



Vaccine Regulation, Licensing and Approval in USA

S. Shashank^a and M. P. Venkatesh^{a*}

^a *Pharmaceutical Regulatory Affairs Group, Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Sri Shivarathreeshwara Nagara, Mysuru – 570015, Karnataka, India.*

Authors' contributions

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

Article Information

DOI: 10.9734/JPRI/2021/v33i60A34530

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/77635>

Review Article

Received 01 October 2021
Accepted 06 December 2021
Published 20 December 2021

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.

Associate Professor;

*Corresponding author: E-mail: venkateshmpv@jssuni.edu.in;

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]

•	Public Health Service Act (42 USC 262-63) sec. 351
•	Food, Drug and Cosmetic Act (21 USC 301-392)
•	Food and Drug Agency Modernization Act (FDAMA) of 1997
•	Food and Drug Agency Amendments Act (FDAAA) of 2007
Title 21 CFR	
•	21 CFR 600-680: Biological product standards
•	21 CFR 314 (21 CFR 601.25[d] [2], specific biological): Adequate and well-controlled trials.
•	21 CFR 312: Investigational new drug application
•	21 CFR 210-211: Good Manufacturing Practices
•	21 CFR 58: Good Laboratory practices
•	21 CFR 56: Institutional review boards
•	21 CFR 50: Protection of human subjects

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 fulfil 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, suitability 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].

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).

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.

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.

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

The VAERS is national safety surveillance program that is formed as a consequence of the

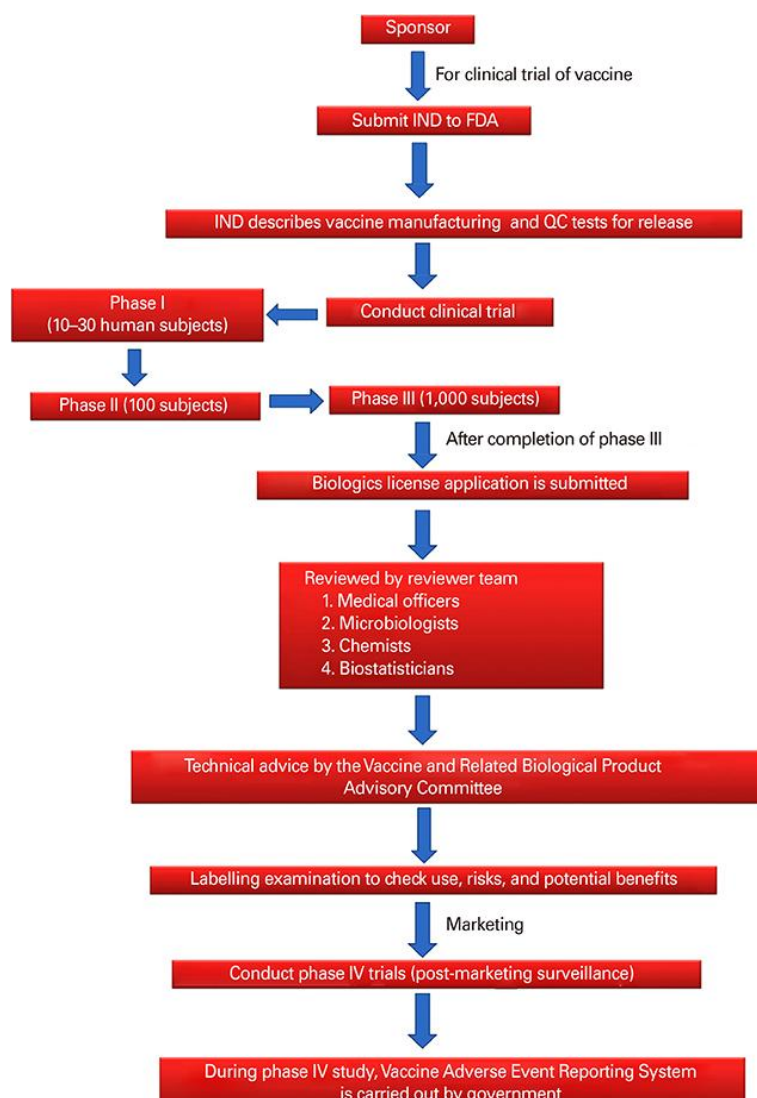


Fig. 1. Post-licensure: Vaccine safety monitoring

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].

VAERS Vaccine Adverse Event Reporting System
www.vaers.hhs.gov

Adverse events are possible reactions or problems that occur during or after vaccination. Items 2, 3, 4, 5, 6, 17, 18 and 21 are **ESSENTIAL** and should be completed. Patient identity is kept confidential. Instructions are provided on the last two pages.

INFORMATION ABOUT THE PATIENT WHO RECEIVED THE VACCINE (Use Continuation Page if needed)

<p>1. Patient name: (first) _____ (last) _____</p> <p>Street address: _____</p> <p>City: _____ State: _____ County: _____</p> <p>ZIP code: _____ Phone: _____ Email: _____</p> <p>2. Date of birth: (mm/dd/yyyy) _____ 3. Sex: <input type="checkbox"/> Male <input type="checkbox"/> Female <input type="checkbox"/> Unknown</p> <p>4. Date and time of vaccination: (mm/dd/yyyy) _____ Time: _____ AM <input type="checkbox"/> PM <input type="checkbox"/></p> <p>5. Date and time adverse event started: (mm/dd/yyyy) _____ Time: _____ AM <input type="checkbox"/> PM <input type="checkbox"/></p> <p>6. Age at vaccination: _____ Years _____ Months 7. Today's date: (mm/dd/yyyy) _____</p> <p>8. Pregnant at time of vaccination?: <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown (If yes, describe the event, any pregnancy complications, and estimated due date if known in item 18)</p>	<p>9. Prescriptions, over-the-counter medications, dietary supplements, or herbal remedies being taken at the time of vaccination: _____</p> <p>10. Allergies to medications, food, or other products: _____</p> <p>11. Other illnesses at the time of vaccination and up to one month prior: _____</p> <p>12. Chronic or long-standing health conditions: _____</p>
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INFORMATION ABOUT THE PERSON COMPLETING THIS FORM

13. Form completed by: (name) _____

Relation to patient: Healthcare professional(staff) Patient (yourself)
 Parent/guardian(caregiver) Other: _____

Street address: _____ Check if same as item 1

City: _____ State: _____ ZIP code: _____

Phone: _____ Email: _____

14. Best doctor/healthcare professional to contact about the adverse event: Name: _____ Phone: _____ Ext: _____

INFORMATION ABOUT THE FACILITY WHERE VACCINE WAS GIVEN

15. Facility/clinic name: _____

Fax: _____

Street address: _____ Check if same as item 13

City: _____

State: _____ ZIP code: _____

Phone: _____

16. Type of facility: (Check one)

Doctor's office, urgent care, or hospital

Pharmacy or store

Workplace clinic

Public health clinic

Nursing home or senior living facility

School or student health clinic

Other: _____

Unknown

WHICH VACCINES WERE GIVEN? WHAT HAPPENED TO THE PATIENT?

<p>17. Enter all vaccines given on the date listed in item 4: (Route is HOW vaccine was given, Body site is WHERE vaccine was given) Use Continuation Page if needed</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 30%;">Vaccine (type and brand name)</th> <th style="width: 15%;">Manufacturer</th> <th style="width: 10%;">Lot number</th> <th style="width: 10%;">Route</th> <th style="width: 10%;">Body site</th> <th style="width: 10%;">Dose number in series</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table> <p>18. Describe the adverse event(s), treatment, and outcome(s), if any: (symptoms, signs, time course, etc.) _____</p> <p>19. Medical tests and laboratory results related to the adverse event(s): (include dates) _____</p> <p>20. Has the patient recovered from the adverse event(s)?: <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown</p>	Vaccine (type and brand name)	Manufacturer	Lot number	Route	Body site	Dose number in series																			<p>21. Result or outcome of adverse event(s): (Check all that apply)</p> <p><input type="checkbox"/> Doctor or other healthcare professional office/clinic visit</p> <p><input type="checkbox"/> Emergency room/department or urgent care</p> <p><input type="checkbox"/> Hospitalization: (Number of days (if known)) _____ Hospital name: _____ City: _____ State: _____</p> <p><input type="checkbox"/> Prolongation of existing hospitalization (vaccine received during existing hospitalization)</p> <p><input type="checkbox"/> Life threatening illness (immediate risk of death from the event)</p> <p><input type="checkbox"/> Disability or permanent damage</p> <p><input type="checkbox"/> Patient died - Date of death: (mm/dd/yyyy) _____</p> <p><input type="checkbox"/> Congenital anomaly or birth defect</p> <p><input type="checkbox"/> None of the above</p>
Vaccine (type and brand name)	Manufacturer	Lot number	Route	Body site	Dose number in series																				

ADDITIONAL INFORMATION

<p>22. Any other vaccines received within one month prior to the date listed in item 4: Use Continuation Page if needed</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 30%;">Vaccine (type and brand name)</th> <th style="width: 15%;">Manufacturer</th> <th style="width: 10%;">Lot number</th> <th style="width: 10%;">Route</th> <th style="width: 10%;">Body site</th> <th style="width: 10%;">Dose number in series</th> <th style="width: 10%;">Date Given</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table> <p>23. Has the patient ever had an adverse event following any previous vaccine?: If yes, describe adverse event, patient age at vaccination, vaccination dates, vaccine type, and brand name <input type="checkbox"/> No <input type="checkbox"/> Unknown</p>	Vaccine (type and brand name)	Manufacturer	Lot number	Route	Body site	Dose number in series	Date Given															<p>24. Patient's race: <input type="checkbox"/> American Indian or Alaska Native <input type="checkbox"/> Asian <input type="checkbox"/> Black or African American <input type="checkbox"/> Native Hawaiian or Other Pacific Islander (Check all that apply) <input type="checkbox"/> White <input type="checkbox"/> Unknown <input type="checkbox"/> Other: _____</p> <p>25. Patient's ethnicity: <input type="checkbox"/> Hispanic or Latino <input type="checkbox"/> Not Hispanic or Latino <input type="checkbox"/> Unknown</p> <p>26. Immuniz. proj. report number: (Health Dept use only) _____</p>
Vaccine (type and brand name)	Manufacturer	Lot number	Route	Body site	Dose number in series	Date Given																

COMPLETE ONLY FOR U.S. MILITARY/DEPARTMENT OF DEFENSE (DoD) RELATED REPORTS

27. Status at vaccination: <input type="checkbox"/> Active duty <input type="checkbox"/> Reserve <input type="checkbox"/> National Guard <input type="checkbox"/> Beneficiary <input type="checkbox"/> Other: _____	28. Vaccinated at Military/DoD site: <input type="checkbox"/> Yes <input type="checkbox"/> No
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FORM FDA VAERS 2.0 (03/21)

SAVE

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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