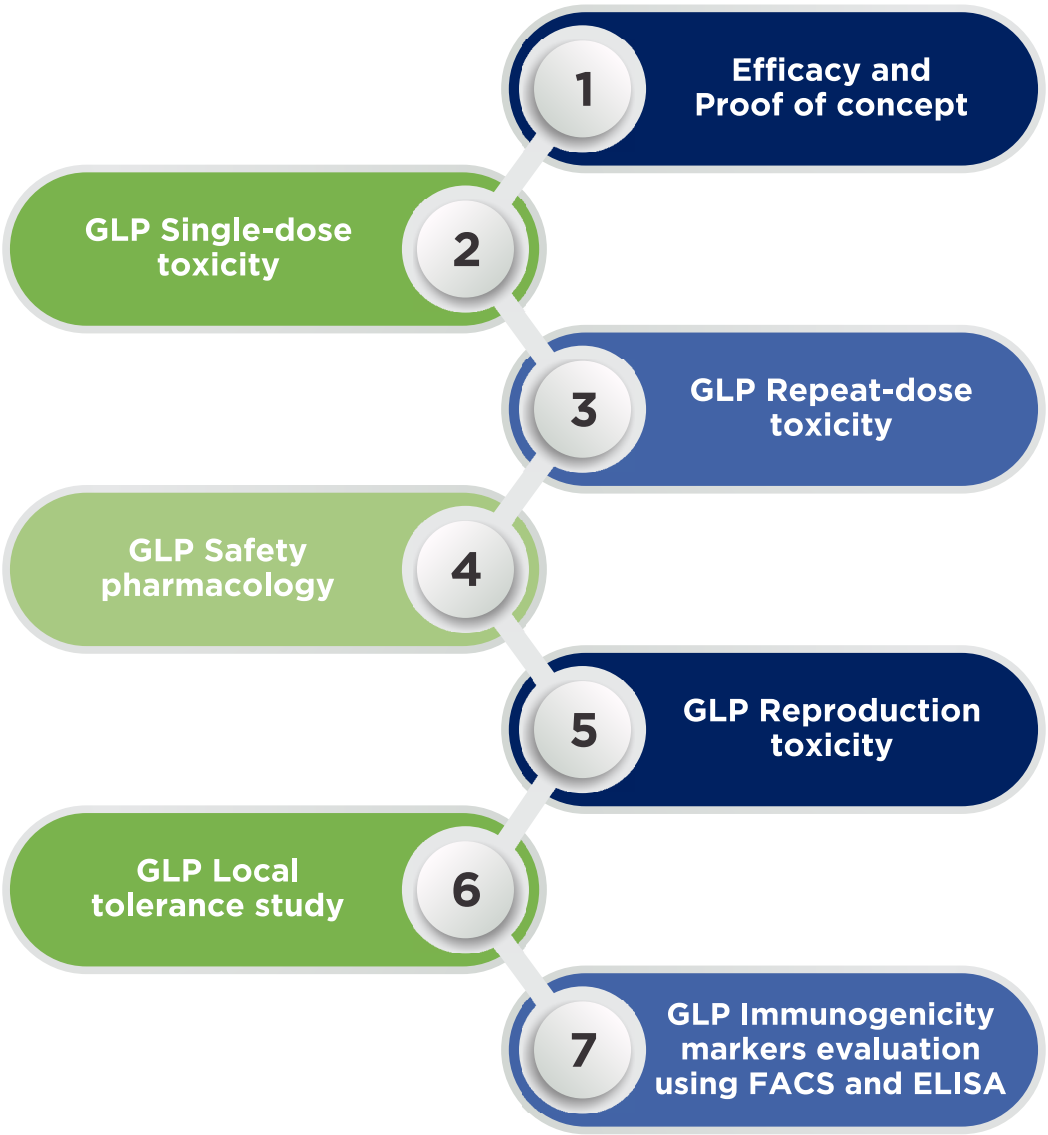
Type of Vaccines	Guidelines
All vaccines	Worldwide Gold Standard: WHO 2005: Guidelines on Non-clinical Evaluation of Vaccines
	China: China Technical Guidelines for Pre-clinical Research on Preventive Vaccines, Notice No. 140 (April 2010)
	Japan: Japanese Guideline for Non-clinical Studies of Vaccines for Preventing Infectious Diseases, (PFSB/ELD Notification No. 0527-1, May 27, 2010)
	India: Drug and Cosmetics Act, 1940 and Drug and Cosmetics Rules, 1945 (December 31, 2016)
	ICH M3(R2): Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (June 11, 2009)
Adjuvanted vaccines	EMA: Guideline on Adjuvants in Vaccines for Human Use, EMEA/CHMP/VEG/134716/2004 (January 20, 2005)
	WHO 2013: Guidelines on the Non-clinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines
DNA vaccines	FDA: Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications (November 2007)
	WHO 2007: Guidelines for Assuring the Quality and Non-clinical Safety Evaluation of DNA Vaccines (Technical Report Series, 941)
Recombinant DNA vaccines	ICH S6(R1): Pre-clinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (July 25, 2011)
Viral vectored vaccines	EMA (EMA/CHMP/VWP/141697/2009): Guideline on Quality, Non-clinical and Clinical Aspects of Live Recombinant Viral Vectored Vaccines (January 01, 2011)
Vaccines for pregnant and child-bearing potential women	FDA (CBER) Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications (February 2006)

Non-clinical **safety testing program**

Study Type	General Remarks
Immunogenicity	To evaluate the vaccine response at the initial stage as a pharmacodynamic studies
	Independent study required to evaluate mechanism if immune response results in toxicity
	Good Laboratory Practice (GLP) compliance is not essential
	Additionally, carried out as a part of a repeat-dose toxicity study
Biodistribution or kinetics	For live attenuated, DNA vaccines, new adjuvant, excipient, device
	Needed in case of alternative routes of administration
	Good Laboratory Practice (GLP) compliance is not essential
Local tolerance	Generally, a part of repeat-dose toxicity study
	Independent study is required for a more detailed evaluation of local reaction, and its mechanism
	Good Laboratory Practice (GLP) compliance is essential
Single-dose toxicity	Provide preliminary tolerability, acute actions, and safety data for a new vaccine
	Sometimes performed as a part of repeat-dose toxicity study
	Indian guidance states that a single-dose toxicity study is conducted in two species using two routes of administration
	Good Laboratory Practice (GLP) compliance is essential
Repeat-dose toxicity	The principal study that supports the safety profile of the vaccine under development
	Study design should mimic the clinical study in terms of animal relevancy (rodent and rabbit) to develop an immune response, vaccine formulation, dosage regimen (n+1 rule), and route of administration
	Well designed to include various endpoints related to in-life measures, post-life measures, systemic toxicity, local reaction, immunogenicity biomarkers, inflammatory markers, reversibility, or delayed effect
	Good Laboratory Practice (GLP) compliance is essential
Reproduction toxicity	Needed to support the use of a vaccine in a particular population
	Expected to evaluate both embryo-fetal and postnatal/neonatal toxicity
	It is generally conducted using Phase 3 human dose and schedule.
	Good Laboratory Practice (GLP) compliance is essential
Safety pharmacology	Required if repeat-dose study or data suggest that the vaccine may affect physiological functions (CNS, CVS, and respiratory)
	To evaluate the potential for undesirable secondary pharmacological actions of vaccines
	Japanese guidance states that safety pharmacology studies are required for all vaccines
	Good Laboratory Practice (GLP) compliance is essential

Genetic toxicity or carcinogenicity	Generally, not required for vaccines except vaccines that contain DNA or other genetic elements
	Synthetic adjuvants are subject to the standard battery of genetic toxicity
	Good Laboratory Practice (GLP) compliance is essential

JRF's Vaccines services



About the Author:

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Kunjan N Shah is a Senior Research Officer in the Toxicology Department at JRF. He has a good experience of conducting various types of short-term and long-term studies (like, sub-acute, sub-chronic, chronic, neurotoxicity, toxicokinetics, ADME, in-vivo dermal absorption, vaccines, and safety pharmacology) and is actively involved in research validations. He has professional experience of more than 9 years in the CRO industry.

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