Regulatory Guidelines for Vaccines and Sera

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***Abstract*—These are the biomedical products that works to build up to protect human body from foreign materials. The products which are used for immunization are known to be immunizing agents. Immunoglobulins and sera provides passive immunity by transferring ready made antibodies produced by an animal or person who has received active vaccination. Serum is a concentrated and purified product of the serum of horses or rabbits that have received active vaccination against a particular antigen. Occasionally it exhibits an allergic reaction right away. Both vaccines and sera plays a crucial role for avoiding and treating infectious disease, strict regulatory compliance is required to guarantee their products are free from contamination are effective and safe with quality product. On the other hand rules are set by the organizations like the world health organization (WHO), U.S Food and Drug Administration (FDA), and the Central Drugs Standard Control Organization (CDSCO) in India, this research determines the national and international regulatory structure controlling vaccines and sera. There are different regulatory process steps which include preclinical research, clinical trials, good manufacturing practices, and post marketing surveillance. Current progress in regulatory science generate a emergency use authorization approval processes and pharmacovigilance system which are under consideration. Along with the obstacles in bonding with global standards, the initiative offers creative regulatory approaches to enhance accessibility and guarantee public health and safety.**

***Index Terms*—Immune response, vaccinations., sera**

I. INTRODUCTION

Vaccines are the greatest achievements in science and public health.[1,2] Due to positive response immunization campaigns and programs many disease that are to be prevented by vaccination are now not common in the united states.[4,6] The regulatory compliance foundation for U.S. Food and Drug Administration regulation of vaccines are used to prevent infectious diseases is provided by section 351 of the federal food, drug and cosmetic act.[3,5,7] The FD and C Act defines pharmaceuticals in part by stating that ''articles are generally used for diagnosis, cure, mitigations, treatment, or prevention of disease.[8,9,12]

Vaccines:

Pharmaceuticals that meet the regulatory compliances for their standards of biological products include vaccines. [10] Prophylactic vaccinations differ from other drugs and biologicals primarily in their mechanism of action risk profile and intended use for a large population, particularly young, healthy persons with the goal of preventing rather than treating disease. [11,13]

Vaccines are more competitive to design, describe, and produce than the majority of pharmaceutical medicines, although being governed by the same laws as other biological products.[14,16] Vaccination, suspension of bacteria or toxins that have been weakened, destroyed or fragmented or other biological preparation that are generally used for preventing diseases such as those made of antibodies, lymphocytes or messenger RNA (mRNA).[15,17] Vaccines can activate the immune system to attack a particular risky agents.[18] Cells produce antibodies which are known to be B cells (B lymphocytes) that activates by vaccine and remain sensitised, prepared to react to chemicals which should ever enter the body. By providing lymphocytes or antibodies that have

already been produced by animal or human donor, vaccination also provides passive immunity.[19,20] Vaccines are generally given through injections (parenteral administration) few vaccines are taken as orally or even by nose like flu vaccines.[21] Most essential way to administer vaccines by applying them to mucosal surfaces such as lining of stomach or nasal passages which appear to stronger antibody response.[22,23]

II. HOW DOES VACCINES WORK ?

Human bodies can react in two ways in organism that causes illness.[1]

- The first is specified by the symptoms which include fever, nausea, vomiting, diarrhoea, rash etc.[2]
- The second is the reaction of the immune system to the infection.[24]
- The immune system becomes stronger with time, which lowers the quantity of infectious agents and gradually discards the symptoms.[25] In order to the second type of reaction without the negative effects of the first, vaccines are made up of either the full disease causing microbe or few of its non – pathogenic components.[7,27]

A preventive vaccine can protect a person from illness or disease in the ways which are mentioned below.

1. A very small part or nontoxic form of pathogen are emerged into the human body with help of vaccines.
2. Human body's immune system generates a killer cells, antibodies or both in reaction to the infection.
3. Body continues a small number of ''memory'' T-cells and B-cells that are speedy trigger a robust immune response by assisting in creation of killer T-cells or antibodies, Respectively, by generating antibodies themselves.[3,5,26,28]

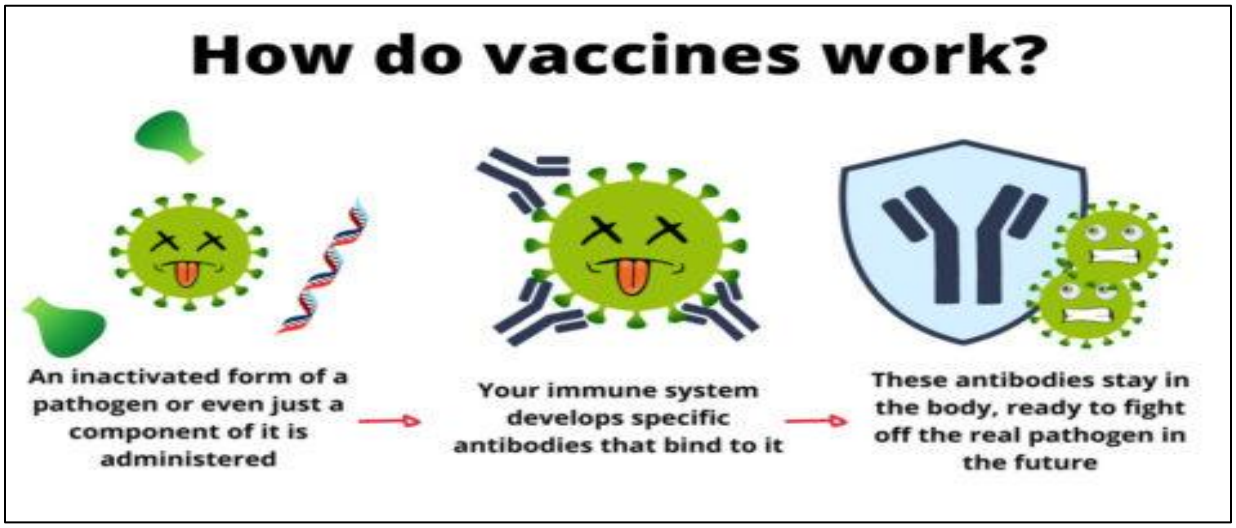


Fig.no. 1. How do vaccines work ?[3]

Types of Vaccines:

Vaccines can be synthesized in many ways based on which they are classified.[29]

1. Live attenuated vaccines.

Genetic engineering weakens pathogens, such as bacteria or viruses which prevent them from spreading and infecting the host. An organism which is connected to the pathogens that normally develops poorly in humans is used in some modified live vaccines.[3,4] Similar to an infected person with a natural infection, the weakened pathogen causes a widespread immune response in the host.[30,31]

Examples.[3,4]

- Oral Sabin polio vaccine.
- MRV Vaccine (Measles, Mumps, Rubella and Varicella)
- Nasal influenza vaccine.
- Rotavirus vaccine.
- Bacille Calmette – Guerin (BCG) Vaccine.

Fig.2 :Oral Sabin Polio

2. Inactivated or Dead Vaccines.

A thermal (high temperature) or chemical (formalin) technique is typically used to destroy or inactivate the disease causing bacterium. When given, these vaccines produces a strong immune response that closely resembles the majority of the reactions that are observed during an infection.[2,3,4]

Examples.

- Typhoid vaccine.
- Influenza vaccine.
- Salk polio vaccine.
- Hepatitis A vaccine.

Fig. 3: Influenza vaccine

3. Acellular or Subunit vaccines.

Acellular refers to the absence of whole cells. The entire virus or bacteria is not present in acellular vaccinations. Rather, they contain proteins or polysaccharides from the bacterial or viral surface. These proteins or polysaccharides are the components that our immune system targets since it perceives them as ‘’foreign’’. [2,3,4]Cellular vaccines come in a variety of forms:

Toxoid vaccine	Examples: • Diphtheria vaccine. • Tetanus vaccine. • Pertussis vaccine.
Conjugate vaccine	Examples: • Haemophilus influenza type b (Hib) conjugate vaccine. • Pneumococcal conjugate vaccine. • Meningococcal conjugate vaccine.
Recombinant vaccine	Examples: • Hepatitis B vaccine. • Human papillomavirus (HPV) vaccine.
DNA / RNA vaccine	Example: HIV vaccine.

A. Toxoid Vaccine.

When pathogenic bacteria attack the body, they release toxic proteins called toxins. Some vaccinations, known as ‘’toxoids’’ because they resemble toxins but are not harmful, are created by chemically inactivating these toxins. They cause the immune system to react strongly.[32,34]

B. Conjugate Vaccine.

Sugar molecules found on the bacterial surface were used to create earlier polysaccharide vaccines, but these proved less successful in infants and young children. Researchers found that conjugating the bacterial polysaccharide molecules to a carrier protein, or chemically linking them, can improve the effectiveness of these vaccinations. When additional proteins are added, the antigen gains the immunological characteristics of the carrier, strengthening the immune response and making it suitable for younger children.[33]

C. C. Recombinant Vaccine.

A small fragment of the disease – causing virus or bacteria’s DNA is extracted. A plasmid or carrier vehicle containing the specific gene allows for the creation of vast amounts of distinct proteins, which are subsequently utilised as vaccinations.[33]

D. DNA / RNA Vaccine.

Human cells are exposed to genetic material, either DNA or RNA, from pathogenic bacteria or viruses. The inserted gene or genes of the pathogen are subsequently used by the cell machinery to make the protein. The immune system of our body recognises this protein as a foreign substance and mounts an attack on the entire infection. Various nucleic acid vaccines are now in the pre- clinical, clinical evaluation, and development stages.[35]

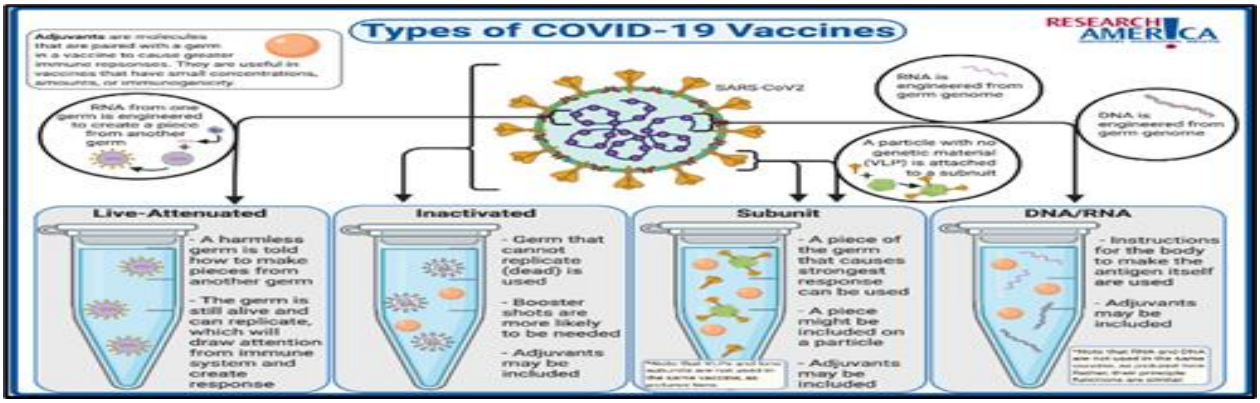


Fig. 4: Types of Covid Vaccines

Immune Sera (serum):

Serum has antibodies in it. It is obtained from an animal that has been immunised via injection of the antigen or by infection with microbes that contain the antigen. [36,37]

Immunoglobulins as Antigens:

The two key terms whether the former entities can truly behave like the latter- they were thoroughly discussed. The fact that Igs are consistently and copiously present in human serum is quite clear. Although it has been proven that there are five types of Igs that are obtained in humans and are also present in mammalian species, it is important to note that despite certain striking similarities between the aforementioned Ig categories there are some minor deviations in their prevalent structures. Remarkably, immunologists took use of occurrences which were led to development of anti – antibodies or antiglobulin which are highly useful for diagnostics.[38,39]

It is generally known that human immune systems are extremely sensitive. As a result, chemicals originating from one mammalian species and then from other mammalian species will mostly show immunogenic properties which will elicit an immune response.[40]

Example:

When injected into ‘’sheep’’, the Ig molecular entities that were originally produced from a ‘’rabbit’’ will behave as fragmented crystallisable (fc) areas. Even so there are notable distinctions between the less foreign substances because of the small variations that are primarily found in the heavy chains belonging to the same class but originating from completely different species. These differences are placed strategically in the heavy chain Fc tail portions of the molecule. Igs are eventually produced by the recipient species and mostly combine with this area. Additionally the end products antibodies against antibodies are typically referred to as ‘’antiglobulin’’.[1,2,3]

Structure of Antibody:

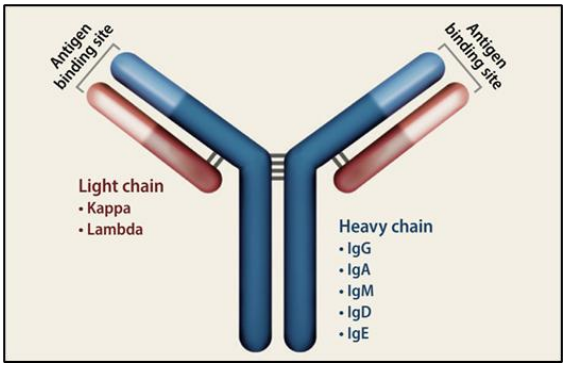
Antibodies are also known as immunoglobulins and are mainly divided into five different types. The structure of antibodies will be limited to two classes. Ig. A and Ig.G molecules.[40]

1. Ig. A Molecule.

It has been noted that the second biggest class of immunoglobulins found in human serum is designated by the Ig A molecule. It is discovered and consist of two heavy chains. It basically has more ‘disulphide bonds’’ that are directly attached to the heavy chains and a greater carbohydrate content (75%). It is noted that bonds precise placement differs significantly from the Ig G. additionally every heavy chain possesses a free SH moiety at the C terminal.[41,43]

2. Ig. G Molecule.

An extensive investigation was conducted on individuals who were specially afflicted with a disease known as myeloma in order to gain a more vivid understanding of the resultant relationship between the basic structure of Ig. G and its biological activities. The cells are synthesising a massive quantity of heavy and light chains that are produced nearly identically, which is considered a neoplastic state. Patients are typically release excessive amounts of light chains Igs. The variable section of the fragment, polymerisation, which eventually leads to the development of amyloids fibrils with particular characteristics.[42]



Immunotherapy: Preformed Ab

Immunoglobulin is there in immune serum globulin (gamma globulin), which is remoted from the combined blood of at least 1,000 human donors. Treatment of choice for immune- deficient people to replace Ab and prevent measles and hepatitis A which endure for two to three months.[45]

Classification of the Serum Preparations:

- Serum Homogeneity – It comes from volunteers who are immunised to donate blood.
- Serum Heterogeneity – It is made from the blood of hyperimmunised animals, such as horses.[47]

History of Development of Vaccine & Sera: [46]

Vaccine:

- In order to prevent smallpox, British physician Edward Jenner used the cowpeas virus (variola vaccina) in 1796.
- French microbiologists Emile Roux and Lexis Pasteur develop a new first rabies vaccine in 1885.
- The first smallpox vaccine lymph doses reached India in May 1802.
- Three year old Anna Dust Hall became the first person in Lodia to receive the smallpox vaccine on June 14, 1802, from Bombay.
- The vaccine was deallocated as lymph to Madras, Poona, Hyderabad and Surat.
- Variolation was prohibited as early as 1804 in some European countries and in the same Indian regions due to the demonstrated advantages of smallpox vaccination. [4,5]

Immune Sera:

- Animal serum is generally used to produce biologicals for humans and animals that are produced from cell culture.
- Growth factors, attachments factors, transport proteins, protease inhibitors, lipids, trace elements, hormones and other small molecules needed for efficient cell growth and protein synthesis are all provided by adding serum to basal culture conditions.
- The majority of cell types use serum as a universal growth supplement, and adding it to basal media can eliminate the need for lengthy media development.
- Serum has several unique benefits that can make it an essential raw material for cell culture even though the biotechnology and pharmaceutical industries are striving to eliminate animal derived materials from their production processes and in certain situations from the development and screening of cell lines.[46,48]
- In roller bottle and microcarrier cultures, serum facilitates the attachment of anchorage – dependent cell lines including the African green monkey kidney cell line (VERO) and the Madin – Darby Bovine kidney cell line (MDBK).
- It can also serve as a shear protectant in agitated suspension cultures (Valez et al. 1986).
- It has been demonstrated that removing serum from cell culture media increases the medium's proteolytic activity which could lead to decreased cell proliferation and lower protein quality (Kretzmer et al. 1994). [47]

Compared to serum free media made with recombinant growth and attachment factors, hormones, and other essential ingredients, adding a cheap serum, like adult bovine serum (ABS), to an enriched basal medium can be substantially less expensive from the standpoint of production economics. Serum is a naturally occurring blood product from a variety of animal species, gestational stages, and geographic regions its usage in biological production.[48]

Vaccine Development:

- Every year, millions of people safely receive them, and most of them have been in use for many years prior to being included to the country's immunisation schedule.
- Every vaccine must pass stringent testing to ensure its safety, just like other medications. [49]

There are five steps in the standardisation process for vaccination approval: pre-clinical, clinical development, conducting an inquiry, acceptance, and exploratory.

1. Stage of exploration: This stage, which usually takes two to four years, includes basic research conducted by government and academic researchers supported by the federal government in an effort to discover artificial antigens that treat illnesses. These antigens may be substances produced by the pathogen, attenuated viral poisons, or detritus that resembles viruses. The immunisation undergoes three stages of testing. (50)
2. The Preclinical Phase: Preclinical research evaluates a putative vaccine's safety and immunogenicity – the capacity to trigger an immune response. Using animal testing and also cell culture methods. It also provides information of biological reactions that scientist have studied on the people and thus studies are recommended as safe dosage for subsequent stage of research to deliver vaccine. To increase the potential vaccine efficacy, researchers may alter it while it is still in the pre clinical phase. Animals are also used in challenge trials which immunise the animals before trying to expose them to the desired disease.(4,50)
3. Clinical Advancement: Once the IND is approved, the next phase is clinical development. The development of a broad research strategy is necessary for clinical testing of vaccines on humans. Phase I, II, and III clinical studies must all be carried out with approval from the regulatory body.(50)
4. IND application: The sponsor, usually a commercial company, files an application for an IND to the USFDA. The sponsor provides an overview of the lab reports, talks about the planned study, and goes into detail about the evaluation and manufacturing processes. The institution that will conduct the clinical study must have an institutional review board approve the clinical protocol. The FDA has 30 days to approve the application. Once the IND application is approved, the vaccine needs to go through three testing stages.(50)

- Phase I studies for vaccines: In order to reach the target population, a limited number of adults roughly 20 to 80 people are involve in phase I vaccine trials when developing a vaccine for children. Before reducing the age of the test subjects, scientists will test the drug on adults. If these tests are not blinded, a placebo may be employed. Determining the vaccine's safety and the intensity of the immune response is the aim of phase I evaluation.(51,53)

- Phase II studies for vaccines: Phase II vaccination studies which generally involves variety of participants, which organise to assess immunogenicity of the vaccines and suggest a design of the common side effects in order to discuss their potential phase III investigations. After phase II testing, sponsors are motivated to meet with CBER to discuss the main objectives.(52)

- Phase III trials for vaccines: While completing phase II vaccine investigations modern to larger trials generating thousands to tens of thousands of participants. The investigational vaccine is performed to test in these phase III studies. Phase III main goal is to evaluate the safety of the vaccinations in a sizable population. According to the study, in order to demonstrate a variance for minimal errors a study would need to register 60,000 participants, half of whom would be in the placebo group or those who had not received immunisations. This replies that there may not been any negatives feedback observe in the smaller subject populations examined in the early stages.(51)

- Phase IV studies: After the vaccine is released, the manufacturer may decide to conduct optional studies known as phase IV trials. The vaccination may continue to assess its efficacy in terms of security and other possible uses.(51)

Vaccine Manufacturing:

Vaccines have to meet some of the strictest design monitoring and compliance requirements of any manufactured product in the modern world because of this fact. For these vaccinations to be produced safely

and reliably, four competencies are required. Before being released and distributed, all four of the new vaccines must pass a rigorous regulatory approval process. These include the production process that outlines how the product is made, the organization's adherence to that process, the product testing, and associated procedures.(3,4)

The Approval Process Consists of Four Primary Parts: After filing an application form for experimental new drug, providing safety and efficacy research[1], preparing preclinical paperwork for animal model proof of concept testing[2] and submitting a biologics license application (BLA) to the FDA[3] and EMA for approval with the required information[4]. Propagation are the steps which consist of living organism used in vaccination gets multiplied or amplified. Dissociated the live thing from the cells which are used for propagation is know as isolation. Purification removes all materials associated with the isolated living organism that will be used in the vaccine. The purified product requires to be combined with solutions to get the necessary concentration.(5)

India's Vaccine Laws: The Indian Council for Medical Research, the Central Drugs Standard Control Organisation, the National Technical Advisory Group on Immunisation, and the Ministry of Health and Family Welfare are among the regulatory bodies that oversee vaccine licensing.(6,55)

The United States' Vaccination Laws: Among the regulatory agencies that are investigated by vaccine registration in the US are the Biologics License Application the Centre for Biologics License Application the centre for biologics evaluation and research and the vaccines and related biological products advisory committee.(53)

Indian Registration Procedure:
The following are some of the regulatory bodies that oversee the vaccine registration process in India:

1. Ministry of Family Health and Welfare Group for Technical Advice.
2. Immunisation at the National Institutes of Health.
3. Central Drug Standard Control Organisation.
4. Central Licensing Approval Authority.
5. Indian Council for Medical Research. (54)

First vaccines are developed, and then clinical trials for produced vaccines are conducted. Ten to thirty substudies make up the initial phase of clinical trials, where immunological research and vaccination safety are evaluated.Phase 2 comprises 100 subs. This stage is sometimes referred to as dose range studies. The third phase, which includes 1000 subscribers, is when the safety and efficacy statistics are recorded. After then, the National Regulatory Authority (NRA) receives the data for approval.(55)

The following step then requires approvals in accordance with GCP and ethical standards:
The Indian Council for Medical Research, or ICMR, publishes ethical and GCP guidelines.

- Following that, a license is granted by the central licensing approval body (CLAA).
- Before vaccines can be added to immunization services after receiving CLAA certification, DTAB approval is needed.
- Following immunization approval, clinical trials are under the purview of CLAA. Following the conclusion of clinical studies, phase 4 trials are conducted for post marketing surveillance and immunizations are commercialized.
- Following phase 4, any safety or effectiveness complaints are sent to the NRA. (52,54)

United State Registration Procedure:
There are different regulatory guidelines for registration of vaccine in USA are:

- CBER (Centre for Biologics Evaluation and Research)
- VRBPAC (Vaccines and Related Biological Products Advisory Committee)
- BLA (Biologics License Application.)
- The FDA's Center for Biologics Evaluation and Research regulates vaccines in the united states. (4,5,56)

The FDA detects each step of the testing procedure to clarify that new vaccines on the market are safe, effective and have low adverse effects. Before being vaccines injected on people, preclinical studies of vaccines using tissue samples and animals models must be authorised clinical trials prior to human testing. An organization that funds such experimental clinical studies. A new drug application. (57)

Regulations And Guidelines: [2,58]

Indian laws governing vaccines:

There are different regulatory bodies involved in vaccination registration.

- Health and Family Welfare Ministry.
- National Immunization Technical Advisory Group
- The Indian council for Medical Research organization for Central Drugs Standard Control.

The United States vaccine laws:

There are Different regulatory agencies for vaccine registration are as follows:

- Centre for Research and Evaluation of Biologics Committee on Vaccines and Related Biologic Products Application for license in Biologics.

Requirements	US	EU	INDIA
Agency	One Agency **USFDA**	Multiple Agencies • **EMEA** • **CHMP** • **National Health Agencies**	One Agency **DCGI**
Registration Process	One registration process	Multiple registration process • Centralized(European community) • Decentralized (at least 2 member states) • Mutual recognition (at least 2 member states) • National (1 member state)	One registration process
TSE/BSE data study	Not Required	Required	Required
Braille code	Braille code is not required on labelling	Braille code is required for labelling	Braille code is not required on labelling
Post approval changes	Post-approved changes in the approved drug: • Minor • Moderate • Major	Post variation in the approved drug: • Type IA • Type IB • Type II	Post-approval changes: • Major • Moderate

Applicable guidelines and Regulations of Biologicals in India:

Under the 1940 Drugs and Cosmetics Act and the 1945 Drugs and Cosmetics Rules, the import and production of pharmaceuticals and biologicals are been worked. It is permitted to import and manufacture biologicals without a license, according to the drug and cosmetics act of 1945. In 1989 regulations for harmful microorganisms and genetically improved organisms or cells are control over the production, use, export, import and storage of similar biologics. The following list which contains a variety of guidelines that aid in the production of similar biologics. In 1990 recombinant DNA Safety Guidelines, 1990 Guidelines for pre-clinical and clinical data generation for RDNA Vaccines, 1999 Guidelines and handbook for institutional biosafety committee CDSCO Industry Guidance, 2008.

1. CTA Capitulation for Assessing Safety and Effectiveness.
2. Conditions for obtaining approval for new drugs.
3. Biological product modifications after approval: Quality, Safety and Efficacy Documents
4. Specifying the need for Biotechnological/ biological products to provide quality information for new drug approval.

Procedure for Biologics Approval:

- Clinical Experiments: To initiate these safety and efficacy, extensive preclinical and clinical experiments are required as part of the approval procedure for innovative biologic.
- Investigational New Drug Application:The manufacturer submits an IND application to the regulatory body prior to starting clinical trials. The proposed clinical testing methodology, manufacturing data, and preclinical data are all included in this application.
- Clinical Trials: Nonlogic Clinical trials have a phased methodology where safety, effectiveness, and adverse effects are assessed in a growing number of volunteers. [1,2]
- New Drug Application: Below is the completion of clinical studies, the producer submits an NDA which includes all relevant information about the product, including as its production method as well as clinical and preclinical data on medication and anticay.[3,4]

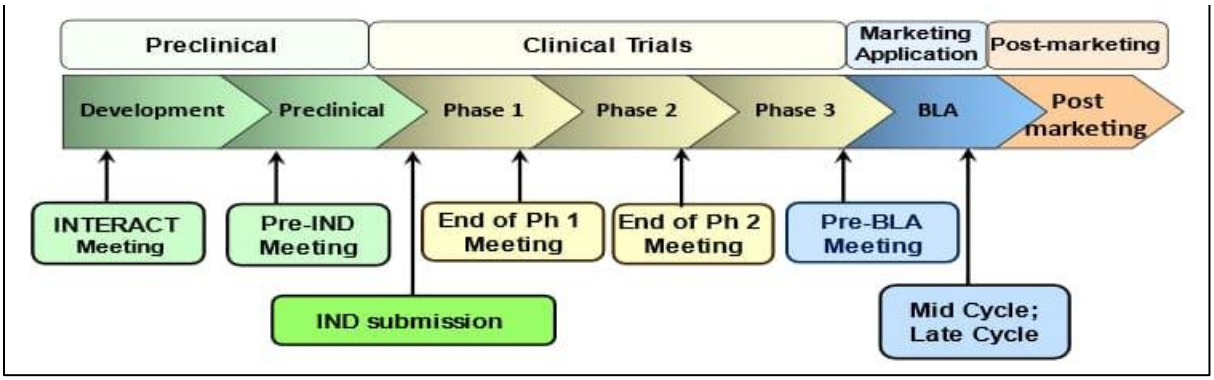


Fig.7: Procedure for Biological Approval

Evaluation and Acceptance:
In order to determine if the biologic should be authorised for commercialisation, the respiratory audit evaluates the NDA and verified data.

Applicable Guidelines:
The guideline for the biological in india are as follows:
Guidelines for Recombinant DNA wellbeing, 1990.

- CDSCO direction for industry, 2008.
- Guidelines and Handbook of IBC's, 2011.
- Application for Clinical preliminary accommodation for assessment of adequacy and wellbeing.
- Permission Conditions of New Drug Approval.
- Information of Quality for submission of drugs for New Drug Approval: biotechnological or biological products.
- Post endorsement changes for biologics: quality, efficacy, wellbeing archive. [62,63]

Biologicals Manufacturing Process:
The biologicals when assembled must be in incredibly sizable form. The information required for assembly movement and enhancing cell banks, clone adjustments, escapements, planning, and sanitisation etc. [1]
the outcome of item portrayal is also sought for. In light of molecular biology improvement of processes: downstream and fermentation comparative analysis of quality the difference between comparative business strategy and marked biology is examined. As per CDSCO guidelines for 2008 semester, the rival must offer a service of value. For the motive of generation, the three accessible manches of animals that have been unlisted the sellout of consuesce must be used. Application for biological trials the clinical, preliminary application requires the following. [62,64]

Information needed to apply for market authorisation:
The applicant must submit the application form in accordance with CDSCO standards and the 2008 document for industry guidance in order to be provided by marketing authorisation. Manufacturing for trade purposes is authorised at a different level or using different procedures in relation to that which are intended for phase 3 trials batch trials.

Post market information is necessary for biologics:

1. The pharmacovigilance strategy:It is generally the pharmacological information pertaining to adverse effect identification, collection, consideration, monitoring, and inhibition.
2. Adverse reaction reporting:All adverse events that generates after the product is administered are reported and analysed.
3. Studies of the Post- Market (PMS):It includes keeping an eye on a pharmaceutical products safety after it has been put on the market. [60]

Information needed for Preclinical Research:
Below mentioned is the information which is required for biological preclinical research: prior to starting with the pre-clinical research, precondition details which are based on the medications, identification, pharmacokinetic effects, adverse events, and utilisation are all included in this. Administration route: It is a process by which a medication enters the body through different routes. Intravenous is a common administration routes. Rate of absorption: the drag's speed as it travels from the intestinal tract to systemic circulation. Elimination rate. [8,10]

III. CONCLUSION

In order to regulate and avoid infectious diseases, public health strategies must be involve the expansion and standardization of vaccines and sera. phased clinical trials, strict scientific research, and organised regulatory monitoring have all contributed to the development of vaccines and sera into dependable, safe and effective immunisation agents. there are mainly two examples of FDA in US and CDSCO in India for regulatory regimes that Assurant vaccinations meet strict quality, safety, efficacy requirements before being made available to the general public. as different technologies like mRna platforms, recombinant DNA techniques, and plant based vaccines production continue to progress, regulatory agencies must keep a close eye on new developments while adjusting to them. to guarantee vaccination access and public trust globally, it is important to advance post marketing surveillance, generate a international collaboration and strengthen regulatory harmonisation. at the end effective vaccination programs and improved global health security are built on a clear and flexible regulatory framework.

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