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# A Comprehensive Study on Comparison of Registration Process of Vaccine in INDIA and USA

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**ABSTRACT:**

Present study was focused on comparison of registration process of Vaccine in INDIA and USA. Vaccination is one of the most cost-effective health interventions available, saving millions of people from illness, disability and death each year. The vaccine industry is highly regulated. Vaccine development is a complex and time-consuming process. Before a new vaccine is approved for release into the market, a stringent regulatory procedure to assess quality, efficacy and safety must be undertaken. The regulation of vaccines in India with respect to the licensing and GMPs is controlled by the Drug Controller General of India (DCGI) and Central and State Drugs Control departments like Central Drugs Standard Control Organization (CDSCO) and Drug Regulatory Authorities (DRAs). Meanwhile, in USA the regulation of vaccines is controlled by USFDA in which Center for Biologics Evaluation and Research committee (CBER) and Biologics License Application (BLA) authorities are responsible for vaccine regulation. Comparison of registration process of vaccine in concern countries determine which country is more reliable based on time consumption, money, complex-lengthy process etc.

**KEY WORDS:** Immunization Schedule, Vaccine registration process, Comparison of regulatory requirements for vaccine registration, DCGI (Drug Controller General of India), CBER (Center for Biologics Evaluation and Research), USFDA (United States Food and Drug Administration), CDSCO (Central Drugs Standard Control Organization)

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## INTRODUCTION[1, 2]

New, safe, and effective vaccines are licensed and introduced to the international market every year. Moreover, advances in biotechnology contribute to the improvement of current vaccines through new formulations of the vaccines in use. Although they are available, these vaccines have not yet become part of the official immunization schedule in many countries. So, registration of vaccines is required to include them in immunization schedule. For licensing of vaccine, different countries follow different guidelines and different registration process.

**Definition of Vaccine** - "A vaccine is a biological preparation that improves immunity to a particular disease".

**Mechanism-**

- It 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 foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

## MATERIALS AND METHODS

- **Registration process of Vaccine in INDIA[3-5]**
  (As shown in Fig 1)

- **Various regulatory guidelines for vaccine registration are:**
  - 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),
  - Central Licensing Approval Authority(CLAA)

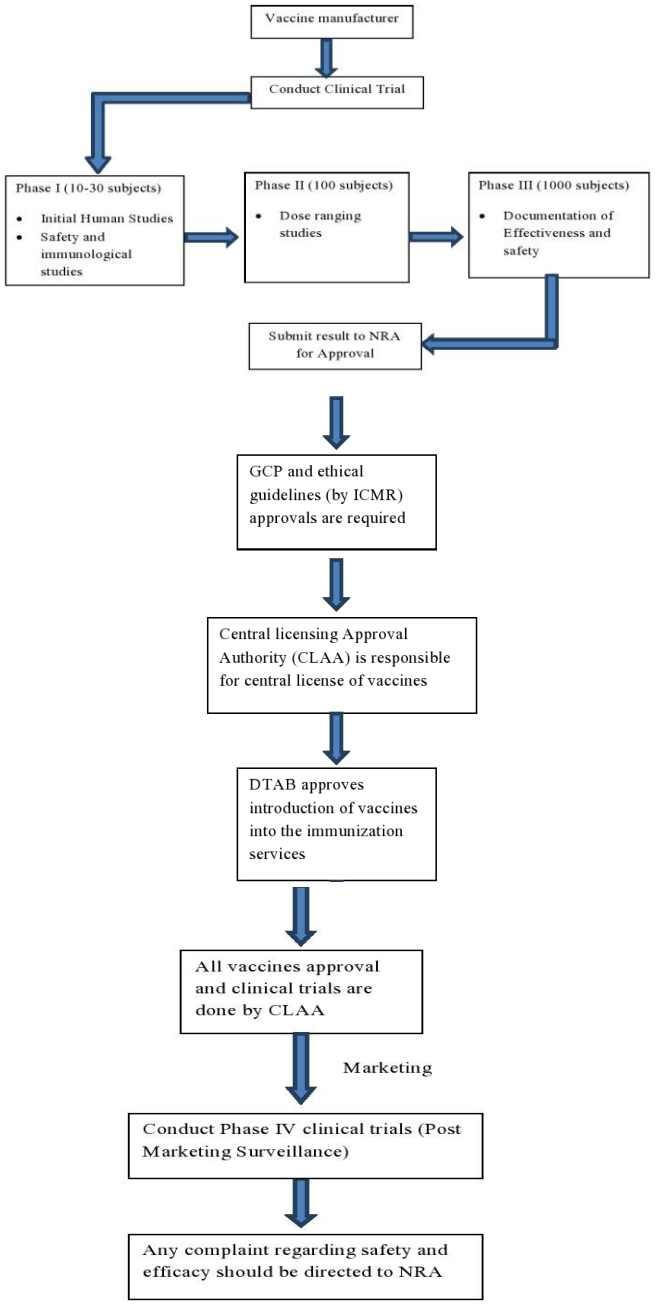


**Figure 1: Registration process of vaccine in INDIA**

- **Registration Process of vaccine in USA[6-9]**
  (As shown in Fig 2)

- **Various regulatory guidelines 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)

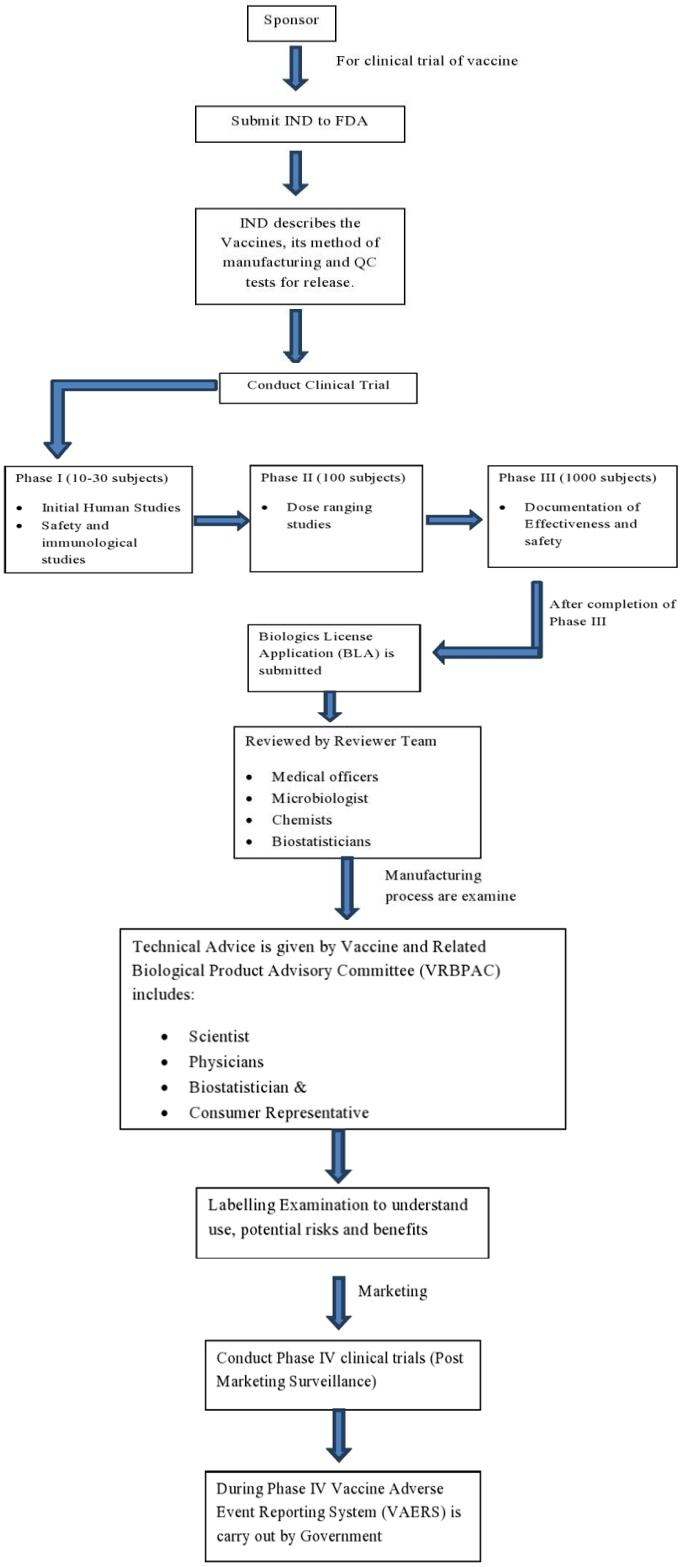


**Figure 2: Registration process of vaccine in US**

**Table 1: Guidance documents required for registration of vaccine in INDIA and USA[10, 11]**

| Guidance documents | Countries | |
|---|---|---|
| | **INDIA** | **USA** |
| **1. Administrative information** | **1.1** Comprehensive table of contents | **1.1** Table of contents |
| | **1.2** Administrative information | **1.2** Administrative Information |
| | **1.2.1** Application in Form 44 and Treasury Challan (fee) | **1.2.1** Application form 28 D |
| | **1.2.2** Legal and statutory documents:<br>a) A copy of plant registration / approval certificate issued by the Ministry of Health / National Regulatory Authority of the country of origin i.e. CDSCO<br>b) A copy of approval, if any, showing the drug is permitted for manufacturing and/or marketing in the country of origin.<br>c) A copy of Pharmaceutical Product Certificate (PPC) as per WHO GMP certification scheme for imported drug products<br>d) A copy of Free Sale Certificate (FSC) from the country of origin for imported drug products<br>e) Certificate of Good Manufacturing Practices of other manufacturers<br>f) Batch release certificate issued by NRA for imported products. | **1.2.2** Legal documents on the product:<br>a) Document recognizing the technical director or technical professional responsible for the product<br>b) Authorization of representative<br>c) Certificate of Pharmaceutical Product (CPP)<br>d) Certificate of Good Manufacturing Practices (GMP)<br>e) Trademark certificate (optional)<br>f) Patent certificate (under national legislation)<br>g) Batch release certificate issued by NRA (imported products)<br>h) Manufacturer's statement that all relevant information has been included and is accurate |
| | **1.2.3** A copy of Site Master File | **NA** |
| | **NA** | **1.2.4** Senior Executive Officer / Senior Medical or Scientific Officer details<br>**1.2.5** Legal Representative in Country<br>**1.2.6** for releasing batches of finished product<br>**1.2.7** Commercial presentation of vaccine |
| | **1.2.8** Certificate of Analysis from Central Drug Laboratory (India) of three consecutive batches. | **NA** |
| | **1.2.9** Product Permission Document (PPD) by CDSCO | **1.2.9** Product Permission Document (PPD) by USFDA |
| | **1.3** Coordinates related to the application | |
| | **1.4** Summary of product characteristics and product labelling<br>**1.4.1** Product characteristics<br>**1.4.1.1** Proprietary, commercial or trade name of vaccine<br>**1.4.1.2** Non-proprietary name or common name of vaccine<br>**1.4.1.3** Concentration<br>**1.4.1.4** Dosage Form<br>**1.4.1.5** Route of administration<br>**1.4.5.6** Storage conditions<br>**1.4.5.7** Strength of each unit of dose<br>**1.4.2** Product Labelling | |

| | | |
|---|---|---|
| | **1.4.2.1** Primary package label<br>**1.4.2.2** Secondary packaged label<br>**1.4.2.3** Package insert<br>**1.4.2.4** Final packaging<br>**1.4.2.5** Monograph for health professionals or information for prescription in extended or reduced form<br>**1.4.2.6** Samples of finished product (in accordance with legislation of each country) | |
| | **1.5** Summary protocol of batch production and control | |
| | **1.6** List of countries where the product has been licensed and summary of approval conditions | |
| | **1.7** List of countries where the drug product is patented. | |
| | **1.8** Domestic price of the drug followed in the countries of origin in INR. | **1.8** Domestic price of the drug followed in the countries of origin in Dollar. |
| | **1.9** A brief profile of the manufacturer's research activity | |
| | **1.10** Brief profile of manufacturer's activity in global market such as:<br>• Manufacturer of active ingredient(s)<br>• Manufacturer of the finished product<br>• Other manufacturers involved in the production process | |
| | **1.11** Information regarding experts | |
| | **1.12** Environmental risk assessment | |
| **2. Quality Information (Chemical, Pharmaceutical and Biological)** | **2.1** Strain details<br>**2.1.1** Name and source (if any)<br>**2.1.2** In case of products derived from r-DNA technology, the following details shall also be furnished<br>- Clone development (for recombinant products)<br>- Details on source Nucleic acid<br>- Nucleic acid sequence | **2.1** Strain detail<br>- Strain<br>- Embryonated eggs |
| | **2.2** Vector(s) detail<br>**2.2.1** Details about vector, please enclose the map of the vector gene<br>**2.2.2** Host(s) that carrying the vector(s)/ target gene(s) | **NA** |
| | **2.3** Substrate details (For cell culture based products)<br>**2.3.1** Details of name and source of substrate | **NA** |
| | **2.4** Master seed and Working seed details | **2.4** Master / Working Seed System Banks |
| | **2.3S Drug substance(s):** Information must be submitted for each drug substance in the product.<br>**2.3.S.1** General information, starting materials and raw materials<br>**2.3.S.2** Manufacturing process for drug substance | **2.3 S Drug Substance**<br>**2.3.S.1** Active ingredient(s)<br>**2.3.S.2** General information, starting materials and raw materials<br>**2.3.S.3** Trade and/or non-proprietary name(s) of |

| | | |
|---|---|---|
| | **2.3.S.3** Characterization of drug substance<br>**2.3.S.4** Quality control of drug substance<br>**2.3.S.5** Reference standards<br>**2.3.S.6** Container closure system<br>**2.3.S.7** Stability of drug substance | active(s) ingredient(s)<br>**2.3.S.4** Structural formula, molecular formula and relative molecular weight (if applicable)<br>**2.3.S.5** Description and characterization of active ingredient<br>**2.3.S.6** General description of the raw materials<br>**2.3.S.7**Analytical certificates signed by the manufacturer and the applicant for licensing<br>**2.3.S.8** Manufacturing process for the active ingredient<br>- Manufacturer(s)<br>- Description of manufacturing process<br>- Flow chart of manufacturing process<br>- Description of batch identification system<br>- Description of inactivation or detoxification process<br>- Description of purification process<br>- Description of conjugation process<br>- Stabilization of active ingredient<br>- Reprocessing<br>- Filling procedure for the active ingredient, in-process controls<br>**2.3.S.9** Material controls<br>- Identification of critical steps in process and controls<br>- Selection and justification of critical steps<br>**2.3.S.10** Validation of manufacturing process.<br>**2.3.S.11** Quality control of active ingredient<br>- Specifications<br>- Description of analytical procedures<br>- Validation of analytical procedures<br>- Batch analysis and consistency results<br>- Justification of specifications<br>- Reference standards or materials<br>- Packaging/container closure system<br><br>**2.3.S.12** Stability of active ingredient<br>- Protocol of stability study, summary and conclusions<br>- Post-approval stability program<br>- Stability data<br>**2.3.S.13** Storage and shipping conditions of active ingredient |
| | **2.4 P Drug product**<br>**2.4.P.1** Description and composition of drug product<br>**2.4.P.2** Pharmaceutical development<br>**2.4.P.3** Manufacture of drug product<br>**2.4.P.4** Control of excipients (adjuvant, preservative, stabilizers and others)<br>**2.4.P.5** Control of drug product | **2.4.P Drug Product**<br>**2.4.P.1** Finished product<br>- Description and composition of finished product<br>- Pharmaceutical development<br>- Active ingredient<br>- Manufacturing process<br>- Packaging/container closure system, |

| | | |
|---|---|---|
| | **2.4.P.6** Reference standards of materials<br>**2.4.P.7** Container closure system<br>**2.4.P.8** Stability of drug product | compatibility<br>- Justification of final qualitative/quantitative formula<br>**2.4.P.2** Manufacture of finished product<br>- Manufacturer<br>- Batch formula<br>- Description of manufacturing process<br>- Control of critical and intermediate steps<br>- Validation and/or evaluation process<br>- Description of batch identification system<br>- Control of adjuvant, preservative, stabilizers and excipients<br>**2.4.P.3** Specifications<br>- Analytical procedures<br>- Validation of analytical procedures<br>- Substances of human or animal origin<br>- Use of new adjuvant, preservatives, stabilizers and excipients<br>**2.4.P.4** Control of finished product<br>**2.4.P.5** Determination and characterization of impurities<br>**2.4.P.6** Analytical certificates signed by manufacturer and applicant for licensing<br>**2.4.P.7** Reference standards or materials<br>**2.4.P.8** Packaging/container closure system<br>- Specifications of primary and secondary packaging<br>- Test and evaluation of packaging materials<br>**2.4.P.9** Stability<br>Protocol of stability study, summary and conclusions:<br>- For freeze-dried products, include stability study of freeze-dried material, diluents and reconstituted product<br>- Thermostability<br>(where applicable)<br>- Post-approval stability program<br>- Stability data<br>**2.4.P.10** Description of procedures to guarantee cold chain |
| | **2.5** Details of equipment and facilities for production of drug<br>product: master formula, batch record and set release documents in respect of consistency batches | **2.5** Equipment and facilities |
| | **2.6** Safety evaluation of adventitious agents | **2.6** Safety evaluation of adventitious agents |
| **3.**<br>**Non-Clinical Reports** | Reports on studies<br>**3.1** Pharmacology<br>**3.2** Pharmacokinetics<br>**3.3** Toxicology<br>- General toxicology | Report on studies<br>**3.1** Pharmacology<br>**3.1.1** Pharmacodynamic studies (immunogenicity of the vaccine)<br>**3.1.2** Pharmacodynamic studies of adjuvant (if |

| | | |
|---|---|---|
| | - Special toxicology<br>(Studies of genotoxicity and carcinogenicity)<br>- Toxicity of new substances used in formulation<br>(new adjuvant, stabilizers, additives) | applicable)<br>**3.2** Pharmacokinetics<br>**3.2.1** Pharmacokinetics studies<br>**3.3** Toxicology<br>**3.3.1** General toxicology - information on:<br>- Design of study and justification of animal model<br>- Animal species used, age and size of groups<br>- Dose, route of administration and control groups<br>- Parameters monitored<br>- Local tolerance<br>**3.3.2** Special toxicology (for vaccines to which it applies)<br>- Special immunological investigations<br>- Toxicity studies in special populations<br>- Genotoxicity and carcinogenicity studies<br>- Reproductive toxicity studies<br>**3.3.3** Toxicity of new substances used in formulation (new adjuvant, stabilizers, and additives)<br>**3.4** Special considerations<br>**3.4.1** For attenuated vaccines an evaluation of possibility of microorganism shedding through natural avenues of excretion |
| **4.**<br>**Clinical Reports** | **4.1** Phase 1 studies<br>**4.2** Phase 2 studies<br>**4.3** Phase 3 studies<br>**4.4** Bridging Studies<br>**4.5** Phase 4 studies and / or Pharmacovigilance Plan if required<br>**4.6** Non-inferiority studies (for combined vaccines, or approved vaccines prepared by new manufacturers)<br>**4.7** Case Report Forms and Individual Patient Listings | **4.1** Phase 1 clinical studies<br>**4.2** Phase 2 clinical studies<br>**4.3** Phase 3 studies<br>**4.4** Combined vaccine made by new manufacturer<br>**4.5** Co-administration studies with other vaccines<br>**4.6** Adjuvant. Evidence and scientific support that justifies the use of adjuvant, when applicable<br>**4.7** Phase 4 studies and/or Pharmacovigilance Plan |

**Table 2: Comparison of registration process of Vaccine in INDIA and USA**

| INDIA | USA |
|---|---|
| Rate of vaccination in INDIA is 3% | Rate of vaccination in INDIA is 17% |
| National Regulatory Authority (NRA) is responsible for regulation of vaccine | Center for Biological Evaluation and Research (CBER)is responsible for regulation of vaccine |
| 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<br>Conduct clinical trial<br>Submit result of clinical trial to NRA<br>After approval CLAA give license to vaccines<br>DTAB (Drug Technical Advisory Board ) gives advise for any improvement<br>Marketing<br>Post marketing surveillance<br>Complaint is submitted to NRA | For registration of Vaccine following steps are required<br>IND submission<br>Conduct clinical trial<br>After completion of Phase 3 BLA is submitted<br>VRBPAC(Vaccine related Biological Product Advisory Committee) gives advise for any improvement<br>Marketing<br>Post marketing surveillance<br>VAERS(Vaccine Adverse Event Reporting System) is carried out by government for any complaint |
| Form 44 and T- license is required to get approval for conducting clinical trial | IND (Investigational New Drug application) is required for conducting clinical trial |
| For any improvement in vaccine Drug Technical Advisory Board gives advise | For any improvement in vaccine, Vaccine and 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- 50,000 INR | Registration fees- 212,787$ |

**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.

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