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Vaccines in the United States: a systematic review on history of evolution, regulations, licensing, and future challenges

Vaccines are credited with reducing or effectively eradicating a number of infectious diseases such as smallpox, measles, and diphtheria. Particularly in nations like the United States, where a large number of infectious diseases were prevalent, vaccines proved to be timely interventions. The approval procedure for vaccines in the United States is regulated by the Center for Biologics Evaluation and Research. Vaccine development is often found to be demanding and requires astute knowledge and understanding of recent developments by physicians and researchers to ensure that effective vaccines are made available to the masses with minimum risk. This article aims to illustrate the regulatory scenario with regards to vaccine development and licensure in the United States with a brief look at the origin of vaccines and their regulations in the nation. Also, it details the challenges faced by the United States vaccine industry to remain relevant in today's constantly evolving world.

Keywords: Vaccine, Center for Biologics Evaluation and Research, Prescription Drug User Fee Act, Vaccine Adverse Event Reporting System, Centers for Disease Control and Prevention

Introduction

Vaccination is regarded as one of the most significant triumphs for mankind in the 20th century. In terms of sheer importance, it is considered to be on par with some of the major discoveries in the medical science field such as the advancement in cancer therapy and the development of antibiotics. Progress, especially in terms of multidisciplinary knowledge, as well as a substantial inflow in funding, have facilitated the development of a wide variety of vaccines and thereby, ushered in the most prosperous period of vaccine development.

Vaccines are a novel class of pharmaceuticals that are aimed at improving immunity to a particular disease. Conventionally, they are made of weakened or killed forms of disease-causing microbes, their toxins or one of their surface proteins. They enable the body to make highly specific antibodies by engaging the adaptive immune systems and through means of immunological memory against prospective infections that may occur in the future [1]. To induce resistance or immunological protection, a vaccine most often contains an attenuated form of the microbe, which is essential to ensure that the pathogen present in the vaccine is not capable of effecting infections in the individual, whilst being adequately efficient for the immune system to recognize them as foreign substances.

The United States of America was one of the pioneering nations to conceptualize and implement a robust immunization system that helped the nation tackle major epidemics such as the smallpox epidemic, the polio epidemic of 1952, and the second measles outbreak from 1981–1991. Today, the US vaccine market has grown into a massive US dollar (USD) 17.4 billion industry and is set to surpass USD 21 billion threshold by 2025. Further, it is expected to continue this tremendous growth due to a rising number of infectious diseases in human beings as well as animals [2].

History of Vaccines Evolution in the United States

The development and use of vaccines in the United States date back to the early 1900s when several epidemics such as the plague, typhoid, and rabies were prevalent among the masses. A significant proportion of the public was infected by these diseases which prompted the research community to intensify their efforts and come up with adequate vaccines to tackle these epidemics. However, the intensification of research efforts, whilst being a boon, also proved to be a bane as it became evident that vaccines were being produced without the conduct of satisfactory safety tests which resulted in a number of devastating tragedies, one of which was the equine-derived diphtheria antitoxin episode of 1901 where more than 20 children became ill and around 14 children died. This triggered the authorities to introduce formal regulations for the development of vaccines following which the US Congress passed the Biologics Control Act on July 1st, 1902 and the Virus-Toxin Law, both of which aimed at guaranteeing the safety and quality of vaccine products. Subsequently, the Pure Food and Drug Act, 1906 and the Federal Food Drug and Cosmetic Act, 1938 were implemented. In the year 1954, The Division of Biologics was formed as an independent authority, to monitor vaccine safety during development and post-marketing, which was later renamed as the Bureau of Biologics and integrated into the Food and Drug Administration (FDA). Today, the Bureau of Biologics is known as the Center for Biologics Evaluation and Research (CBER) [3].

Regulations and Legislations

As per the US FDA, vaccines are categorically placed under the class of Biologics and hence, the CBER is the agency responsible for ensuring the strength, purity, and efficacy of

vaccines manufactured and marketed in the United States. In addition to the aforementioned responsibility, the CBER is also authorized to facilitate the development and approval of vaccines. This includes the review of dossier submissions for vaccine registration and marketing, which predominantly happens in the CBER's Office of Vaccine Research, and Review, Office of Biostatistics and Epidemiology and the Office of Compliance and Biologics Quality. The CBER follows a single set of criteria for approving vaccines irrespective of the technology employed in their production. The criteria have been established based on particular sections of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Section 351 of the Public Health Service Act (PHS Act). Since the legal definition of a "vaccine" is in agreement with that of a "drug" as per the FD&C Act, vaccine manufacturers are also required to comply with the current Good Manufacturing Practice (cGMP) regulations as specified in 21 Code of Federal Regulations (CFR) Part 210 and 211. Essentially, the regulations applicable to vaccines such as the labeling requirements, protection of clinical trial subjects, institutional review boards, and preclinical studies, under the PHS Act, can be found in 21 CFR Parts 600 through 680 [4].

The legislation of vaccines in the United States has undergone considerable evolution over the years to keep in touch with advances achieved by the scientific community. Acts such as the Prescription Drug User Fee Act, 1992 (PDUFA) and the FDA Modernization Act, 1997 were implemented and amended periodically in order to acknowledge the changes in technology, trade, and public health concerns brought about by the advent of the 21st century. While the PDUFA in 1992 was aimed at granting manufacturers the opportunity to accelerate the review process of products, the subsequent amendments provided the FDA with new funding to collect, assess and approve safety data and develop a robust adverse event surveillance system. On the other hand, the FDA Modernization Act, 1997 modernized the regulations for vaccines by synchronizing the procedures for review of vaccines and other biologicals with that of drugs in general, thereby effectively eradicating the need for an establishment license for biological products. Most recently, the Food and Drug Administration Amendments Act (FDAAA), 2007 brought about substantial reforms to the legislation of drugs and biological products including vaccines. Firstly, the FDAAA decreed that products which required a post-approval Risk Evaluation and Mitigation Strategy to submit the same to the approval application. It also reauthorized the Best Pharmaceuticals for Chil-

dren Act along with the recommissioning of the Pediatric Research Equity Act [5].

Regulations and legislations factor in almost every facet of vaccine development, manufacture, and approval. The entire operation, right from the development of vaccines to the approval and post-marketing surveillance, is a complex and long drawn out affair that requires substantial resources in the form of labor, skill, and funding.

The Licensure of Vaccines

At the outset, a multidisciplinary team is constituted, which is tasked with reviewing vaccine applications and other dossier submissions in accordance with the requisite PDUFA guidelines. This multidisciplinary team will comprise of a regulatory project manager, clinical officers, statisticians, product reviewers, pharmacologists, toxicologists, and other scientific experts from fields such as virology, bacteriology, immunology, etc. Since vaccine development follows a similar pathway as that of drugs and other biologics, the sponsor is required to submit an Investigational New Drug (IND) application to the FDA to initiate the clinical trials. Whilst submitting an IND application, the sponsor must provide data generated from animal testing carried out using the first prepared pilot lots. The IND will describe the vaccine, the procedure employed in its manufacture and the quality control data. Also, detailed specifications of the protocol for the proposed clinical trials to be conducted in human beings shall be included. The IND application will be reviewed through a 30-day period during which the FDA will consider whether the proposed vaccine poses any unjustifiable risks to the human subjects [6].

It should be noted that it is essential for manufacturers to meet the requirements specified under the cGMPs for facilities that produce vaccine lots. Although a manufacturing license does not specifically state that a manufacturing facility shall be compliant with the cGMPs, it is highly recommended as the compliance with cGMPs demonstrates total control over product components, equipment, manufacturing conditions, records, and personnel employed.

Pre-marketing vaccine trials essentially proceed in three phases, as is the case for most conventional drugs. The initial phase of studies, known as phase 1 studies, is conducted with an eye on obtaining satisfactory safety and immunogenicity data. This phase is generally carried out in a small population of closely monitored subjects. The second phase, more com-

monly known as phase 2 study, is a dose-ranging study and enlists the participation of several hundred subjects. Lastly, phase 3 studies are carried out in thousands of subjects to provide further assurance of the safety and efficacy of the vaccine being tested. If the FDA, at any point of the clinical studies, feels that the data submitted raises questions with regards to the safety and efficacy of the drug, then the sponsor may be requested by the FDA to conduct additional studies. If all the three phases of the vaccine clinical trials are successfully completed, the sponsor can proceed with the submission of a Biologics License Application (BLA) [7,8].

A BLA shall furnish all the specifications with regards to the safety and effectiveness of the vaccine and shall make an appropriate risk/benefit assessment. Simultaneously, the proposed site of manufacture of the vaccine will undergo pre-approval inspection by an FDA team. The 21 CFR, part 601 specifies the requirements for a vaccine to be approved under the conditions of accelerated approval. The following are the requirements: (1) Approval will be given on the basis of appropriate and well-controlled clinical trials that furnish evidence that the vaccine has an effect on a surrogate endpoint, to anticipate the clinical uses or based on the effect on a clinical endpoint apart from survival or irremediable morbidity. (2) Approval will be based on the fact that the sponsor will be willing to further carry out studies for the vaccine in order to substantiate and illustrate its clinical benefit when there is apprehension as to the correlation between the surrogate endpoint and the clinical benefit. (3) Usually, post-marketing studies will already be initiated at the time of approval. These studies shall be conducted under appropriate conditions with due diligence. The protocol of these studies shall be provided to the FDA along with the BLA [9].

On completion of FDA's review, the sponsor and the FDA will have to present their findings individually to the FDA's Vaccines and Related Biological Products Advisory Committee. The regulatory approval process for vaccines in the United States is depicted in Fig. 1.

Post-marketing Surveillance of Vaccines

Postmarketing surveillance is a crucial aspect of monitoring the safety of vaccines. The FDA continues to monitor vaccines post-approval, particularly through the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink [10].

VAERS is a national early warning system, operated by the

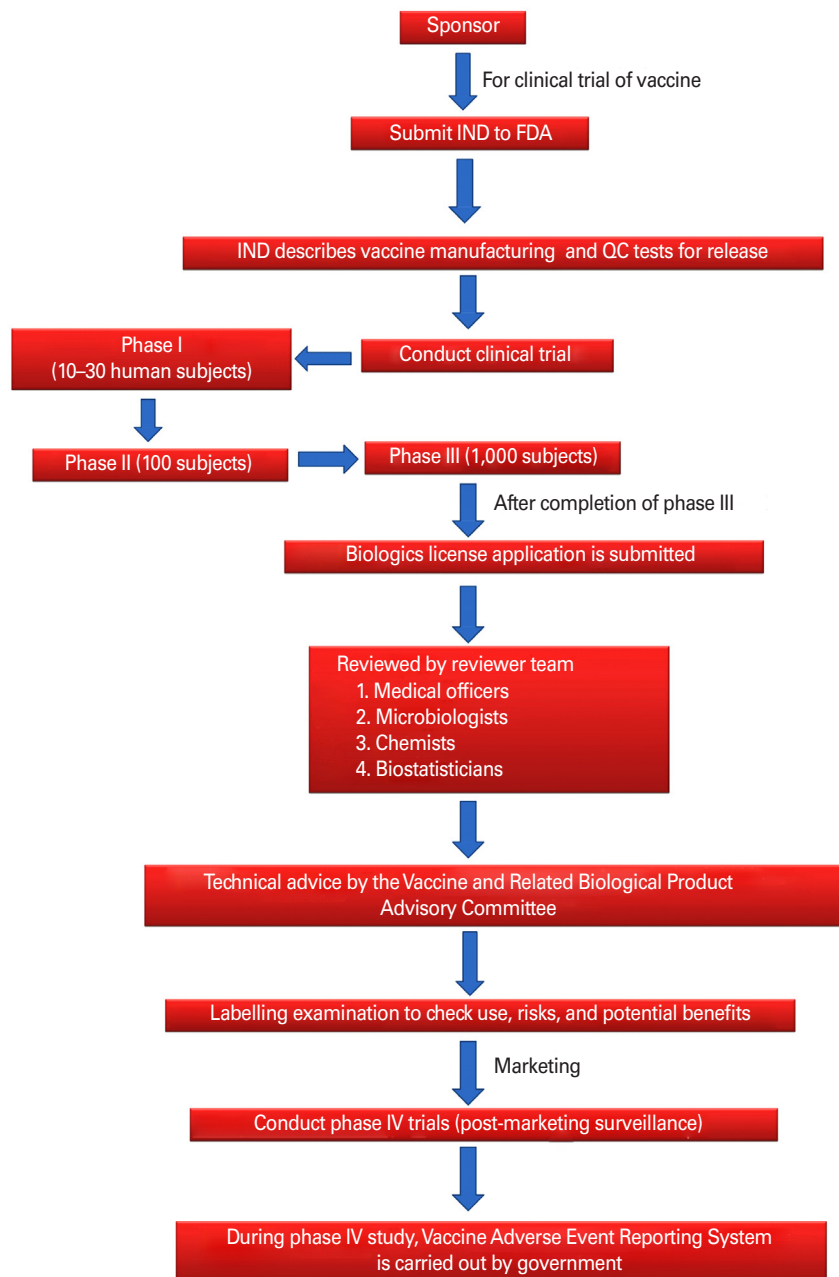


Fig. 1. The regulatory approval process for vaccines in the United States. IND, Investigational New Drug; FDA, Food and Drug Administration; QC, quality control.

Centers for Disease Control and Prevention (CDC) and the FDA, to discern probable safety issues in the US-approved vaccines. The primary aim of the VAERS is to detect any indication of adverse events affiliated with vaccines. Here, the reporting system is of a spontaneous, voluntary nature and hence, VAERS does not search for individuals who undergo the adverse event, rather it passively acquires information from individuals who decide to report. Anyone, from physicians to patients to the relatives of the patient, can report the adverse

event. Reporting is done directly or indirectly through manufacturers, who will, in turn, forward the same to the VAERS. The VAERS will accept reports of any adverse event that is possibly associated with US-approved vaccines and will use this data to survey vaccine safety. Post-reporting, the CDC will probe the event and try to ascertain whether the event was caused by the vaccine or not. Furthermore, the VAERS assimilated information is available online for the public to access, which provides a high level of transparency to the op-

erative procedure of VAERS [11,12].

On the other hand, the Vaccine Safety Data link is a central database that was established by the CDC in 1990. This database contains information and data collected from medical officers with regards to vaccines and vaccinations carried out amongst the masses. Members of the research community will have access to this data by having their studies approved by the CDC upon submission. However, a major issue plaguing the Vaccine Safety Database was the fact that the data is obtained from an actual population and not from randomized, controlled clinical trials. This makes the task of collecting and assessing data demanding. This problem, since, has been overcome to an extent by employing the Rapid Cycle Analysis program. This program supervises real-time data to examine the rate of adverse events in a population vaccinated in recent times. Since 2005, this system has been put into use to monitor new vaccines [13].

Future Challenges

In today's world, vaccines have firmly established themselves as an indispensable form of therapy in countering some of the most life-threatening infectious diseases known to man. However, vaccines continue to face a number of credible challenges with regards to the development of new vaccines, costs of production and marketability, and the emergence of the anti-vaccination movement. Some of the most significant challenges that vaccines encounter in the United States today are as documented below.

Elusive vaccines

A little more than 80 years since Edward Jenner's discovery of the smallpox vaccine, the scientific community has not succeeded in developing a number of spectacular vaccines. The most common examples being the malaria and human immunodeficiency virus (HIV) vaccines. Whilst a number of efforts have been made to develop vaccines to counter these diseases, successful results remain a distant dream, primarily due to the reason that causative parasites have demonstrated an extraordinary ability to become drug-resistant relatively quickly, thereby rendering them ineffective. Also, in the case of HIV, it has become increasingly difficult to initiate human vaccine trials due to changes in norms and regulations which have instated definite rules against human experimentation and abuse during trials [14,15].

Costs of production and profits

One of the biggest problems associated with vaccine development and production is the question of profits. When evaluating the market and the probable profits to be gained, it is not surprising to notice that high-income countries are able to generate more profits for the pharmaceutical companies as compared to low-income countries. In order to counter this particular problem, a tiered approach was recommended where the pricing would benefit all parties involved. It was suggested that by employing this approach, developing countries would benefit from the availability of vaccines that would otherwise be unavailable due to the prevalence of uniform prices, manufacturers would have increased revenue and thereby increased profits and the developed countries would have to pay a slightly lesser amount for the vaccines than in the case of the unavailability of low-income markets [16].

Also, pharmaceutical companies acknowledge the fact that the availability of cheap vaccines in developing countries represents a major risk to their interests in high-income countries through the possibility of "back-door entry" of cheaper vaccines. This issue becomes exponentially profound when comparatively assessing the limited time for which a patent applies and the protracted timescales involved in taking a vaccine from the developmental stages to the marketing approval [16].

Human challenge trials

Human challenge trials are trials where subjects are intentionally infected with an infectious organism. The organisms will closely resemble a wild pathogenic type, or an adapted, attenuated wild-type or a genetically modified organism. Although it is not essential to conduct human challenge trials for the development of every vaccine, there are several advantages to human challenge trials. Animal models are often found to be inaccurate in replicating the conditions that are reflected in human diseases and also several infectious disease vaccines may inherently be species-specific and therefore are unlikely to yield positive results when tested in animals. In such a scenario, human challenge trials become extremely essential. However, the question of safety and ethics always arises with respect to the conduct of trials in human subjects. Also, it should be noted that all diseases for which potential vaccines can be produced are not appropriate for the conduct of human challenge trials [17].

All human challenge trials are subjected to the most stringent ethical considerations and therefore it becomes the re-

sponsibility of investigators and the sponsors to ensure minimization of risk to subjects and to work within the regulatory framework to meet the aim and purpose of the study.

Anti-vaccination movement

Vaccines today are being criticized by a number of critics and skeptics and this has provided dishonest, corrupt researchers an opportunity to set into motion a chain of events that led to the inception of the anti-vaccination movement. This situation has further been intensified by parents who have long looked towards vaccine researchers for answers to the autism quandary and have now grown frustrated at the lack of results. Also, the advent of online blogging and journalism has led to people sharing false stories of vaccine horrors, thereby further spreading the flame of fear towards vaccines in the minds of the ordinary public. This difficulty has led to a situation where young children and infants may once again be exposed to the dangers of infectious diseases, although vaccines are readily available for the same [18].

Conclusion

Vaccines are essential tools in safeguarding public health from mortality and morbidity that arises from the prevalence of infectious diseases. Today, a vast number of vaccines are being developed and marketed by manufacturers in the United States, and these vaccines are being used by a large population. Numerous vaccines with major potential have been developed to prevent contagious and serious diseases. Vaccine development for emergent and re-emergent diseases is a critical issue that is being addressed actively by both researchers and regulators and, several initiatives are being undertaken by the FDA to encourage vaccine developers to work on diseases that do not yet have a treatment. CBER and FDA are working tirelessly to put forward stringent regulations for vaccine licenses to be approved and to ensure that vaccine safety is examined regularly post approval, while on the other hand, researchers are abiding by all ethics and regulations put forward by the authorities, thereby guaranteeing the availability of safe and effective vaccines in the market.

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