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Comparison of regulatory approval process for vaccines development and manufacturing in India & USA

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Abstract

The Vaccine Development is a complex and time-consuming process because of stringent quality assessment procedures. The vaccine is approved for release into the market, a stringent regulatory procedure to assess quality, efficacy and safety must be maintained. The regulation of vaccine in India with the licensing and GMP is controlled by the drug controller general of India (DCGI). The USA regulation was controlled by the USFDA in center biologics evaluation and research committee (CBER) and Biologics license application (BLA). These Authorities are responsible for vaccine regulations in India & USA. The current review articles highlight the comparison of registration process of vaccines in INDIA and USA.

Introduction

A vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as a threat, destroy it, and to further recognize and destroy any of the microorganisms associated with that agent that it may encounter in the future. Vaccines can be prophylactic (to prevent or ameliorate the effects of a future infection by a natural or "wild" pathogen), or therapeutic (to fight a disease that has already occurred, such as cancer).Some vaccines offer full sterilizing immunity, in which infection is prevented completely.

The administration of vaccines is called vaccination. Vaccination is the most effective method of preventing infectious diseases; widespread immunity due to vaccination is largely responsible for the worldwide eradication of smallpox and the restriction of diseases such as polio, measles, and tetanus from much of the world. The effectiveness of vaccination has been widely studied and verified; for example, vaccines that have proven effective include the influenza vaccine, the HPV vaccine, the chickenpox vaccine. The World Health Organization (WHO) reports that licensed vaccines are currently available for twenty-five different preventable infections [1].

Effects

There is overwhelming scientific consensus that vaccines are a very safe and effective way to fight and eradicate infectious diseases. The immune system recognizes vaccine agents as foreign, destroys them, and "remembers" them. When the virulent version of an agent is encountered, the body recognizes the protein coat on the virus, and thus is prepared to respond, by first neutralizing the target agent before it can enter cells, and secondly by recognizing and

destroying infected cells before that agent can multiply to vast numbers.

Limitations to their effectiveness, nevertheless, exist. Sometimes, protection fails because of vaccine-related failures such as failures in vaccine attenuation, vaccination regimes or administration or host-related failure due to the host's immune system simply does not respond adequately or at all. Lack of response commonly results from genetics, immune status, age, health or nutritional status. It also might fail for genetic reasons if the host's immune system includes no strains of B cells that can generate antibodies suited to reacting effectively and binding to the antigens associated with the pathogen.

Even if the host does develop antibodies, protection might not be adequate; immunity might develop too slowly to be effective in time, the antibodies might not disable the pathogen completely, or there might be multiple strains of the pathogen, not all of which are equally susceptible to the immune reaction. However, even a partial, late, or weak immunity, such as a one resulting from cross-immunity to a strain other than the target strain, may mitigate an infection, resulting in a lower mortality rate, lower morbidity, and faster recovery.

Adjuvants commonly are used to boost immune response, particularly for older people whose immune response to a simple vaccine may have weakened.

The efficacy or performance of the vaccine is dependent on several factors:

- the disease itself (for some diseases vaccination performs better than for others)
- the strain of vaccine (some vaccines are specific to, or at least most effective against, particular strains of the disease)
- whether the vaccination schedule has been properly observed.
- idiosyncratic response to vaccination; some individuals are "non-responders" to certain vaccines, meaning that they do not generate antibodies even after being vaccinated correctly.
- assorted factors such as ethnicity, age, or genetic predisposition.

If a vaccinated individual does develop the disease vaccinated against (breakthrough infection), the disease is likely to be less virulent than in unvaccinated victims.

Important considerations in an effective vaccination program:

1. careful modeling to anticipate the effect that an immunization campaign will have on the epidemiology of the disease in the medium to long term
2. ongoing surveillance for the relevant disease following introduction of a new vaccine
3. maintenance of high immunization rates, even when a disease has become rare

In 1958, there were 763,094 cases of measles in the United States; 552 deaths resulted. After the introduction of new vaccines, the number of cases dropped to fewer than 150 per year (median of 56). In early 2008, there were 64 suspected cases of measles. Fifty-four of those infections were associated with importation from another country, although only thirteen percent were actually acquired outside the United States; 63 of the 64 individuals either had never been vaccinated against measles or were uncertain whether they had been vaccinated.

Vaccines led to the eradication of smallpox, one of the most contagious and deadly diseases in humans. Other diseases such as rubella, polio, measles, mumps, chickenpox, and typhoid are nowhere near as common as they were a hundred years ago thanks to widespread vaccination programs. As long as the vast majority of people are vaccinated, it is much more difficult for an outbreak of disease to occur, let alone spread. This effect is called herd immunity. Polio, which is transmitted only among humans, is targeted by an extensive eradication campaign that has seen endemic polio restricted to only parts of three countries (Afghanistan, Nigeria, and Pakistan). However, the difficulty of reaching all children as well as cultural misunderstandings have caused the anticipated eradication date to be missed several times.

Vaccines also help prevent the development of antibiotic resistance. For example, by greatly reducing the incidence of pneumonia caused by *Streptococcus pneumoniae*, vaccine programs have greatly reduced the prevalence of infections resistant to penicillin or other first-line antibiotics.

The measles vaccine is estimated to prevent a million deaths every year.

Development of vaccines

Most vaccines have been in use for decades, with millions of people receiving them safely every year. As with all medicines, every vaccine must go through extensive and rigorous testing to ensure it is safe before it can be introduced in a country's vaccine programme [2].

Exploratory Stage

This stage involves basic laboratory research and often lasts 2-4 years. Federally funded academic and governmental scientists identify natural or synthetic antigens that might help prevent or treat a disease. These antigens could include virus-like particles, weakened viruses or bacteria, weakened bacterial toxins, or other substances derived from pathogens.

vaccine is subject to three phases of testing.

Pre-Clinical Stage

Pre-clinical studies use tissue-culture or cell-culture systems and animal testing to assess the safety of the candidate vaccine and its immunogenicity, or ability to provoke an immune response. Animal subjects may include mice and monkeys. These studies give researchers an idea of the cellular responses they might expect in humans. They may also suggest a safe starting dose for the next phase of research as well as a safe method of administering the vaccine.

Researchers may adapt the candidate vaccine during the pre-clinical state to try to make it more effective. They may also do challenge studies with the animals, meaning that they vaccinate the animals and then try to infect them with the target pathogen.

Many candidate vaccines never progress beyond this stage because they fail to produce the desired immune response. The pre-clinical stages often lasts 1-2 years and usually involves researchers in private industry.

IND Application

A sponsor, usually a private company, submits an application for an Investigational New Drug (IND) to the U.S. Food and Drug Administration. The sponsor describes the manufacturing and testing processes, summarizes the laboratory reports, and describes the proposed study. An institutional review board, representing an institution where the clinical trial will be conducted, must approve the clinical protocol. The FDA has 30 days to approve the application. Once the IND application has been approved, the vaccine is subject to three phases of testing.

Phase I Vaccine Trials

This first attempt to assess the candidate vaccine in humans involves a small group of adults, usually between 20-80 subjects. If the vaccine is intended for children, researchers will first test adults, and then gradually step down the age of the test subjects until they reach their target. Phase I trials may be non-blinded (also known as open-label in that the researchers and perhaps subjects know whether a vaccine or placebo is used).

The goals of Phase 1 testing are to assess the safety of the candidate vaccine and to determine the type and extent of immune response that the vaccine provokes. In a small minority of Phase 1 vaccine trials, researchers may use the challenge model, attempting to infect participants with the pathogen after the experimental group has been vaccinated. The participants in these studies are carefully monitored and conditions are carefully controlled. In some cases, an attenuated, or modified, version of the pathogen is used for the challenge.

Phase II Vaccine Trials

A larger group of several hundred individuals participates in Phase II testing. Some of the individuals may belong to groups at risk of acquiring the disease. These trials are randomized and well controlled, and include a placebo group.

The goals of Phase II testing are to study the candidate vaccine's safety, immunogenicity, proposed doses, schedule of immunizations, and method of delivery.

Phase III Vaccine Trials

Successful Phase II candidate vaccines move on to larger trials, involving thousands to tens of thousands of people. These Phase III tests are randomized and double blind and involve the experimental vaccine being tested against a placebo (the placebo may be a saline solution, a vaccine for another disease, or some other substance).

One Phase III goal is to assess vaccine safety in a large group of people. Certain rare side effects might not surface in the smaller groups of subjects tested in earlier phases. For example, suppose that an adverse event related to a candidate vaccine might occur in 1 of every 10,000 people. To detect a significant difference for a low-frequency event, the trial would have to include 60,000 subjects, half of them in the control, or no vaccine, group (Plotkin SA et al. *Vaccines*, 5th ed. Philadelphia: Saunders, 2008).

Vaccine efficacy is tested as well. These factors might include 1) Does the candidate vaccine prevent disease? 2) Does it prevent infection with the pathogen? 3) Does it lead to production of antibodies or other types of immune responses related to the pathogen ?. After a successful Phase III trial, the vaccine developer will submit a Biologics License Application to the FDA. Then the FDA will inspect the factory where the vaccine will be made and approve the labeling of the vaccine.

After licensure, the FDA will continue to monitor the production of the vaccine, including inspecting facilities and reviewing the manufacturer's tests of lots of vaccines for potency, safety and purity. The FDA has the

right to conduct its own testing of manufacturers' vaccines.

Post-Licensure Monitoring of Vaccines

A variety of systems monitor vaccines after they have been approved. They include Phase IV trials, the Vaccine Adverse Event Reporting System, and the Vaccine Safety Datalink.

R&D ⇨ Pre clinical ⇨ Phase-I ⇨ Phase-II ⇨ Phase-III ⇨ BLA ⇨ Phase-IV

Stages of Vaccine Development

Phase IV Trials

Phase IV trial are optional studies that drug companies may conduct after a vaccine is released. The manufacturer may continue to test the vaccine for safety, efficacy, and other potential us.

Manufcturing Of Vaccines

It is this fact that drives the requirements for vaccines to be among the most rigorously designed, monitored, and compliant products manufactured today. The ability to manufacture these vaccines safely and consistently is built on four competencies:

1. The manufacturing process that defines how the product is made;
2. The compliance of the organization to successfully complete that process;
3. The testing of the product and supporting operations; and
4. The regulatory authorization to release and distribute the product

New vaccines are subjected to a well-defined regulatory process for approval. The approval process consists of four principal elements:

- Preparation of preclinical materials for proof-of-concept testing in animal models; manufacture of clinical materials according to current GMP; and toxicology analysis in an appropriate animal system.
- Submission of an investigational new drug (IND) application for submission to FDA for review.
- Testing for safety and effectiveness through clinical and further nonclinical studies (Phase I to Phase III clinical studies).

Submission of all clinical, nonclinical, and manufacturing data to the FDA and EMA in the form of a Biologics License Application (BLA) for final review and licensure

Propagation entails the multiplication (or amplification) of the living organism used in the vaccine;

Isolation entails the separation of the living organism from the cells or growth media used in the propagation step;

Purification removes all materials that may be adhering to the isolated organisms, or selectively separates the portion of the living organism to be used in the vaccine;

Formulation involves the mixing of the purified product in solutions to obtain a desired concentration. It may also include the addition of preservatives to some vaccines, to ensure the sterility of the product over a longer period of time, or to prevent cross-contamination during dose extraction from vials.

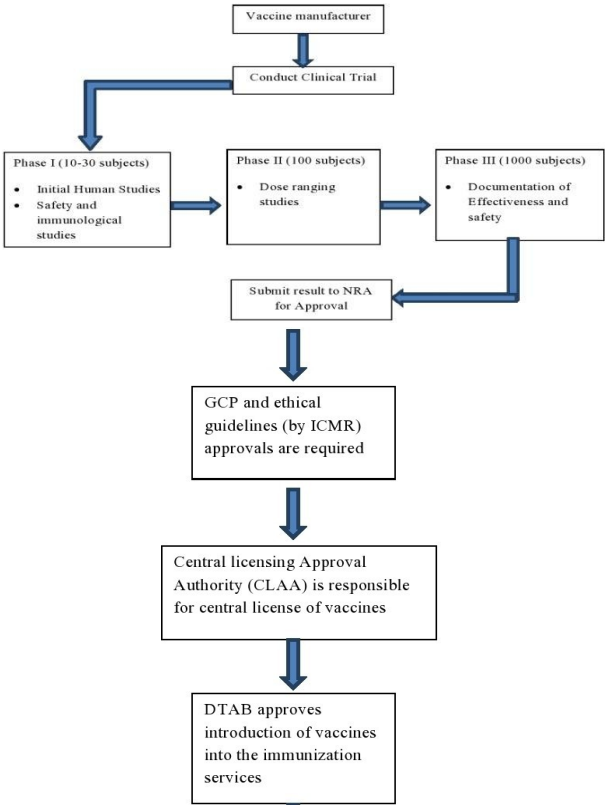
At the end of the manufacturing process, vaccines are typically filled in vials or syringes and packaged for shipping to healthcare providers.

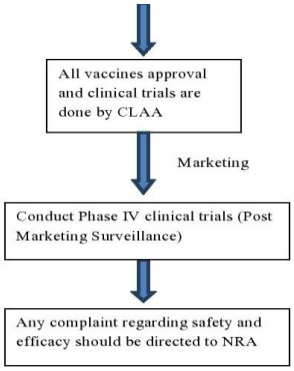
Propagation → Isolation → Purification → Formulation

Regulatory Approval Process For Vaccines In India

Various regulatory Authorities for vaccine registration are [3-5]

- Ministry of Health and Family Welfare
- National Technical Advisory Group on Immunization (NTAGI),
- Indian Council for Medical Research (ICMR),
- Central Drugs Standard Control Organization (CDSCO)



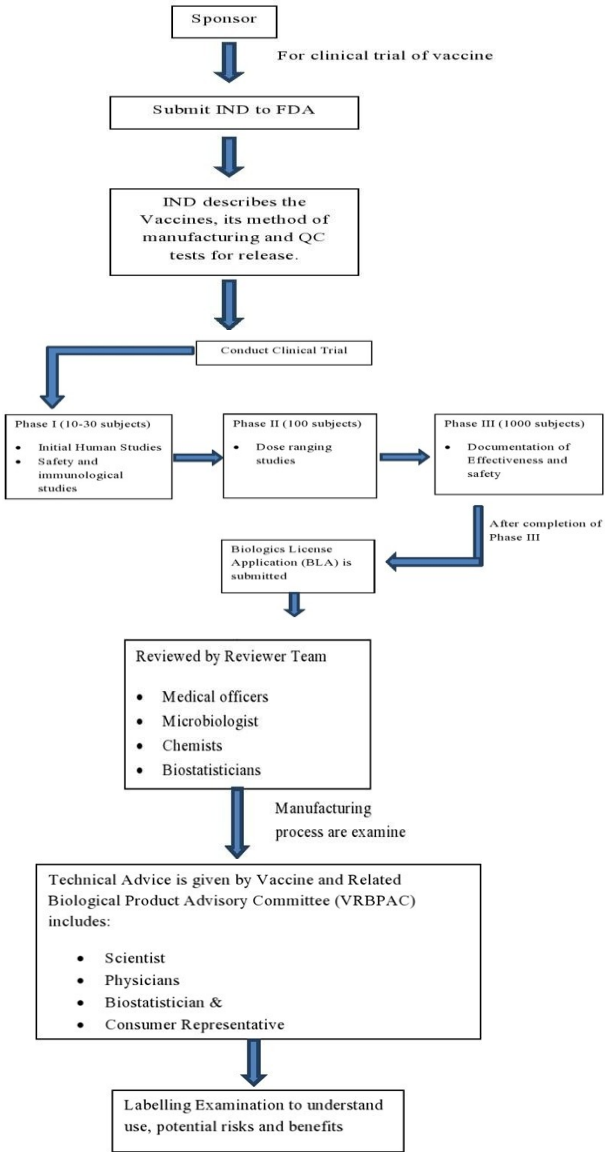


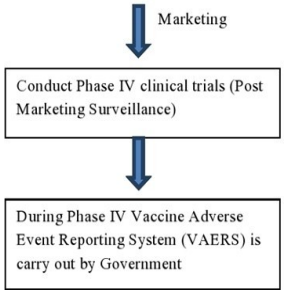
Approvals Process Of Vaccines In USA

Various regulatory authorities for registration of vaccine in USA are

- CBER (Centre for Biologics Evaluation and Research)
- Vaccines and Related Biological Products Advisory Committee (VRBPAC)
- Biologics License Application (BLA)

Registration Process Of Vaccines In USA [6-9]





Comparison of Registration Process of Vaccine in INDIA and USA [10-12]

INDIA	USA
• Rate of vaccination in INDIA IS 3%.	• Rate of vaccine in USA is 17%.
• National regulatory authority (NRA) is responsible for registration of vaccine.	• Center for biological evaluation & research(CBER) is responsible for obtaining license.
• Central licensing approval authority (CLAA) is responsible for obtaining license.	• Biologics license application (BLA) is responsible for obtaining license.
• For registration of vaccine following steps are required.	• For registration of vaccine following steps are required.
• Conduct clinical trial • Submit result of clinical trail to NRA.	• IND submission • Conduct clinical trail.
• After approval CLAA give license to vaccines.	• After completion of phase 3 BLA is submitted.
• DTAB (Drug technical advisory board) gives advise for any improvement.	• VRBPAC(Vaccine related biological product advisory committee) gives advise for any improvement.
• Marketing	• PMS
• Post marketing surveillance complaint is submitted to NRA.	• Vaccine adverse event reporting system is carried out by governament for any complaint.
• For 44 ?& T- license is required to get approval for conducting clinical trail	• For any improvement in vaccine, vaccine & related biological product advisory

	committee gives advise.
• 8-12 weeks are required for complete evaluation of application for registration of vaccine.	• 180 days are required for complete evaluation of application for registration of vaccine.
• Registration fees 50000 INR.	• Registration fees 212,787$.
• Form CT-04 (the clinical trial application form including applicant name; sponsor nature/constitution and contact information; clinical trials site contact information and details; contact information for person responsible for compensation payment, if any; correspondence address; new drug/investigational new drug name(s) and details (i.e., therapeutic class, dosage form, composition, and indications); clinical trial phase; protocol number with date; and EC and investigator names) (See Form CT-04 in the 2019-CTRules for additional details)	• Cover sheet (Form FDA 1571 (USA-76)) (including, but not limited to: sponsor contact information, IP name, application date, phase(s) of clinical investigation to be conducted, and commitment that the EC will conduct initial and continuing review and approval of each study proposed in the investigation) (See USA-40).
• Treasury Challan receipt demonstrating payment of corresponding fee or transaction ID.	• Table of contents
• Chemical and pharmaceutical information.	• Introductory statement and general investigational plan • Investigator's brochure (IB).
• Animal pharmacology data	• Protocols
• Animal toxicology data • Human clinical pharmacology data.	• Chemistry, manufacturing, and control data • Pharmacology and toxicology data • Previous human experience with the investigational drug.
• Active ingredient information (for INDs and global clinical trials (GCTs)) • Formulation data (for INDs and GCTs). • Therapeutic class (for INDs and GCTs)	• Additional information • Relevant information (e.g., foreign language materials and number of copies - see Submission Process subtopic for details).
• Clinical protocol	• Clinical study protocol

Conclusion

As new, safe and effective vaccines are introduced every year in market, it is important to include them in official immunization schedule. To include vaccines in to immunization schedule INDIA follows the guidelines as per CDSCO (Central Drug Standard Control Organization) requirements and USA follows guidelines as per USFDA (United States Food and Drug Administration) requirements. By the comparison of registration process of vaccine and from the study of guidance documents of INDIA and USA it is concluded that on quality bases US market is far better than INDIAN market as per the data required by USFDA agency.

Abbreviations

DCGI: Drug controller general of India
CBER: Center for Biological Evaluation and Research
USFDA: United States Food and Drug administration
BLA: Biological Licensing application
CDSCO: Central Drug Standard Control Organization

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