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Review Article

REGULATORY FRAMEWORK: VACCINE DEVELOPMENT IN US, INDIA AND EU

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ABSTRACT

Vaccine development usually takes around 7 y to come to the market after getting necessary regulatory approvals. But recent pandemics like Covid, Ebola, Swine Flu, have resulted in the collaboration of efforts between the government doing investments in vaccine development, academia, regulatory bodies, and industry. This has shortened the timelines for approval for vaccines. In 2009, HINI, Swine flu vaccines took 93 d for identifying the vaccine candidate for clinical trials. In 2014, for Ebola vaccine, it was deployed while the epidemic was still going on. Ebola vaccine was developed in 5 y. In case of Covid (SARS-CoV-2) clinical trials were approved when 2 mo of the pandemic onset. Within a time of 9 mo about 138 vaccine candidates are being reviewed for approval of EUA. This highly helps in the shortening of vaccine development and necessary approval. In this paper, we focused on the regulatory framework of vaccine development in INDIA, US and EU.

Keywords: Vaccines, Regulation, USFDA, IND, BLA, FDA, MAA, USA, EU, India

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INTRODUCTION

Vaccines are one of the most significant achievements of science and public health. Many diseases that can be prevented by vaccination are now rare in the United States due to successful immunization programmes. Drugs are described as substances that are employed in the treatment, mitigation, medicine, or prevention of disease. Typically, disease-causing microorganisms, their toxins, or a denatured or dead version of one of their surface proteins are used to create vaccines [1-4]. Vaccines belong to a brand-new category of pharmaceutical medicines that can be classified as both medications and biological products. Some pharmaceutical products could be considered medications or biological products. A vaccination is a prescription medication used to increase immunity to a particular disease. An injection of a chemical known as a vaccination is given to a patient in order to treat or prevent an ailment or sickness that is brought on by a particular causative agent. The vaccine provides instructions on how to trigger an immune response in order for the body to defend itself against infectious diseases. The vaccination industry is strictly controlled and the process of creating vaccines is challenging and time-consuming [5-8]. The vaccine typically contains a component that mimics a germ in which it causes disease, this substance is frequently derived from a weakened or dead variety of the disease-causing bacteria toxin or from its surface proteins. The material causes the immune system to become activated, allowing it to identify and destroy the substance as a threat as well as any associated microorganisms that the host may later come into contact with to stop or minimise the symptoms of a future infection by a natural or wild virus Vaccinations can be therapeutic or preventative Some vaccines provide full sterile immunity, which completely prevents infection [9-12]. Vaccine restrictions are still region-or country-specific, and they are getting more complicated every day. As a result, unified criteria for the vaccination approval process in emerging and developing nations are required. The United States Food and Drug Administration, Centre for Biologics Research and Development oversees the vaccines and associated goods. To request permission to produce and sale the vaccines in the USA, fill out the FDA Application 356h, Biologics License Application (BLA). The European Union (EU) uses a mechanism known as the Marketing Authorization Application (MAA) to control how vaccines are approved [13-15].

Information sources and search strategy

We searched PubMed and Google Scholar for relevant articles. PubMed was searched with the keyword's 'vaccine' in any field and 'regulations' in any field without any language, time, or other restrictions. A Google Scholar search was performed with the keyword's 'vaccine' and 'regulations' in the title of the article with no other restrictions. References provided in full papers were also used to identify additional papers for review. The last date of the search was 5th August 2022. We used the software Endnote X7 (Thomson Reuters, Carlsbad, CA 92011, USA) to filter articles.

How do vaccines work

Vaccines reduce the risk of infection by working with the body's natural defences to safely develop immunity to disease [16]. It was depicted in the [fig. 1]. There is a strong consensus among researchers that vaccinations are a very secure and efficient method of preventing and treating communicable diseases. The human body recognises vaccine elements as external substances, gets rid of them and keeps a record of them. The body recognises the protein coat on the virus when it encounters a virulent form of an agent and is prepared to respond by first neutralizing the targeted agent before it can enter cells and then by recognising and removing infected cells before that agent can expand to massive numbers. Despite this, there are restrictions on their applicability because sometimes immunity is compromised due to host-related factors such as the host immune system not responding properly or at all or vaccine-related factors such as deficiencies in vaccine attenuation, schedules, genetics, Immunological health, age, physical condition, and dietary quality are the most frequent causes of a lack of response. If the host immune system lacks any B cell strains that can develop antibodies capable of responding and attaching to the pathogen antigens, it may also fail due to genetic factors. Adjuvants are frequently employed to enhance immune reactions, especially in older participants whose immune reactions to a straightforward vaccination might have been compromised [17]. The variables which influence the vaccines performance are The condition itself, the vaccination variety, how well the vaccine schedule has been followed, idiosyncratic reaction to immunization, some people are non-responders to specific vaccines, which means that even after receiving the proper immunizations they do not produce antibodies, many variables including age, genetic inclination or race.

Vaccine development

Millions of individuals receive them safely each year, and the majority are already employed for many years before being included in the nation's vaccination schedule. Each vaccine, like other

pharmaceuticals, must pass rigorous testing that confirms its safety. The standardization process for vaccine approval is an exploratory stage, pre-clinical stage, clinical development, conducting an investigation, and acceptance stages.

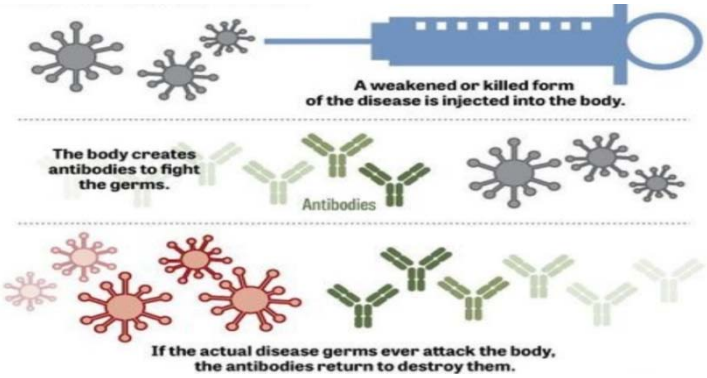

Fig. 1: How do vaccines work, [Source: https://www.indiascienceandtechnology.gov.in/covid-19-vaccine/vaccine-introduction] [18]

Exploratory stage

This level typically occurs in two to four years and encompasses fundamental investigations by governmental and educational researchers with federal funding to find artificial antigens that cure diseases. These antigens could be pathogen-derived compounds, attenuated viral toxins or virus-like debris. Three steps of testing are conducted on the vaccination.

Pre-clinical stage

Pre-clinical research examines a prospective vaccine's immunogenicity or capacity to elicit an immune response as well as its safety using cell-culture methods and animal testing. Studies provide scientists an understanding of the biological reactions they would anticipate in people; they might also recommend a secure initial dosage for the subsequent research stage, a secure way to give the vaccine. When the potential vaccine is still in the pre-clinical stage, researchers might modify it to try to increase its efficacy. The animals might also be used for challenge trials, which entail immunizing the animals before attempting to expose them to the intended pathogen. Many potential vaccines never move past this point because they don't elicit the necessary immune response. Preclinical stages typically take between one and two years and involve researchers from private enterprises.

Clinical development

With IND approval, the clinical development step gets underway. Clinical testing using vaccinations on humans requires the creation of a general study plan. Phase I, II, and III clinical trials must all be conducted after receiving regulatory authority permission. It could take up to eight years to complete the final stage of clinical development [19]. It was depicted in the [fig. 2].

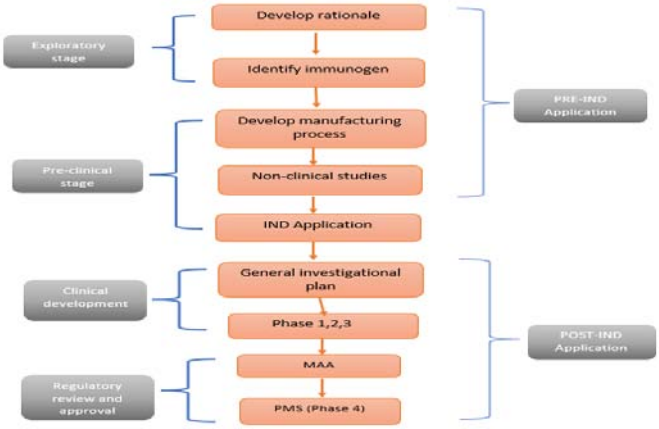

Fig. 2: The general phases of a vaccine's development cycle

IND application

The USFDA submits an application for an IND from a sponsor, typically a commercial firm. The sponsor summarises the lab reports, discusses the proposed study, and details the manufacturing and evaluation procedures. A clinical protocol needs to be authorised by an institutional review board that represents the organization that will perform the clinical study. The application requires 30 d to be accepted by the FDA. The vaccine must undergo 3 steps of testing after the IND application is accepted [20, 21].

Phase I vaccine trials

A small number of adults, approximately 20-80 individuals, are included in the phase I vaccine trials while creating a vaccine for kids in order to reach the target population. Scientists will first test the substance on adults before lowering the age of the test subjects. A placebo may be used in these tests if they are not blinded. The goal of phase I assessment is to determine the vaccine's security and strength of the immunological reaction.

Phase II vaccine trials

To assess the vaccines' immunogenicity and give a preliminary design of the common adverse effects, phase II vaccine studies involving several hundred participants are conducted in order to discuss their prospective phase III studies. Sponsors are encouraged to meet with the CBER at the end of phase II testing to serve the purpose of the research.

Phase III vaccine trials

Following the successful conclusion of phase II vaccine studies, the trials progress to bigger trials involving thousands to tens of thousands of participants. The investigational vaccination is tested in these phase III trials versus a placebo in a randomised double-blind fashion. Phase III is intended to evaluate the safety of the vaccination in a sizable population. One study found that smaller subject populations studied in early phases might not have seen any uncommon adverse effects; according to one study to find a variation for a minimal occurrence, a study would need to enrol 60k people, half of whom would be in the placebo group, or those who had not received vaccinations placebo.

Phase IV trials

The vaccine creator might choose to do optional investigations known as phase IV trials once the vaccine is made available. The vaccine might keep evaluating its security effectiveness and other potential applications [22, 23].

Manufacturing of vaccines

Due to this reality, vaccinations must adhere to some of the most stringent design monitoring and compliance standards of any modern manufactured product. Four skills are the foundation for the safe and reliable production of these vaccines. These includes the production procedure that specifies how the product is created, the organization's conformance with that procedure, the product testing and related procedures, all four new vaccinations are subject to a clear regulatory approval process before being allowed to be released and distributed.

There are four main components to the approval procedure

Preparedness of preclinical documents for animal model proof-of-concept tests, the submission of an application for an Investigational New Drug, testing for efficiency and safety, and submission of a Biologics License Application (BLA) containing required data to the FDA and EMA for approval. Propagation is the process by which the living organism employed in vaccination is multiplied or amplified. The living organism should be separated from the cells used in the propagation step in order to be isolated. Purification eliminates any compounds that are connected to the isolated living creature that will be used in the vaccine. Formulation involves the mixing of the purified product in solutions to get the desired concentration. In order to maintain the products' sterility for a longer period of time to avoid cross-contamination while extracting doses from vials, preservatives may also be added to some vaccines. Vaccines are normally packaged for transportation to healthcare professionals after the manufacturing process is complete and placed in vials or syringes [24, 25].

Propagation ⟶ Isolation ⟶ Purification ⟶ Formulation

Vaccine regulations in India

Various regulatory agencies for vaccine registration are the Ministry of Health and Family Welfare, National Technical Advisory Group on Immunization, Indian Council for Medical Research, Central Drugs Standard Control Organization [27-31]. Further information of vaccine regulations in India were depicted in [fig. 3].

Vaccines regulations in USA

Various regulatory bodies for vaccine registration in the US include Centre for Biologics Evaluation and Research, Vaccines and Related Biological Products Advisory Committee, Biologics License Application [32, 33].

Regulatory approval and review

After the Phase 3 trials, the producer must submit a CBER of USFDA on FDA form 356h biologic licence application to request permission to manufacture and commercialize the vaccine to a large population. Depending on whether the application is being reviewed as a priority or under a regular review, it could take anywhere from 6 to 12 mo to complete. Phase 4, often known as post-marketing surveillance, will start after the approval procedure. Within 15 d of the vaccination administration, any adverse events or effects must be notified to the authority [34, 35]. Regulatory approval in USA was depicted in [fig. 4].

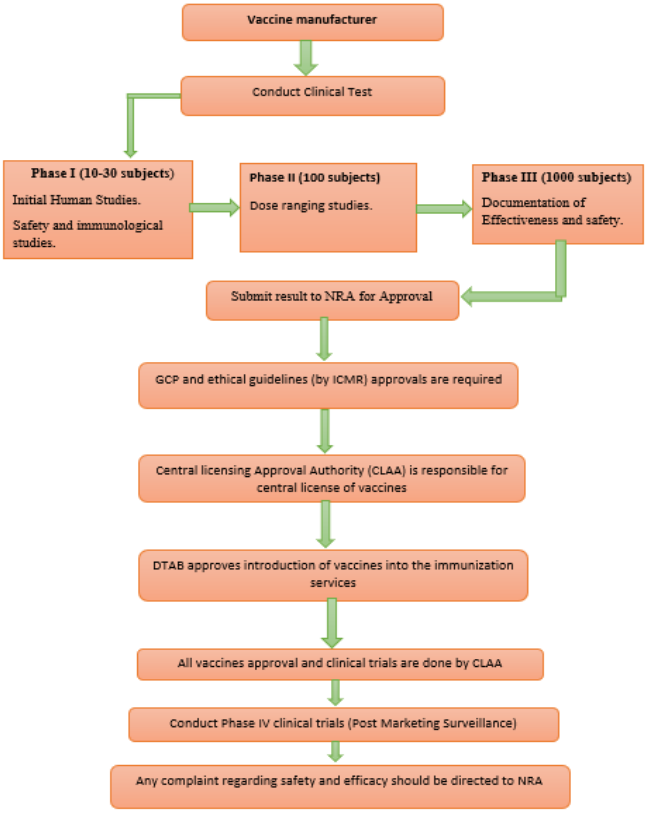

Fig. 3: Process for regulatory approval of vaccines in India

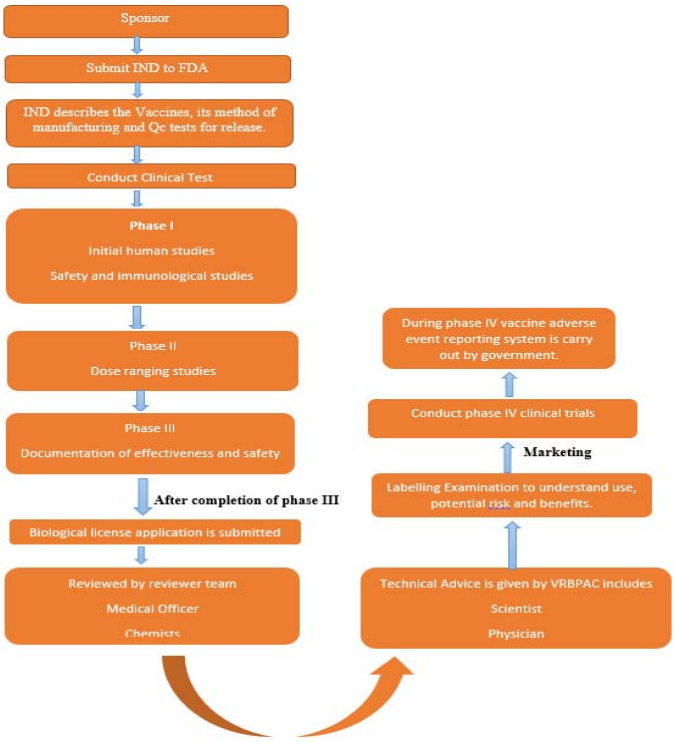

Fig. 4: Registration process of vaccines In USA

Biologic license application process (BLA)

The decision to file a BLA begins the application procedure on day 1 during the application submission procedure. The meetings must be scheduled on the 45th day. The manufacturer will have 60 d to file the BLA with the appropriate materials and schedule the inspection window and other related tasks. The applicant's eligibility for priority or standard review will be decided by FDA. Additionally, if the vaccine product significantly enhances public health, the manufacturer may ask for priority consideration.

While priority reviews might take up to 6 mo, normal reviews can take up to 12 mo, if the application is chosen for priority consideration, the FDA will also let the applicant know within 60 d on day 74. It will be known if there is a routine review on day 75. The compliance of the vaccine product will be thoroughly examined the application will be distributed for review before being accepted [36-38]. Process of BLA were depicted in [fig. 5].

Regulatory approval process of vaccines in EU

Marketing authorization registration quality assessment evaluation of quality, effectiveness, and safety of vaccines through pharmacovigilance and risk assessment plans [39, 40].

Marketing authorization

CHMP grants marketing authorization after assessing the whole filing for the product's safety, efficiency, quality, and risk-benefit ratio. The regulatory authorities must first give their permission before reviewing the dossier for conformity in areas like clinical, laboratory testing and manufacturing. Marketing Authorisation Application (MAA) of EU were illustrated in [fig. 6].

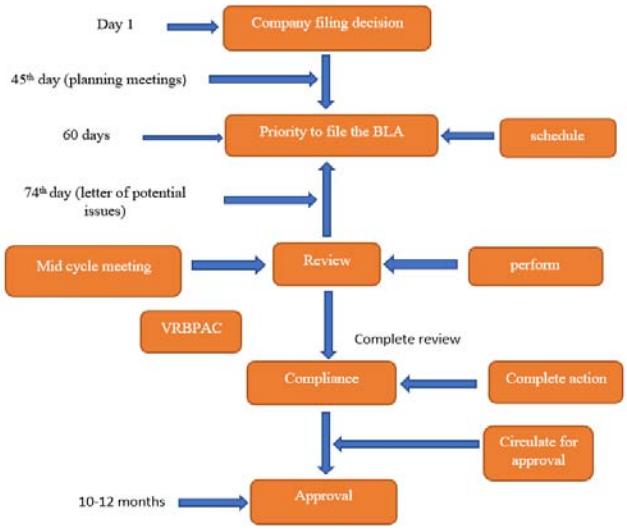

Fig. 5: Biological license application (BLA) flow chart

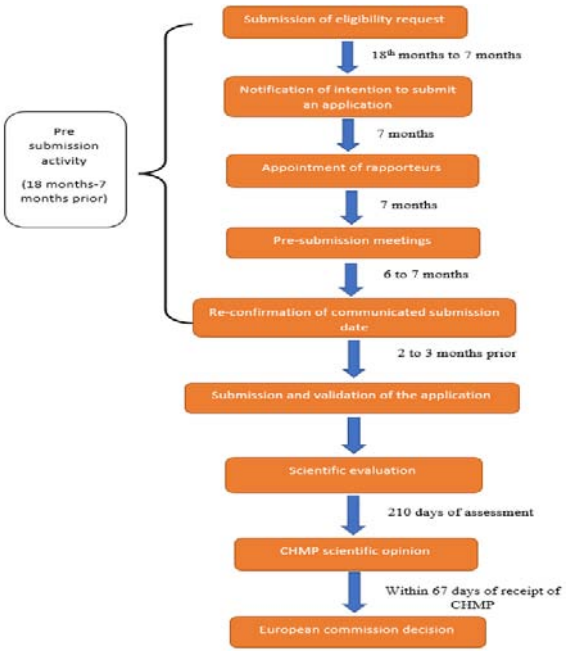

Fig. 6: Marketing authorisation application (MAA) of EU

Registration

The EU uses Centralized, Decentralized, Mutual recognition, and Nationalised mechanisms to approve vaccines. When requesting a marketing authorization for a vaccination product, the manufacturer typically favours the centralized process, since a centralised process is used to approve a single marketing authorization for a vaccination product across the EU. Patients, as well as the healthcare system may easily get vaccines. The application made to the European Medical Agency for marketing vaccination products across the EU will be evaluated by CHMP [41-43]. Registration Process of Vaccines in EU were illustrated in [fig. 7].

Quality assessment

The vaccines will be quality-checked before being released into the market after getting marketing authorization from the European Directorate for Quality of Medicines, which manufactures an official European control laboratory to help with the quality evaluation procedure.

Risk management plan and pharmacovigilance

After being released onto the market, vaccines are checked for adverse reactions to verify they meet the safety profile set throughout the product innovation. The risk management strategy is also designed to identify uncommon occurrences that would not have been obvious during clinical development.

Vaccine antigen master file (VAMF)

In the case of the Centralised method, the vaccine manufacturer must submit an application for a vaccine antigen master file prior to MAA approval. European Medicines Agency VAMF certification 2005. The makers will be able to choose between the marketing authorization procedure and the VAMF submission process during the pre-submission meeting with the scientific committees in general, centralised procedures are recommended, and the CHMP will conduct a scientific examination of the provided dossier. EMEA 2005 adverse events in the EU vaccine are recorded using the eudra vigilance system. The patient, the doctor, or the manufacturer can all report an adverse occurrence according to the eudra vigilance system. The report will be evaluated and the CHMP will take appropriate action by either approving or rejecting the product from the marketplace in 2003 the European Medicines Agency [44-46]. Approval process of Vaccine Antigen Master File (VAMF) were illustrated in [fig. 8].

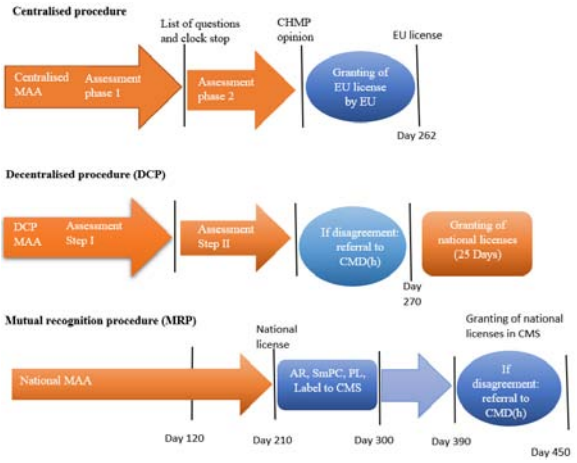

Fig. Registration process of vaccines in EU

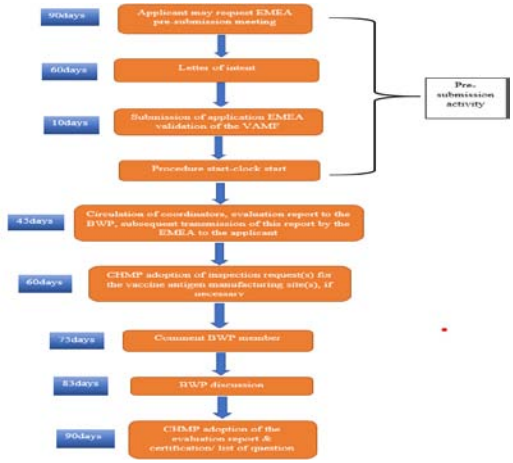

Fig. 8: Approval process of vaccine antigen master file (VAMF)

Table 1: Comparison of vaccine marketing authorization application markets in India, the United States, and the European Union

	USA	EU	INDIA
Regulatory Agencies	Federal Food and Drug Administration.	European Medicine Agency.	Central Drug Standard Control Organization.
Regulatory Ministry	Department of Health and Human Services	European Commission.	Ministry of Health and Family Welfare
Regulation	Public Health Services Act	European Directive	The Pharmacy Act,1948
Guidelines	✓ 21 CFR 600-Biological Products: General ✓ 21 CFR 601-Licensing ✓ 21 CFR 610-General Biological Products ✓ Standards ✓ 21 CFR 610.60-Labelling Standards ✓ Guidance for Industry Content and format of chemistry, manufacturing, and controls informationand establishment description information for vaccine/related product	✓ EU Directives. ✓ Directive 2001/83/EC. ✓ Regulation (EC) No 726/2004. ✓ Guideline on quality aspects are included in the product information for vaccines for human use. ✓ Guideline on dossier structure and content for Pandemic Influenza Vaccine Marketing Authorization Application	✓ Drug and Cosmetics act, 1940. ✓ Drugs and Cosmetic Rules, 1945. ✓ Pharmacy Act, 1948. ✓ Information. ✓ Information Technology Act, 2000. ✓ Indian Medical Act, 1956 and Code of Ethics Regulations.
Classification of Vaccine as per source	● Live attenuated ● Inactivated ● Subunit ● Toxoid ● Conjugate ● DNA recombinant vector	● Live attenuated ● Killed inactivated subunit.	● Live attenuated ● Inactivated ● Subunit ● Toxoid ● Conjugate ● Valence vaccine ● Heterotypic vaccine ● mRNA vaccine.
MAA Fees	$4,154,664	€286,900	50000 INR
Advisory Committee	Vaccine Related Biological Product Advisory Committee (VRBPAC)	Scientific Advisory Group on Vaccine (SAG-V). Vaccine Working Party.	Drug Technical Advisory Board.
Classification of Vaccine as per source	•Live attenuated •Inactivated •Subunit •Toxoid •Conjugate •DNA recombinant vector	•Live attenuated •Killed inactivated subunit.	•Live attenuated •Inactivated •Subunit •Toxoid •Conjugate •Valence vaccine •Heterotypic vaccine •mRNA vaccine.
MAA Fees	$4,154,664	€286,900	50000 INR
Advisory Committee	Vaccine Related Biological Product Advisory Committee (VRBPAC)	Scientific Advisory Group on Vaccine (SAG-V). Vaccine Working Party.	Drug Technical Advisory Board.
ADR Reporting	Vaccine Adverse Event Reporting System (VAERS)	EudraVigilance System	Post Marketing Surveillance.
Post Marketing Requirements	Product-Specific PMS Requirements	Pharmacovigilance and Risk Management Plan	Marketing.
Regulatory Definition	Vaccine is an immunogen, the administration of which is intended to stimulate the immune system to result in the prevention, amelioration, or therapy of any disease or infection.	Vaccine is a biological preparation that improves immunity to a particular disease.	The process of implementing the vaccine is called vaccination. it is responsible for the clearance of many diseases, especially infectious disease like smallpox and chicken pox. The word vaccine is derived from the Latin word "Vaccines."
MAA Validity	Perpetual	5 y	5 y

Table 2: Indian regulatory update during covid-19 pandemic

S. No.		Notices related to	Description of the notice	Reference
1	Related to diagnosos, prevention, treatment, and management of Covid-19.	Regulatory pathway for RandD of Drugs, Vaccines, Clinical trials, and *In vitro* Diagnostics (IVD) kits for the diagnosis of COVID‐19.	Two notices (no. X‐11026/07/2020‐PRO) were issued by CDSCO on March 19, 2020, about drugs/vaccines and diagnostic kits for COVID.	47
		Polymerase chain reaction and RAPID/CLIA/ELISA kits approved for testing of COVID‐19.	CDSCO issued an updated list of approved PCR kits, a list of RAPID/CLIA/ELISA kits for COVID‐19 on June 8 also included Name of the firm, Type of kit, and Country name.	
		Letter regarding manufacturing of oxygen for medical use during COVID.	CDSCO issued a notice (no. DCGI/MISC/2020/96) on April 7, addressing all State/Union Territory (UT) Drug controllers to ensure the availability and supply and to grant licenses to manufacture oxygen for medical use within 24 h of receiving application, fees, etc.	
		Notification S. O. regarding manufacture and stock for sale or distribution of Vaccines for COVID‐19.	Ministry of Health and Family Welfare issued a notification (no. S. O. 1511 (E) on May 18, 2020, for lessening the timelines for vaccine development for Covid-19 by allowing applicants to submit the application for manufacturing during the conduct of clinical trial.	
		Advisory notice regarding voluntary registration of Personal Protective Equipment.	An advisory notice (no. DCGI/Misc/2020 [119]) was issued by the CDSCO May 22, 2020, highlighted that all manufacturers of Personal Protective Equipment (PPE) be aware of latest rules governing Medical Devices.	
2	Office		An office memorandum (no. BT/03/27/2020‐PID) was issued by	48

	memorandum regarding rapid response regulatory framework for Covid-19 vaccine development		the Ministry of Science and Technology, Department of Biotechnology regarding Rapid Response Regulatory Framework for COVID‑19 Vaccine development, on May 26, 2020. i)Rapid Response Regulatory Framework for fast‑track processing of applications relating to Recombinant Vaccines for COVID‑19. ii)A checklist for preclinical toxicity studies, consideration of preclinical data generated outside India, and consideration of data on clinical studies. iii) Parallel application for conduct of clinical trials during preclinical studies and abbreviated pathway for COVID‑19 vaccine development.	
3	Related to clinical trials during the covid-19 pandemic	Notice regarding conduct of clinical trials Circular regarding extension of validity of BA/BE study centres.	The CDSCO released a notice [9] on Mar 30, 2020 (no. DCGI/MISC/2020 [104]) regarding conduct of clinical trials during the COVID‑19 outbreak. It was specified that any communication between sponsor/Ethics Committee (EC)/Investigator regarding the implementation of protocol Amendments/Deviations/Modifications due to the current scenario might be sent via E‑mail/any other electronic mode to Indian HA. A circular (no. 7‑5/2020/Misc/070) was issued on April 30 by the CDSCO regarding extension of validity of BA/BE study centres based on various representations received from stakeholders.	48
4	Indian council of medical research guidelines for ethics committees during covid-19		The Indian Council of Medical Research (ICMR) has released, on May 6, 2020, National Guidelines for Ethics Committees reviewing Biomedical and Health Research (April 2020 and role of ECs in conducting ethical research during the COVID‑19 pandemic.	49
5	Related to new drugs, import/manufacturing of drugs during the Covid-19 pandemic	Circular regarding procedure for lot release of human vaccine during the COVID pandemic. Notice regarding submission of notarized/apostilled documents for import of drugs, medical devices, and *in vitro* diagnostic kits. Letter regarding extension of WHO Good Manufacturing Practice/Certificate of Pharmaceutical Products.	In order to ensure the continued availability of vaccines and essential drugs and considering the challenges of logistics and workforce, a circular (no. X‑11026/65/2020‑BD) was issued by the CDSCO on April 3. Two notices were issued by the CDSCO on April 15 (no. Import/Misc/101/2020‑DC) and April 23 (no. 29/Misc/03/2020/DC (60) for drugs and medical devices, respectively, which stated that considering the COVID pandemic, an applicant may submit applications for import registration documents once situation normalizes. The CDSCO office issued a notice (no. 7‑5/2020/Misc/070) on May 1, [15] addressing all state/UT drug controllers. Considering the COVID outbreak validity of certificates such as WHO Good Manufacturing Practice/Certificate of Pharmaceutical Products expiring from March to August 2020 may be extended by 6 mo from the date of expiry of the certificate.	49
6	Related to miscellaneous during the covid-19 pandemic	Notice regarding the COVID‑19 outbreak.	The CDSCO office issued a notice (no. DCGI/ MISC/2020/(99) on March 23[16] regarding emergency situation arising out of the COVID‑19 outbreak and mentioned that due to lockdown, permissions/queries/clarifications it was stated to send it on E‑mail IDs of applicants urgently in public interest.	50

CONCLUSION

The fundamental biotechnological advancement that significantly improves the state of world health is the development of vaccines. Before a product is released onto the market, a strict regulatory procedure must be followed to evaluate its quality efficacy and safety. The health of people living in emerging or developing nations will be improved by following standardized protocols and obtaining regulatory approval of vaccines which is secure and efficient in a coordinated manner. The development of vaccines in emerging nations will surely benefit from an understanding of the laws of developed nations like India, USA and the EU. Vaccines ensuring safety, efficacy, quality of vaccines developed through new platforms is challenging as it has no previous regulatory experience is available in such cases. In cases of vaccines given full authorization we should keep track of adverse effects and efficacy to address new infections and reduction in mortality and morbidity in non-immunised groups and immunised groups. Using the following steps regulators can incorporate new adaptive models to the toolkit of decision making and modifying the regulatory pathways for usage in emergency situations. Due to their complexity and the fact that they create consequences after being administered to patients, vaccination regulations are strict. Understanding the rules and MAA criteria for vaccinations in India, the United States, and the European Union was the goal of the current discussion.

This work contributes to the development of uniform registration practises among EU and Indian regulations. To ensure that the immunizations are quickly available to the entire world's population, we need a standardised registration process.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

Declare none

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