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# Clinical Evaluation of Vaccines

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**Abstract:**
Vaccine is a biological preparation which provides a immunity and helps in prevention of diseases. Though it can be considered as a important factor to children because the children are more prone to disease. Vaccines are prepared by either by living or killed micro-organisms. However it has been prepared it should have its own safety and efficacy till the entire shelf life of the product. Vaccines are also having the certain regulatory pathways and considerations before entering into the market. Some of the considerations are based on the WHO norms which are followed globally. By the follow up of regulatory guidance, the products have their standard value. This article also explains about the phases of clinical trials involved in developing a new vaccine.

**Keywords:** Vaccines, CTD, Clinical trials, Immunization

## INTRODUCTION:

Vaccine is a preparation of killed micro-organisms, living attenuated organisms or living fully virulent organisms that are administered to produce or artificially increase immunity to a particular disease. [1]

Vaccine is an antigenic substance prepared from the causative agent or a synthetic substitute used to provide immunity against one or several diseases. [2]

### Current clinical evaluation of vaccines:

The clinical vaccine development has developed to prove the safety and efficacy of vaccines. The whole process requires minimum of 10-15 years and a budget required is a very huge amount. The vaccine development plan should consist of:

- Finding the group of people with relevant factors (i.e.) target population.
- Risk assuming of the particular targeted disease along with the natural factors.
- Finding out the dose and route of administration
- Method to stimulate immunity level
- Regulatory strategies

To develop a vaccine it takes minimum of 20-25 years to get into market. The development can be summarized as:

Antigen identification and production: 2-5 years
Pre-clinical (animal studies):1-2 years
Clinical trials : 4-8 years
Filing and licensing : 1-2 years
Surveillance : 2-5 years [3]

### Stages of clinical trials:

There are various phases involved in the development of vaccines. Before carry on the clinical trials there are few stages to pass through. The stages are

a) Exploratory stage
b) Pre-clinical stage

a) Exploratory stage:
Exploratory stage is the introductory part of development this can be performed in our laboratory. This research helps in identifying the foreign matter, such as virus, bacteria, which are disease causing micro-organisms also helps in finding out the viral and bacterial toxins. This may takes up to 2-4 years.

b) Pre-clinical stage:
Pre-clinical stage involves the cell-line study, tissue culture study to determine the safety of the people by enhancing the immunity, when a vaccine is given. In this study, they prefer animals for the better assessment of safety and efficacy results. Animals such as mice and monkeys are used in the study because it shows similar biological responses as of humans. This stage can be called as a decision making stage for further development of vaccines. Because when irregular immune (or) cellular response have been shown, the process fails and cannot involve the further development of vaccines.

### Clinical trial phases:

There are totally 4 phases of clinical trials in vaccines.

PHASE-I:

The main objective of the phase-I trials is to assess the safety and reactogenicity. The alternate aim of the phase-I clinical trials are immunity response, the dose, immunization schedule and the route of administration of vaccine can also be evaluated.

Study design: Non- blinded Clinical trials.

Randomized clinical trials can be preferred, but it has some possibility to show errors during this phase of study. This can be done only when a placebo (or) any other vaccine can be compared. In order to prevent the occurrence of bias, this can be used as either single blinded (or) double blinded.

Study site:

This phase study should be carried out in a tertiary care hospital, because there is a chance of developing ADR's after the administration and so the subjects should be kept for observation.

Outcome:

Safety and immunogenicity

PHASE-II:
The ultimate aim of phase –II trial is to determine the
- ✓ Preparation of vaccine
- ✓ Excellent dose
- ✓ Immunization schedule.

On performance of the phase-II clinical trials some of the multiple factors are to be considered.
- ✓ Age
- ✓ Ethnicity
- ✓ Gender

Study population:
100-1000 number of patients, huge no. of subjects can help to improve and conclude better assessment of safety and efficacy of vaccines. Study population may include adults, infants, children and pregnant woman.
These studies can be performed in both males and females whose age lies between 9-25 years.
Study design:
Randomized Controlled Design-comparison with placebo or with any other vaccine.
Study site:
This study is a society placed study where the details can be collected more about the population (i.e) demography, mitigation, sex ratio, disease patterns. The population may be from schools, colleges and nearby surrounding communities.
Outcomes:
Efficacy end points, immunogenicity.

PHASE-III
The main aim of this phase for the registration and marketing of a vaccine. This also evaluates the final formulation of a vaccine. In this phase they also explain about the vaccine efficacy.
Vaccine efficacy is defined as the prevent reduction in incidence (of a infection) among vaccinated.
$(I_v\text{-}I_V/I_U)*100= (1\text{-}I_V/I_U)*100\ \%=(\ 1\text{-RR})*100\%$
$I_U$-Incidence in unvaccinated population
$I_V$-Incidence in vaccinated population
RR-Relative Risk.
Study population:
More than 1000 subjects of targeted population
Study Design:
Randomized Controlled Design.
To eliminate the errors and elaborates existing chances of identifying a difference in investigational vaccines and control.
Outcomes:
Efficacy and safety determined can file the application to the regulatory agency for the marketing of a product. [3][4]

**VAERS:**
The CDC and FDA have introduced a new system called as The Vaccine Adverse Event Reporting System in the year 1990.It has been established to identify the expected adverse reactions in related to vaccines. Approximately 30,000 adverse events are reported in VAERS. With the help of this system, they had found out two adverse drug reactions.

a) Vaccine for rotavirus had caused a intestinal problem.
b) Yellow fever vaccine when injected it created a neurologic and gastrointestinal disease.

**Importance of VAERS**:
- Helps in identifying unique, special type of adverse reactions.
- Notice the changes in the elevated level of known ADR
- Detect the potential patient risk factor for unique type of ADR.
- Determine the safety of newly licensed and invented vaccines.[5]

**Manufacturers and importers of biological:**
For manufacturers:
a) NOC for form 29
b) Test license
c) Post approval changes
d) Marketing Authorization
e) Clinical Trial permission

For importers:
a) Registration
b) Import license
c) Marketing Authorization
d) Clinical trial permission (Phase 1,2,3)

Manufacturers used to access and monitor the QC, documentation of all the process involved in the development of vaccines where as in regulatory formalities it takes some time to review the process development. To carry out the clinical trials, first they need to get NOC from the concerned regulatory authority.

**MANUFACTURERS:**
a) NOC for form 29:
Form 29- Application for the test license to examine, test or analysis of the given batches. In order to get form 29 priory NOC should be obtained from the CDSCO. The form of NOC should be submitted along with the following documents:
- Manufacturer product details
- Sources of MSL\WSL
- Manufacturing Process flow
- Site plan
- List of equipment and testing facility.
- Qualified personnel details in handling the post approval batches.

b) Test License:
Form-29 is a test license which is a license to manufacture biological for purpose of examination, test or analysis. when form-30 is applied to SLA it issues the license in form-29. The test license should be renewed once in a year from the date of issue.
To get a test license a list of documents shall be attached along with the form 29 & 30. The following documents are:
- Form 29 & Form 30 along with the fees

- List of biological to be manufactured /tested
- Details of the pharmaceutical aids used.
- Details of existing similar products in the market
- NOC

C) Post Approval Changes:

It is mandatory to file for a new drug or manufacturing license when there is a major quality approval changes and can file additional manufacturing license in case of moderate quality changes along with a clear, detailed description of where the changes have been made.

Along with this, the applicants should also present their clear and supportive evidences about the effect of change on quality, stability, validation, animal toxicity, and clinical data.

If there is a change in the manufacturing premises, the license can apply for additional product permission to the concerned licensing authorities.

d) Marketing Authorization:

Now-a- days biosimilars are the fastest growing products in India Biologics may consists of DNA Vaccines, monoclonal antibodies. The biological product should also follow the same pathway of innovator new drug. The manufacture has to submit a form 41 application and the international submission requirements of CTD which includes of five modules.

e) Clinical Trial Phases:

Permission of clinical trials:

There are totally 3 phases:

Phase-I

- Can be carried out in India or any other countries
- Performed only by the trained personnel.
- Trial may be conducted at 1-2 centers.

Phase-II trials can be conducted within 10-12 volunteers to specific each dose level and this study may conducted at 3-4 centers and can be performed by a well-trained person in therapeutics.

Phase-III trials are the most important part of the clinical trials which is performed to determine the efficacy of the products as well as ADR's. This study can be conducted at 3-4 different centers with a minimum of 100 subjects. When the drug is discovered in India for the first time it should be treated minimum to 500 subjects.

When new biological developed and marketed in India, the CDSCO requires the following documents are:

- Form 44
- Treasury chellan of Rs.5000
- Sources of bulk drugs and Raw materials.

**IMPORTERS:**

When the biological are to be imported CDSCO has to check and permit the import of biological [Form -8] has been submitted along with an approval form of [form-10]

Registration process for Importer:

Vaccine manufacturer

⇩

Conduct clinical trials

⇩

GCP and ethical guidelines approvals are required

⇩

Submission of results to national regulatory authority

⇩

Marketing authorization (Form 45) from CDSCO

⇩

Application for registration (Form 41) and Import license are submitted and approval received

⇩

Conduct of phase- IV and submission of PSUR.

A) Registration:

The registration certificate is issued in Form -41 for biological under rule 27 A by the licensing authority. The drug with its manufacturing site needs to be registered for import.

B) Import license:

Import license are issued in form 10.The applicant fills the form-8 to obtain the form 10 and form 10-A

It is issued under the rule -24 granted by the licensing authority.

An import license is valid for period of 3 years from the date of its issue.

C) Marketing Authorization:

Marketing authorization is an important step during import of product which ensures the quality control.

D) Clinical trial phases:

Permission of clinical trials:

There are totally 3 phases:

Phase-I

- Can be carried out in India or any other countries
- Performed only by the trained personnel.
- Trial may be conducted at 1-2 centers.

Phase-II trials can be conducted within 10-12 volunteers to specific each dose level and this study may conducted at 3-4 centers and can be performed by a well-trained person in therapeutics.

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- Treasury chellan of Rs.5000
- Sources of bulk drugs and Raw materials[6]

**CONTENTS OF A VACCINE DOSSIER:**

The common submission format of vaccines is a CTD format. CTD usually consists of a five modules. It consists of:

MODULE-1:

1.1 Table of contents
1.2 Correspondence
1.3 Site master file
1.4 Compliance information
1.5 Vaccine composition, presentations and scheduling information
1.6 Supplemental pre-clinical and clinical information
1.7 Regulatory actions
1.8 Distribution information.

MODULE-2:

2.1 CTD Table of contents
2.2 CTD introduction
2.3 Quality overall summary
2.4 Non clinical overview
2.5 Clinical overview
2.6 Non clinical written and tabulated summaries
2.7 Clinical summary and biopharmaceutical studies.

MODULE-3:

3.1 Table of contents of module 3
3.2 Body of data
3.3 Literature references
3.2A Appendices

MODULE-4:

4.1 Table of contents of module 4
4.2 Study reports
4.3 Literature references

MODULE-5

5.1 Table of contents of module 5
5.2 Tabular listing of all clinical studies
5.3 Clinical study reports [7]

**DVCRN:**

These are the committee which is organized and monitored by the World Health Organization (WHO).They are certain members involved in the DVCRN=Developing Country Vaccine Regulators Network.

This committee meets once in a year to improve the NRA (National Regulatory Affairs) in developing countries where the vaccines are manufactured, authorized and evaluation of vaccines clinical trials takes place.

**Members of DCVRN**

There are total of 9 countries involved:

- Brazil
- Cuba
- India
- Indonesia
- Islamic republic of Iran
- People's republic of china
- Republic of Korea
- South Africa

Trials: There are totally 2 types of trials involved in the vaccine trial approval:

a) One-Sided:

- This trial has been conducted to know how the new vaccine produces a relative risk or hazard of a particular disease or infection.
- When it is done based on immune response, the effect may be in a variation in proportions of subjects, in particular response to the pre-specified manner.
- Since these evaluations are one-sided, the interference depends either on the upper limit (or) lower confidence limit.

b) Two-sided:

- Comparison of two vaccines lots
- Designed to prove that one group in similar in both the directions to that of another group.
- When the evaluation of lot is inherently two-sided, it can be taken as too high (or) too low when on comparison with another lot.
- The lots can be manufactured when two sided confidence interval is showing appropriate relative effect (i.e) when it falls within the pre-specified limits.[8]

**MODULES AS PER WHO:**

MODULE-1: Vaccine Safety Basics:

- Vaccines Promote health
- Vaccines have an expansive reach
- Vaccines have rapid impact
- Vaccines save lives and Costs.

Vaccines are unlike than other pharmaceutical products which will show some adverse effects such as (redness at injection site and fever) and major effects such as (seizures and anaphylaxis). [9]

MODULE-2: Types of vaccines and adverse reactions

Vaccines can be differentiated based on their preparation and the antigen involved. Totally there are 4 types of vaccines, they are

a) Live Attenuated Vaccines
b) Inactivated Killed antigens
c) Sub units
d) Toxoids

a) Live attenuated Vaccines:

Under the live attenuated vaccines there are two types of vaccines. Monovalent vaccines contains only one strain used in antigen (eg: measles) and whereas polyvalent vaccines are the vaccines which consists of two or more than two strains/serotypes of same antigen have been used. Combination vaccines are the vaccines which contain many antigens combine together in a one particular single injection, which helps in the prevention of different diseases (or) multiple strains involving in causing of a same disease.

Adverse reactions with LAV's are Tuberculosis, oral polio vaccine, measles, Rotavirus and yellow fever.

b) Inactivated Vaccines:

These vaccines are made up of micro-organisms once they have been destroyed through physical mode or chemical mode and these organisms would not trigger in development of disease.

c) Subunit vaccines:

These are like inactivated whole cell vaccines where they require only the antigens part of the pathogen to provide a greater immune response.

d) Toxoid Vaccines:

Toxoid vaccines are the vaccines which can be prepared by the toxins released by the bacteria.

| S.NO | TYPES OF VACCINES | IMMUNE RESPONSE | STABILITY |
|---|---|---|---|
| 1. | Live attenuated Vaccines | These microorganisms gives continual antigenic stimulation and provides enough time for cell production<br>They are much capable of replicating within cells | It causes harm to individuals with compromised immune systems.<br>Errors in immunization<br>Comparatively less safe of attenuated vaccines. |
| 2. | Inactivated Vaccines | Does not have any immune response and this can be a short lived.<br>Large number of whole-cell vaccines is needed in order to provide sufficient immune response.<br>Less and strong immune response | No risk in stimulating the disease<br>Safe and more stability<br>Very high stability profile` |
| 3. | Sub Unit Vaccines | Must ensure a correct composition of sub units which will provide a strong immune response in a effective pathway.<br>No guarantee for the future immune response | No risk in stimulation of disease<br>Safer and more stable when compared with LAV |
| 4. | Toxoid Vaccines | It acts only as an adjuvant.<br>Not immunogenic | Stable and prolonged action<br>Exists only local and systemic reactions. |

COMPONENTS OF A VACCINE:

Vaccines are usually comprised of a antigens, stabilizers, adjuvants, antibiotics and preservatives.

Antigens:

These are evolved from the chemical structure of causative organisms and be considered as a "foreign particle'' to immune system which helps in eliciting a greater immune response.

Stabilizers:

These are the agents which help in maintaining the efficacy of vaccines at time of storage. Since the vaccine requires a very high stability profile in order to withstand its immune response. Some of the factors influence the stability of vaccines. They are temperature, acidity or alkalinity of vaccine.

Antibiotics:

These are the agents which exists their major role in manufacturing process in order to present any contamination in tissue cell culture.

Preservatives:

These are the agents which are added to protect the vaccines from any of the bacterial or fungal growth. E.g.: Thiomersal [10]

MODULE -3: Adverse Events Following Immunization:

AEFI is any untoward medical reaction that occurs during immunization and does not have any normal relationship with usage of vaccine. This may be of accidental signal, unusual laboratory finding, and symptom of a disease.

AEFI is divided into five types:

Vaccine product-Related reaction
Vaccine quality defect-Related reaction
Immunization error-Related reaction
Immunization anxiety-Related reaction
Coincidental event

Vaccine product-Related reaction:

An AEFI is developed a triggered by a vaccine because of one or more fundamental properties of a vaccine product. e.g.: Limb swelling on following of DTP vaccination.

Vaccine Quality defect-Related reaction:

This is developed by a vaccine because of some quality defects of the vaccine product due to its administration device as given by the manufacturer.

Immunization error-Related reaction:

This occurs due to improper handling of vaccine (or) errors in prescribing or in administering this can be preventable.

Immunization anxiety-Related reaction:

This may occur due to concern about the immunization

Coincidental immunization:

This AEFI occurs by something rather than the vaccine, Immunization error, or Immunization anxiety.

When the AEFI is considered to be as serious

a) Results in death
b) Life-Threatening
c) Birth defect.[11]

MODULE-4: SURVEILLANCE

It deals with the vaccine pharmacovigilance. Pharmacovigilance also known as drug safety or tranquilize well-being and that is the science which deals with the discovery, assessment about the understanding prevention and also the addressing of the adverse drug reaction.

Vaccine Pharmacovigilance follows up three steps:

1) Signal Detection
2) Development of causality hypothesis

3) Testing of causality hypothesis

1) SIGNAL DETECTION:

It helps in the identification of signals, which determines that AEFI occurs due to vaccine and not because of any other conditions. This surveillance system usually develops the safety signals.

2) DEVELOPMENT OF CAUSALITY HYPOTHESIS:

Generate a hypothesis stating that casual action took place between the adverse event and vaccination depending upon those reported signals.

3) TESTING OF CAUSALITY HYPOTHESIS:

The developed hypothesis can be tested using the epidemiological methods using the available datasets. [12]

MODULE-5: VACCINE SAFETY INSTITUTIONS AND MECHANISMS

They mainly concentrates on analyzing, diagnosing, correcting and protecting from the disease, helps in analyzing the specific vaccine lots and prevents from any accidental contamination.[13]

MODULE-6: COMMUNICATION:

There are some concerns due to some communication problems some of them are arising of programs, unsafe injections, frequent changing of regulations, vaccine campaigns, improper monitoring and handling of rumors. These are some of the concerns due to improper communications to the public. In order to avoid these problems the information should reach to the public through proper circular creating awareness in each and every places including rural, urban areas and cities.[14]

## CONCLUSION:

Since vaccination is considered as a vital part of every healthy well-being, it is the duty of we the health care professionals should awake and aware of the pros and concern of the vaccination. So the vaccine should also have certain regulatory requirements through which all the vaccine products and biologics pass through and creating a good hope among the public. The regulatory considerations of the vaccines are explained and the submission format also been explained. Hence this can help in prevention of diseases and can save many children birth.

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