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Research Article

A COMPREHENSIVE STUDY ON REGULATORY REQUIREMENTS FOR REGISTRATION OF VACCINES IN USA, EUROPE AND CANADA

Janki Dobariya[1]*, Ronak Dedania[2], Zarna Dedania[3] and Vineet Jain[4]

[1,2,4] Department of Pharmaceutical Regulatory Affairs, Bhagwan Mahavir College of Pharmacy, Surat, Gujarat, India

[3]Department of Pharmaceutical Quality Assurance, Bhagwan Mahavir College of Pharmacy, Surat, Gujarat, India

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ABSTRACT

Vaccines are the most important health intervention. A vaccine is a biological preparation which increases the immunity to a specific disease. The development of a vaccine is a complex and tedious process. A strict regulatory process to determine the safety, efficacy, and quality must be achieved throughout the development of a vaccine for its authorization. In the USA vaccines are regulated by the Center for Biologic Evaluation and Research (CBER) under the USFDA. In Europe, vaccines are regulated by the European Medicines Agency (EMA) and authorization is granted by the European Commission (EC). In Canada, vaccines are regulated by Biologics and Genetics Therapy Directorate (BGTD) under Health Canada (HC). For Registration of Vaccine, Biologics license application (BLA) in the USA, Marketing authorization application (MAA) in Europe and New Drug Submission (NDS) Application in Canada should be submitted. After the registration of a vaccine, post-marketing surveillance system such as Vaccine Adverse Event Reporting System (VAERS) in the USA, Pharmacovigilance system in Europe and Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) in Canada monitors the safety of a vaccine.

INTRODUCTION

Vaccination is one of the most important health interventions, it saves a large number of people from illness, disability, and death every year. A vaccine meets the definition of both drug and a biological product. A vaccine is a biological preparation which increases the immunity to a specific disease. Typically, a vaccine contains an agent that resembles a disease-causing microorganism. It is made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. This agent triggers the body immune system to recognize the agent as foreign, destroy it, and keep a record of it, so that the immune system can more easily recognize and destroy any of these microorganisms that later encounters.

Vaccines may be therapeutic (means vaccines against cancer are also being investigated) or prophylactic (means to prevent or ameliorate the effects of a future infection by any natural or "wild" pathogen), The term vaccine was elucidated by Edward Jenner's 1796 use of cowpox (Latin variola vaccinia, taken from the Latin vaccīn-us, from vacca, cow), to inoculate humans and providing them protection against smallpox.[1]

New, safe and effective vaccines are introduced and authorized in the market each year, so it is important to incorporate them in the official immunization schedule. To include vaccines into immunization schedule USA follows guidelines as per USFDA (United States Food and Drug Administration) requirements, Europe follows guidelines as per EMA (European Medicines Agency) requirements and Canada follows guidelines as per Health Canada requirements. The regulatory bodies like USFDA, EMA, and Health Canada ensures the safety, effectiveness, and availability of licensed vaccines through its extensive regulatory review mechanisms.[2]

Regulatory Aspects of Vaccines in USA

In USA, vaccine products are regulated by the Center for Biologics Evaluation and Research (CBER). The recent authority of CBER for regulation of vaccine product exists in section 351 of the Public Health Service Act and the Food, Drug, and Cosmetic Act. The public health service act is executed by the Code of Federal Regulations (CFR) that comprehends the general rules issued in the Federal Register by the Federal Government Agencies. Title 21 CFR Parts 600-680

Corresponding author:* **Janki Dobariya
Department of Pharmaceutical Regulatory Affairs, Bhagwan Mahavir College of Pharmacy, Surat, Gujarat, India

covers the rules particularly related to biologicals including vaccine products.[3]

Development of Vaccines in USA

The clinical development of vaccine follows the identical pathway as for other biologics. In the commencement of the vaccine development, laboratory tests are carried out before conducting the animal or human trials. If the result demonstrates the potential of a vaccine, the animal trials are carried out. If the product is safe then clinical trials on human subjects are carried out.[4]

There are 3 over-all Phases of Vaccine Development

- Pre-clinical phase
- Clinical development phase
- Regulatory review and approval procedures

Pre-clinical Phase

The pre-clinical trial involves tissue or cell-culture systems besides animal studies for measurement of vaccine immunogenicity, or its capacity to stimulate an immune response. These trials provide a viewpoint to investigators about the cellular responses, that can be assumed in humans. This also provides information regarding safe initial dose and safe mode of vaccine administration. Investigators may familiarize the product during the pre-clinical phase for making it further expressive. The pre-clinical phase is typically of 1-2 years and often includes investigators of private industry.[3]

Investigational new Drug Application

An Investigational New Drug Application (IND) should be submitted to the Food and Drug Administration (FDA) by a sponsor before the commencement of clinical trials with vaccines. The IND contains the description of a vaccine, its manufacturing procedures, quality control tests, its safety data, its capability to produce an appropriate and defensive immune response (immunogenicity) and future clinical trial protocol in human studies. FDA takes 30 days for approval of an application. After approval vaccine is subjected to 3 phases of clinical trial.[5]

Clinical Development Phase

Premarketing vaccine clinical trials are carried out in 3 phases. Phase 1 clinical trial concentrates on safety and immunogenicity, and involves 20–100 healthy volunteers. During the Phase 1 trial, investigators start learning the relation between the dose size and side effects. Investigators additionally attempt to learn the vaccine effectivity. Phase 2 trials are dose-ranging trials and comprises several hundred volunteers. This phase contain studies that provide further data on common short-term side effects and relation between the dose size and immune response.

Phase 3 trials involve hundreds or thousands of volunteers and offer documentation of safety and effectiveness. Immunized individuals are compared with individuals who have received a placebo vaccine so investigators can gain more knowledge on safety and effectiveness of test vaccine and recognize common side effects. The outcomes of the clinical trials are a part of FDA's assessment for determination of the safety and effectiveness of an individual vaccine. From the outcomes of the trial, it is essential to confirm that the benefits of vaccine overshadow the potential risks for individuals who will be suggested to take the vaccine. Phase 4 trials are non-compulsory and may be carried out after the release of a vaccine. It involves safety and effectivity testing by manufacturers.

Regulatory Review and Approval Procedures

After the successful accomplishment of phase three clinical trial, the Biologics License Application (BLA) should be submitted to the FDA. The multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.) then evaluate the safety and efficacy data based on proposed risk and benefit for disapproval or approval of the vaccine. Throughout this period, the manufacturing facility experiences a pre-approval inspection.[6]
FDA will take 180 for evaluation of BLA. The application fees for the application that requires clinical dataare $ 2,588,478 and the application fees for the application that does not require clinical data are $ 1,294,239.[7]

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

After evaluation of BLA, the sponsor and the FDA can present their verdicts to the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). This committee (scientists, physicians, biostatisticians, and a consumer representative) gives advice to the FDA regarding the safety and efficacy of the vaccine. FDA approves vaccine labeling and continuously monitors the vaccine production once the vaccine and the manufacturing procedures are approved. After licensing, FDA also observes the product and of production activities as long as the manufacturer embraces a license for the product. The manufacturer may require to provide a sample of each batch of vaccine to FDA for evaluation.[8]

Post Licensure vaccine Monitoring

There are several systems that observe vaccines after their approval. They include Phase 4 clinical trials and Vaccine Adverse Event Reporting System (VAERS).[6]

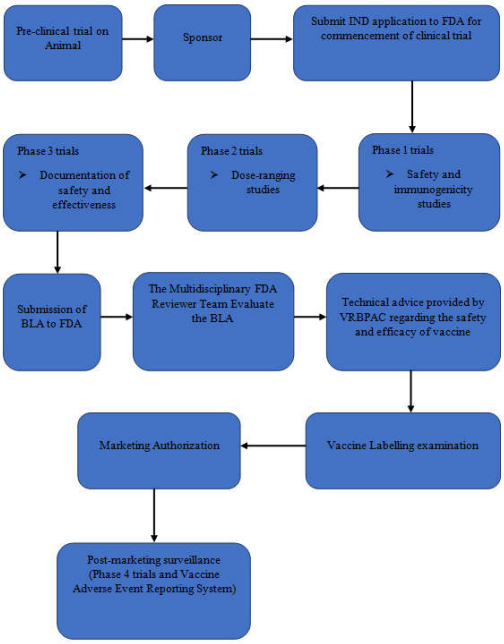

Figure 1 Development of vaccines in USA[3-6]

Regulatory Aspects of Vaccines in Europe

The European Medicines Agency (EMA) is responsible for the regulation of vaccines in Europe. Applications should be submitted to the EMA and licenses are allotted by the European Commission (EC).[9]

Registration or licensing of pharmaceutical products in Europe can be done by different procedures such as:

- Centralised Procedure
- Mutual Recognition Procedure (MRP)
- National Procedure[10]

Development of Vaccines in Europe

There are two phases of vaccine development, preclinical phase, and clinical phase. The preclinical phase involves the determination of vaccine safety. This stage includes antigen selection and in-vitro and in vivo tests for safety determination. The data from the preclinical trial provides an idea regarding the initiation of clinical trials.

After preclinical studies, clinical trials are carried out. Clinical development involves 4 phases of trials. Phase 1 trials are small scale trials, carried out on healthy humans for determination of the safety and immunogenicity of the vaccine. After completion of the phase 1 trial, phase 2 trials are carried out to determine the efficacy of the vaccine. These trials are larger.

Phase 3 trials are carried out on a large scale for evaluation of efficacy on patients. After long term retention of safety and efficacy, the manufacturer will be able to submit a Marketing Authorization Application to the EMA for licensing of a vaccine.

Phase 4 trials are carried out after licensing of a vaccine. This phase is also called as pharmacovigilance and includes detection of adverse effect after vaccination.[11]
Before the commencement of a clinical trial, a sponsor must submit a clinical trial application to the competent authority. 60 days are required for the evaluation of clinical trial application.[12]In Europe, 210 days are required for evaluation of Marketing authorization application. The application fees for evaluation of application is 2,86,900 EURO[13]

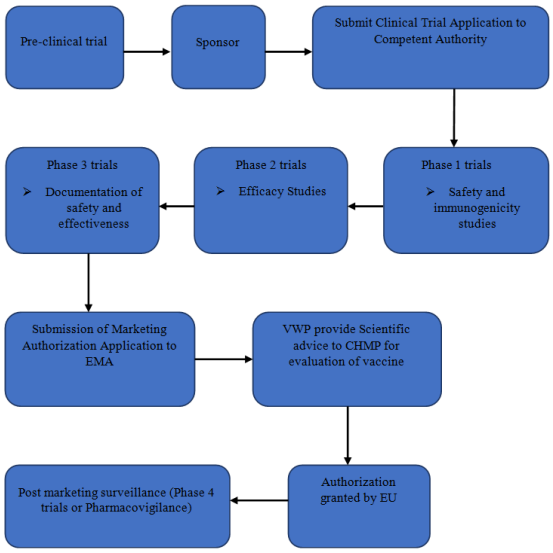

Figure 2 Development of vaccines in Europe[9-12]

Regulatory Aspects of Vaccines in Canada

HC is the regulatory body in Canada. Health Canada is accountable for increasing the safety and effectiveness of biologics, including human vaccine. Within the Health Products and Food Branch(HPFB) of HC, the Biologics and Genetic Therapies Directorate (BGTD) is responsible for "Canada's vaccines regulatory program" in partnership with the Health Product and Food Branch (HPFB) Inspectorate and the Marketed Health Products Directorate. Within Canada vaccines are included under the "Food and Drugs Act" and the "Food and Drug Regulations". Vaccines are regulated within a particular group of principles for a biological drug.[14]

Development of Vaccines in Canada

There are two phases of vaccine development, preclinical phase, and clinical phase.

The preclinical phase involves the determination of vaccine safety. After the demonstration of safety in preclinical phase clinical trials are carried out in 4 phases. Before the commencement of a clinical trial, the clinical trial application must be submitted.

Phase 1 trials involve testing of the product in a small group of candidates for determination of safety and side effects of the product. Phase 2 trials are carried out in a larger group around a hundred candidates for determination of the safety, effectiveness and the appropriate dose of the product. Phase 3 trials are carried out in a larger group around a thousand candidates for confirmation of effectiveness and for monitoring side effects of the product. After successful completion of phase 3 trials, marketing authorization application must be submitted. Phase 4 trials are carried out after the approval and marketing of the product. During this phase, long term risk and benefits of the vaccines are observed. The BGTD will take 300 days for evaluation of a new drug submission application.[15]The application fees are $ 3,48,606.[16]

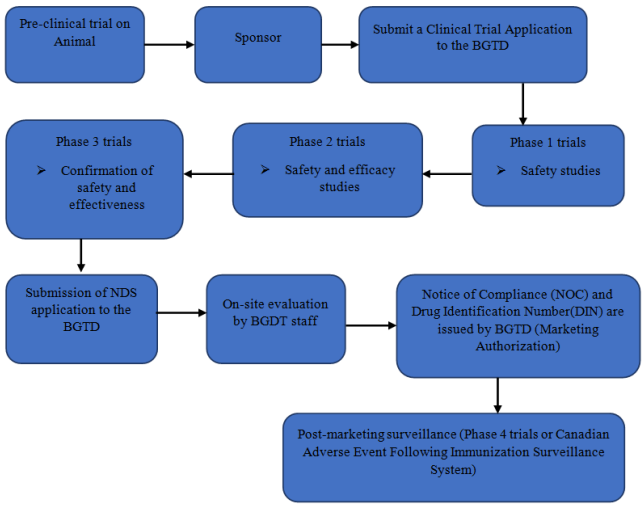

Figure 3 Development of vaccines in Canada[14-15]

Regulatory Requirements for Registration of Vaccine in USA, Europe and Canada[17-25]

Table 1 Regulatory Bodies

Country	USA	Europe	Canada
Regulatory Bodies	CBER under US FDA	EMA, EC	BGTD under HC

Table 2 Clinical Trial Application

Sr. No	Parameter	USA	Europe	Canada
1	Clinical Trial Application (CTA)	Investigational New Drug Application (IND)	Clinical trial application	Clinical trial application
2	CTA Format	eCTD (Electronic Common Technical Document)	Electronic Format	eCTD (Electronic Common Technical Document)
3	CTA application Form	FDA form 1571	Clinical Trial Application Form	Clinical Trial Application Form
4	Simplified Investigational Medicinal Product Dossier	-	If data can be available by referring the other submission	-
5	Approval Period	30 days	60 days	30 days

Table 3 Marketing Authorization Application

Sr. No	Parameter	USA	Europe	Canada
1	Application for registration of vaccine	Biologics Licence Application (BLA)	Marketing Authorization Application (MAA)	New Drug Submission (NDS) Application
2	Application Format	eCTD	eCTD	eCTD
3	Transmission of electronic submission	FDA Electronic Submission Gateway	EMA eSubmission Gateway	Common Electronic Submission Gateway
4	Approval Period	180 days	210 days	300 days
5	Application fees	With Clinical Data-$ 2,588,478 Without Clinical Data- $ 1,294,239	2,86,900 EURO	$ 3,48,606

Table 4 Administrative Information

Sr. No	Parameter	USA	Europe	Canada
1	Forms	FDA Form 356h	Application Form	Application Forms Fee Forms Certification and Attestation Forms
2	Labelling	Labelling history List of current labelling changes in the present submission Justification for changes	Labelling leaflets	Inner and Outer Labels Non-Canadian Labelling Reference Product Labelling
3	Regional Information	Marketing annual reports	Response Documents	Health Canada Summaries

Table 5 Quality Information (Drug Substance)

Parameter	USA	Europe	Canada
Drug Substance	Description and Characterization Manufacturer Method of Manufacture Detailed Description Process Controls Manufacturing Consistency Drug Substance Specifications Reprocessing Container Closure System Drug Substance Stability	General Information Manufacturing Process Characterisation Control of Drug Substance Reference standards or materials Container Closure System Stability of the Drug Substance	General Information Manufacture Characterisation Control of Materials Controls of Critical Steps and Intermediates Process Validation and/or Evaluation Manufacturing Process Development Control of Drug Substance Reference Standards or Materials Container Closure System Drug Substance Stability

Table 6 Quality Information (Drug Product)

Parameter	USA	Europe	Canada
Drug Product	Composition and Characterization Manufacturer and Facilities Manufacturing Methods Drug Product Specifications Lyophilization Environmental assessment report Container closure system Drug Product Stability Establishment Description Adventitious Agents Safety Evaluation	Description and composition of the drug product Pharmaceutical development Manufacturing process Control of excipients Control of drug product Reference standards and materials Container closure system Drug Product Stability Facilities and Equipment Adventitious Agents Safety Evaluation Excipients Regional Information	Description and Composition of the Drug Product Pharmaceutical development Manufacture Control of excipients Control of drug product Reference standards or materials Container closure system Drug Product Stability Facilities and Equipment Adventitious Agents Safety Evaluation Excipients Regional Information

Table 7 Nonclinical Information

Parameter	USA	Europe	Canada
Study Reports	Pharmacology Study Reports Pharmacokinetics Study Reports Toxicology Study Reports	Pharmacology Study Reports Pharmacokinetics Study Reports Toxicology Study Reports	Pharmacology Study Reports Pharmacokinetics Study Reports Toxicology Study Reports

Table 8 Clinical Information

Parameter	USA	Europe	Canada
Study Reports	Reports of human pharmacokinetic studies	Biopharmaceutic Study Reports	Biopharmaceutic Study Reports
	Reports of human pharmacodynamic studies	Reports of studies pertinent to pharmacokinetics using human biomaterials	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
	Reports of efficacy and safety studies	Reports of human pharmacokinetic studies	Reports of Human Pharmacokinetic (PK) Studies
	IND safety reports	Reports of human pharmacodynamic studies	Reports of Human Pharmacodynamic Studies
	Periodic safety reports	Reports of efficacy and safety studies	Reports of Efficacy and Safety Studies
		Reports of post-marketing experience	Reports of Post-Marketing Experience

Post-marketing Surveillance Systems for Vaccines in USA, Europe and Canada

Vaccine Adverse Event Reporting System (VAERS) in USA

In the USA, the Vaccine Adverse Event Reporting system is a very important system for monitoring the product after their approval and marketing. The post-marketing safety monitoring is essential for recognizing the safety matters that can be spotted after vaccination of large and diverse population.

The VAERS is national safety surveillance program, that is formed as a consequence of the National Childhood Vaccine Injury Act (NCVIA) of 1986 and administered by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC). The VAERS gathers and evaluates information from reports of adverse events resulting after immunization, and helps for recognizing the important safety concerns that might not be revealed before licensure.[26]

Objectives of VAERS

- To observe rise in known side effects such as arm soreness where a shot was given.
- To recognize potential patient risk factors for specific categories of health problems associated with vaccines.
- To evaluate the safety of newly licensed vaccines.
- To watch for unanticipated or uncommon patterns in adverse event reports.
- To serve as a monitoring system for vaccinations administered in public health emergencies.

Reporting the Vaccine Adverse Event to the VAERS

Generally, vaccine adverse events are reported via health care providers, vaccine manufacturers, vaccine recipients (or their parents/guardians) and state immunization programs. Generally, the patients, parents, and guardians should pursue the help of a health-care professional in reporting to VAERS. The reports can be submitted online, by fax or via email.

All the significant adverse event happening after the administration of any U.S. licensed vaccine must be submitted to VAERS. As per the National Childhood Vaccine Injury Act (NCVIA), the following events must be reported:

- All the events listed by the vaccine manufacturer as a contraindication to subsequent doses of the vaccine.
- All the events listed in the Reportable Events Table that occurs within the specified time period after vaccination.

Evaluation of VAERS reports

The data submitted to the VAERS are reviewed by the CDC and the FDA. The FDA evaluates the reports to determine whether the event is effectively reflected in product labeling. The FDA thoroughly observes reporting trends for specific vaccine batches. If the vaccine possesses a significant risk to the public, the FDA can recall the vaccine from use.[27]

Pharmacovigilance System for Vaccines in Europe

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem.
The EMA synchronizes the European Union (EU) Pharmacovigilance System and provides processes for supporting the EU Pharmacovigilance.

The clinical trial provides appropriate information regarding the safety and efficacy of the product before authorization. During the clinical trials, subjects are chosen carefully under controlled condition. So, at the period of authorization product has been tested in a small number of subjects for a specific period of time. Product may be used in a large number of populations after its licensing for a long period. In this situation, some side effects can occur. So, it is important to observe the product safety throughout its use within healthcare practice via Pharmacovigilance.

In Europe, the pharmacovigilance system is operated via cooperation between the EU Member States, EMA and the European Commission.[28]

Conduct of Vaccine pharmacovigilance

Vaccine pharmacovigilance involves the vaccinee, for pediatric vaccination, their parents, healthcare professionals, Marketing Authorization Applicant, clinical trial sponsors, competent authority and WHO.

Factors Associated with Vaccine Safety Profile

Vaccine-Intrinsic factors

This involves types of vaccine (some live vaccines), novel vaccines (new adjuvant), some immunogenic adjuvants, stabilizers, preservatives, combined vaccines, batch related adverse events, immunization schedule and route of administration.

Host Factors

This involves special age groups, pregnancy and immunocompromised individuals (sensitive to serious adverse reaction).

Risk Management plan

Risk Management plan involves:

Safety Specification

This involves nonclinical aspects for further consideration, identified and potential interactions with co-administration of other vaccines, epidemiology of the target disease and

background incidence of adverse events of interest, and potential of transmission of infectious agents.

Pharmacovigilance plan

This involves special consideration for routine and additional pharmacovigilance activities. This involves a plan for gathering the data on long-term duration of protection, need for booster dose and pharmacovigilance method for collection of these data.

Risk minimization plan

This involves risk minimization activity for minimizing the risk of adverse events. It must list the safety concernsfor which risk minimisation activities are planned.

Spontaneous Reporting

This involves Adverse Events Following Immunisation (suspected adverse events, vaccine failure, and vaccine error), Periodic Safety Update Reports (summary and analysis of immunization error and anxiety related reactions), and Signal Detection (unexpected adverse reaction signals from preclinical and clinical data).

Risk Minimisation and Regulatory Action

This involves regulatory tools and risk minimization activities such as precautionary measures, product information, risk communication, and audit and outcomes assessment.[29]

Canadian Adverse Events Following Immunization Surveillance System (CAEFISS)

In Canada, the Canadian Adverse Events Following Immunization Surveillance System is a federal public health post-marketing vaccine safety monitoring system.

The Canadian Adverse Events Following Immunization Surveillance System is responsible for

- ✓ Continuously observing the marketed vaccine safety within Canada.
- ✓ Identification of the increase in the occurrence or severity of previously identified vaccine-related reactions.
- ✓ Identification of the previously unknown adverse events following immunization that maybe associated with the vaccine.
- ✓ Identification of areas that require additional investigation and research.
- ✓ providing appropriate information about adverse events following immunization reporting profiles for marketed vaccines within Canada.

Adverse Event Following Immunization Reporting in Canada

In Canada, the CAEFISS reports are submitted by public health authorities of particular territories. They receive them from local public health units and federal authorities that provide immunization within their jurisdiction. These reports are generated via nurses, physicians, and pharmacists. Adverse Events Following Immunization (AEFI) received by National Defence and the Canadian Armed Forces are reported directly to the Agency. On rare cases, AEFI reports are submitted to the Agency directly from physicians, pharmacists, travel clinics and the public. Marketing authorization holder can directly report to the health agency.[30]

CONCLUSION

Vaccines are important for safeguarding individuals and communities from the mortality and morbidity associated with many infectious diseases. Vaccines are developed, tested, and regulated in a very similar manner to other drugs. The number of the human subject involved in vaccine clinical trials are also higher than other drugs. Stringent regulatory requirements must be achieved throughout the vaccine development to include them in the immunization schedule. To include the vaccine in the immunization schedule USA follows Guideline as per US FDA requirement, Europe follows guideline as per EMA requirements and Canada follows guideline as per HC requirements. Novel vaccines containing new adjuvants and new drug delivery system provides new challenges to the regulatory bodies of different countries. So, it is important to identify and implement the appropriate strategies for demonstration of safety and efficacy of new a vaccine.

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