Vaccine Regulation, Licensing and Approval in USA

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Authors’ contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

ABSTRACT

Vaccines are the foremost effective public and personal preventive health interventions, leading to vital reductions in vaccine-preventable diseases and in substantial price savings to the United States health care system. A vaccine is a biological preparation that will increase the immunity to a particular illness. Vaccine development is commonly found to be difficult and needs sharp understanding and information of recent developments by physicians and experts to confirm that safe and effective vaccines are manufactured with minimum risk. A strict regulative method to see the safety, efficacy, and quality should be achieved throughout the event of vaccine development for its authorization. The Office of Vaccines Research and Review at the CBER of the US-FDA is the federal administrative body charged with guaranteeing the safety, purity, and efficacy of vaccines within US. The licensing rules are published in the Title 21 CFR Part 60. Current authority for the regulation of vaccines is in Section 351(a) of the Public Health Service Act (PHS). Vaccine licensure, development of recommendations to be used, and implementation of these recommendations resulting in uptake, community protection, and result on illness burden represent a posh system that needs collaboration within the areas of basic science, public health, vaccine delivery and outcome observance, and public perception.
Keywords: Vaccine; IND; CBER; BLA; ACIP; VAERS.

ABBREVIATIONS

ICH : The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
CBER : Centre for Biologics Evaluation and Research
FDA : Food and Drug Administration
CDC : Centre for Disease Control and Prevention
CFR : Code of Federal Regulations
PDUFA : Prescription Drug User Fee Act
IND : Investigational New Drug
BLA : Biologics License Application
ACIP : Advisory Committee on Immunization Practice
VRBPAC : Vaccine and Related Biological Product Advisory Committee

1. INTRODUCTION

Advisory Committee on Immunization Practices (ACIP), a group of medical and public health experts develops vaccination recommendations. ACIP comprises of 15 experts who are the voting members and are responsible for making vaccine recommendations.

The Food and Drug Administration (FDA) has seven product and research centres to fulfil its basic public health mission to safeguard and promote the health of people of America. The Centre for Biologics Evaluation and Research (CBER) is one in all seven main centres for the US-FDA that is a part of the U.S. Department of Health and Human Services. CBER is liable for assuring the safety, purity, potency, and efficacy of biologics and other related products as well. Not all biologics are being regulated by CBER. Monoclonal antibodies and different therapeutic proteins are being regulated by the FDA Centre for Drug Evaluation and Research (CDER) [1].

The development, introduction and widespread use of vaccines in industrialized and developing countries have resulted in right smart progress against a number of the foremost devastating of human diseases. In fact, the world's only complete victory over an infectious disease resulted from a vaccine. New, safe and effective vaccines are being introduced and authorized within the market annually, therefore it is vital to include them in the official immunization schedule. To incorporate vaccines into immunization schedule USA follows guidelines as per US FDA [2].

As per the US-FDA, vaccines are unconditionally placed beneath the category of Biologics and hence, the CBER is the agency liable for guaranteeing the strength, purity, and effectiveness of manufactured vaccines within United States.

2. CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER)

The Centre for Biologics Evaluation and Research (CBER) of the US-FDA is the national administrative unit within United States. CBER is liable for the scientific review of license applications for brand new biologics, together with vaccines. CBER examines new biologics submitted by vaccine manufacturers for safety and effectiveness, additionally as method consistency and regulative compliance. Additionally, to its role in licensing vaccines and facilities that manufacture vaccines, CBER has active laboratory analysis and post-marketing surveillance programs that complement and support its regulative activities. CBER additionally works closely with scientific committees at the World Health Organization (WHO) and is functioning towards bigger international harmonization of vaccine standards [2].

The development of vaccines is a complex process, and each step within the life cycle from testing of materials used for production to post-licensure lot-release testing is subject to rigorous oversight by CBER. After licensure, CBER continues to manage the assembly and performance of vaccines to confirm the continued safety and efficacy aspects [3].
I. Regulations, Legislation and Guidance documents

Table 1. Regulations and Acts relevant to Vaccine development process [4]

<table>
<thead>
<tr>
<th>Title 21 CFR</th>
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<tr>
<td>21 CFR 600-680: Biological product standards</td>
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<td>21 CFR 314 (21 CFR 601.25[d] [2], specific biological): Adequate and well-controlled trials.</td>
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<tr>
<td>21 CFR 312: Investigational new drug application</td>
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<td>21 CFR 210-211: Good Manufacturing Practices</td>
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<td>21 CFR 58: Good Laboratory practices</td>
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<td>21 CFR 56: Institutional review boards</td>
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<td>21 CFR 50: Protection of human subjects</td>
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Guidance documents describe FDA’s interpretation of our policy on a regulatory issue (21 CFR 10.115(b)). These documents usually discuss more specific products or issues that relate to the design, production, labeling, promotion, manufacturing, and testing of regulated products. Guidance documents may also relate to the processing, content, and evaluation or approval of submissions as well as to inspection and enforcement policies. Guidance documents are not regulations and alternative approaches may be chosen to comply with laws and regulations.

II. Federal laws and regulations:

The legislation of vaccines within the United States has undergone considerable evolution over the years to stay in-tuned with advances achieved by the scientific community. Acts like Prescription Drug User Fee Act, 1992 (PDUFA) and therefore the FDA Modernization Act, 1997 has provided CBER to facilitate vaccine review processes and finally to release safe and effective vaccines to the market.

2.1 Prescription Drug User Fee Act of 1992

The Prescription Drug User Fee Act (PDUFA) was enacted in the year 1992. This granted the FDA authority to assemble user fees from manufacturers to accelerate the review of drug and biological applications and post-marketing drug safety activities in accordance with performance goals developed by the USFDA. The legislation was later reauthorized in 1997 (PDUFA II), 2002 (PDUFA III), and 2007 (PDUFA IV). In addition, to reauthorizing and supplementing the PDUFA, the new law provided the FDA with new funding to assemble, develop, and review safety information and develop adverse-event-surveillance systems and analytical tools.

2.2 FDA Modernization Act of 1997

The FDA Modernization Act (FDAMA) of 1997 revived PDUFA user fees and performance goals and provided further funding to support drug premarket review activities. The FDAMA enclosed measures to modernize the regulation of biological product by synchronizing their review method therewith of medication and eliminating the necessity for an establishment license for biologicals. Expedited approval mechanisms for dangerous conditions were licensed similarly because the use of surrogate finish points in clinical trials. The FDAMA conjointly enclosed a paediatrics exclusivity provision that granted 6 months of market exclusivity to sponsors who conducted paediatric studies on the active ingredients of their medicine at the request of the FDA. In 2002, the terms of this provision were reauthorized within the Best Pharmaceuticals for Children Act. Additionally, the law provides for a distended info on clinical trials, which can be accessible by patients. With the sponsor’s consent, the outcomes of such clinical trials were enclosed in the database.

2.3 Food and Drug Administration Amendments Act of 2007

The Food and Drug Administration Amendments Act (FDAAA) of 2007 provided vital reform to the regulation of medication and biologics. It in
addition mandated that merchandise for post-
approval Risk Evaluation and mitigation strategy
(REMS) which is required to possess the REMS
submitted to their license application. 
Additionally, to reauthorizing and increasing the
PDUFA, the new law provided the FDA with new
funding to gather, develop, and review safety
data and develop adverse-event–surveillance
systems and analytic tools [4].

III. Regulatory aspects:

Vaccine development and commercialization
is a complicated process. Before a novel vaccine
is approved for marketing, a demanding
regulatory procedure to assess quality, efficacy
and safety must be undertaken. The CBER
provides regulatory guidance to sponsors
throughout vaccine development through a
managed review method that encompasses the
life cycle of development. Various regulatory
guidelines for registration of vaccines within US
are:

- Centre for Biologics Evaluation and
  Research (CBER)
- Biologics License Application (BLA)
- Vaccines and Related Biological Products
  Advisory Committee (VRBPAC)
- Vaccine adverse event reporting system
  (VAERS) [4].

Preclinical evaluation:

Preclinical Testing Sponsors typically should
conduct pharmacodynamics (PD) studies like in
vitro binding assays and in vivo studies that
assess the product’s pharmacological activity
and outline its mechanism of action. Biologics
usually endure single-dose and repeat-dose
toxicity studies using relevant species, as noted
earlier. Safety medicine studies, that evaluate the
product’s practical effects on major body systems
and specific organs, and local tolerance testing
will be done singly or subsumed in toxicity
testing. This data is employed to predict margins
of safety for human studies, preclinical studies
ought to be decent to rule out explicit toxicity and
establish potential toxic effects which may occur
throughout the clinical trial. Many vaccines never
progress beyond this stage as they fail to
produce the desired immune reaction. The pre-
clinical stage sometimes last for 1-2 years and
regularly involves researchers in private industry.
Sufficient preclinical data should be provided to
the CBER in the investigational new drug (IND)
application to form a determination that it’s
moderately safe to proceed with the clinical
investigation [5,6].

Pre-IND stage:

The pre-IND phase primarily comprises of
laboratory development and testing of candidate
vaccines and development of the manufacturing
process. Sponsors are inspired to fulfill with
CBER reviewers for a pre-IND meeting to
discuss preclinical studies, clinical study design,
information needs and other scientific problems
that require solution before the initiation of
clinical trials. Procedures and policies for the
conduct of conferences with the CBER are
summarized within the FDA guidance document.

Investigational new drug stage:

The clinical development of a novel innovative
vaccine begins with the sponsor requesting
permission to initiate the conduct of a clinical
study with an investigational product through the
submission of IND application. Title 21 CFR 312
describes the content of original IND submission
and therefore the regulatory requirements for
conduct of clinical trials beneath the IND
regulations. The IND submission describes the
vaccine, its manufacture, control testing for
unleash of the vaccine, the planned scientific
explanation, obtainable preclinical animal safety
testing results, and a proposed clinical study
protocol.

Clinical development phase:

Phase I studies are designed to assess vaccine
safety and tolerability and to come up with
preliminary immunogenicity information and
register between 20-100 subjects. Phase II
studies which generally enroll several hundred
subjects to evaluate the immunogenicity of the
vaccine and supply preliminary estimates on
rates of common adverse events. Phase II
studies are typically designed to generate data to
inform the conduct of design of phase III studies.
Sponsors are encouraged to meet the CBER at
the end-of-phase-II meeting to discuss their
proposed phase III study. The phase III clinical
trial provides the important documentation of the
vaccine’s safety and effectiveness needed to
evaluate the risk/benefit relationship of the drug
and to support licensure and generally enroll
several thousand subjects. Manufacturing
reproducibility is generally addressed during the
phase III trial by evaluation of lot consistency and
ensuring process validation. The general
considerations for clinical trial studies to support vaccine licensure include safety, efficacy, and immunogenicity. Ideally, effectiveness ought to be incontestable in randomized, double-blind, well-controlled studies [6].

IV. Regulatory Review and Approval Procedures

After the thriving accomplishment of phase three clinical trial, the Biologics License Application (BLA) ought to be submitted to FDA. The multidisciplinary office reviewer team later evaluate the safety and efficacy information on the basis of proposed risk and benefit for disapproval or approval of the vaccine.

Biologics License Applications (BLA):

The Biologics License Application (BLA) is a request for grant of permission to introduce or deliver for introduction, a biological product into interstate commerce (21 CFR 601.2). The BLA is regulated beneath 21 CFR 600 – 680. A BLA can be submitted by any legal person or entity who is engaged in manufacture or a person for a license who takes responsibility for compliance with product and institution standards.

Form FDA 356h is the application to market and promote a new biologic for use in humans. The Form FDA 356h comprises of following information:

- An outline of information submitted as a part of the appliance.
- Information on the person submitting the biologics license application.
- A preclinical information section.
- A clinical data section that has safety and efficacy information on the product.
- Draft labelling of the product to be commissioned.
- Data on chemistry, manufacturing, and controls of the product
- A data summary of validation of vital processes and assays concerned within the manufacture of the product.
- A description on facility where the product is manufactured.
- Case report form tabulations on the manufacturer's clinical expertise with the product.
- Case report forms and serious event narratives.
- An index

The information on the chemistry, manufacturing and controls ought to conjointly contain copies of vital standard operating procedures associated with the manufacture of the drug. In some cases, manufacturers are needed to submit data concerning whether they are ready for a scrutiny by the FDA [7].

V. Licensure phase:

After a sponsor submits a BLA, the agency assembles a multidisciplinary review team comprising reviewers that specialize in varied disciplines, like clinical and toxicology issues. The FDA then decides, within the first 60 days a requirement to allow a substantive review. The FDA might issue a refuse-to-file call if the BLA does not meet this threshold. During the filing period, the FDA will also decide whether or not to designate the Biologics License Application as a ‘standard’ or ‘priority’ application. For CBER-regulated applications, ‘priority’ refers to that the biologics would represent a significant improvement within the safety or effectiveness of prevention, diagnosis and treatment of serious or life-threatening disease.

After FDA has begun substantive review of the BLA, reviewers might issue information request (IR) and discipline review (DR) letters to the person. IR letters ask specific information while review is in progress. Reviewers issue DR letters at the end of a specific discipline review to convey early thoughts on doable deficiencies. These letters do not essentially replicate the input of the supervisors. IR and DR letters do not stop the review clock. Applicants may reply to IR and DR letters with additional information. Therefore, this kind of submission would possibly represent a major amendment to the application; if so, the FDA would possibly extend the PDUFA goal date.

Next, FDA would possibly request for an advisory committee’s (ACIPs) advice on the application. By statute, the FDA should refer an original BLA to ACIP or explain in the action letter for the application, reason why that step was not taken. The FDA typically requests the federal advisory committee to address specific queries and vote on the answers, but the ACIPs advice does not bind the FDA.

After the agency completes its review process of the BLA, it’ll issue an approval letter or complete response letter (CRL) which states that the agency cannot approve the BLA in its current
form. A CRL lists known deficiencies and later recommends sponsor to take actions to place the BLA in a position for approval. An applicant might file a ‘resubmission’ to deal with the deficiencies. The review timeline for a resubmission depends on its content however is either 2 or 6 months from receipt. An applicant can also request resolution of any dispute regarding the CRL. If the FDA denies approval of the application, the applicant might request, and therefore the Commissioner should issue, a notice of chance for hearing [6,7].

The Advisory Committee on Immunization Practices (ACIP) is chartered as a federal advisory committee that produces recommendations for the utilization of FDA-licensed vaccines to the director of the Centres for Disease Control and Prevention (CDC). ACIP recommendations are what suppliers typically use to decide that vaccines ought to be administered to that people. ACIP recommendations can be made after review of data that were not considered by the FDA, including illness burden, public health impact, cost-effectiveness, and other information not contained within the BLA submitted to the FDA by the vaccine manufacturer [8].

On completion of FDA's review, the sponsor and therefore the FDA will have to produce their findings one by one to the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). The committee's recommendations are strongly considered in the CBER's call to license a vaccine. The committee might suggest that additional studies be performed before licensure [9].

Vaccine and Related Biological Product Advisory Committee (VRBPAC):

The VRBPAC is a standing FDA advisory committee composed of scientific consultants and clinicians, client representatives, and a non-voting member from industry. The Committee reviews and evaluates information regarding the security, effectiveness, and applicable use of vaccines and related biological products that are meant to be used in the prevention, identification or diagnosis of human diseases and as required, any other products for which the Food and Drug Administration has regulatory responsibility. The Committee additionally considers that as required, any other products for which the Food and Drug Administration has regulatory responsibility that provides scientific support for the regulation of those products and makes applicable recommendations to the Commissioner of Food and Drugs [10].

VI. Post-licensure Phase:

Lot-release testing:

Vaccine production depends on living microorganisms and there are several points throughout the manufacturing method to introduce contaminants. Regulatory needs mandate that all licensed vaccines undergo appropriate lot testing before the release to market. Requirements for release testing of authorized vaccines can be found in Title 21 CFR 610. The tests embody those for microorganism and fungal sterility, general safety, purity, identity, suitableness of constituent material and potency. Depending on the product, extra testing (to confirm adequate inactivation) could also be needed. Additionally, constituent materials like diluents and preservatives should meet standards for sterility [11].

Facility Inspection:

After licensure, observance and monitoring of the vaccine and production activities, as well as periodic facility inspections should continue as long the manufacturer holds a license for the product. Licensed institutions are inspected a minimum of each two years aside from those facilities that manufactures influenza vaccines. These institutions are inspected annually. The aim of the review is to determine if the licensed vaccines are manufactured and tested as delineated within the license application and in accordance with applicable rules. Manufacturers that fail to fulfill product standards or do not comply with cGMP’s might have their licenses suspended or revoked, betting on the character of the inspectional finding.

FDA approval for licensure relies on,

1) A satisfactory review of all information indicating that the product is safe and effective for its meant use.
2) Review and acceptance of the manufacturer’s labelling.
3) A satisfactory review of manufacturer’s protocols that summarize the manufacturing and testing on a specified number of vaccines lots to ascertain the consistency of the method.
4) Confirmatory testing by CBER on product samples received from the manufacturer
5) A satisfactory FDA review of the manufacturer’s vaccine production facilities [11].

After the vaccines are released into market, they are monitored and observed closely in individuals who are administered with the vaccine. The main aim of this is to look for any serious adverse events. There are a number of systems which monitors vaccine once they are approved.

1) Vaccine Adverse Event Reporting System (VAERS): [12,13]

The VAERS is national safety surveillance program that is formed as a consequence of the National Childhood Vaccine Injury Act (NCVIA) of 1986 and administered by the Food and Drug Administration (FDA) and centres for Disease Control and Prevention (CDC).

VAERS receives reports of adverse reactions and events that occurs following vaccination. Healthcare professionals, vaccine manufacturers, and therefore the public can submit reports to VAERS. While very important in monitoring vaccine safety, VAERS reports alone cannot be used to determine if a vaccine caused or contributed to an adverse event or illness. The reports may contain information that is inaccurate, incomplete, unverifiable or coincidental. Most reports to VAERS are voluntary, which suggests they are subject to biases. Data from VAERS reports should always be interpreted with these limitations in mind.

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![Flowchart](image)

**Fig. 1.** Post-licensure: Vaccine safety monitoring
The advantage of VAERS is that it can quickly provide an early warning of any problem relating to the safety of a vaccine. VAERS is designed to rapidly detect unexpected or unusual patterns of adverse events, also known as the safety signals. If there is a safety signal found in VAERS, further studies can be done in safety systems such as the CDC’s Vaccine Safety Datalink (VSD) or the Clinical Immunization Safety Assessment (CISA) project. These systems do not have similar limitations as that of VAERS, and possess to have a better potential to assess health risks and possible link or relationship between adverse events and a vaccine [14].

Fig. 2. Vaccine adverse event reporting system
2) Vaccine safety Datalink (VSD):

The Vaccine Safety Datalink is a central database that was established by the CDC in 1990. The VSD uses electronic health data from every participating site. This includes data on vaccines: the sort of vaccine given to every patient, date of vaccination, and alternative vaccinations given on a similar day. The VSD additionally uses data on medical illnesses that are diagnosed at doctors’ offices, urgent care visits, emergency department visits and hospital stay. The VSD conducts vaccine safety studies based on queries or considerations raised from the medical literature and reports to the Vaccine Adverse Event Reporting System (VAERS). Once there are new vaccines that are counselled to be used in or if there are any changes in how a vaccine is recommended, the VSD can monitor the safety of these vaccines [15].

3) Post-License Rapid Immunization Safety Monitoring (PRISM):

The Post-License rapid immunization Safety monitoring (PRISM) program is the immunization safety monitoring element of FDA’s Mini-Sentinel project, a program to actively monitor the safety of vaccines using electronic health data. Scientists use PRISM to actively monitor and assess information from a representative set of the general population. FDA wanted to assess the surveillance capabilities of this massive claims-based distributed database for information safety surveillance by characterizing the underlying data [16].

4) Clinical Safety Immunization Safety Assessment (CISA):

CDC’s Clinical Immunization Safety Assessment (CISA) Project was established in the year 2001 to handle the unmet vaccine safety clinical research wants of United States. CISA is a national network of vaccine safety specialists from the CDC’s immunization Safety office (ISO), seven medical research centers, and alternative partners, which provides a comprehensive vaccine safety public health service to the nation. Vaccine safety specialists conduct individual case reviews and clinical analysis studies concerning vaccine safety [17].

3. CONCLUSION

Today, a colossal variety of vaccines are being developed and marketed by manufacturers within the United States and these vaccines are being employed by large population to prevent contagious and severe diseases. The primary responsibility here is to make sure the quality, safety, and effectiveness of vaccines are not compromised. The implementation of a powerful regulatory system can facilitate these goals, which are particularly vital for vaccines that are inherently tougher to develop, characterize, and manufacture than most pharmaceutical products. CBER and FDA are operating indefatigably to place forward rigorous laws for vaccine licenses to be approved and to make sure that vaccine safety is examined regularly post approval, whereas on the opposite hand, researchers area unit permanent by all ethics and laws put forward by the authorities, thereby guaranteeing the availability of safe and effective vaccines within the market. In addition, post-marketing surveillance of vaccines is closely examined by the Center for Disease Control and Prevention (CDC) and also the FDA through Vaccine Adverse Event Reporting System (VAERS).

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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