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# A Review of Quality Management of Vaccines by the Food & Drug Administration:

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**Abstract**

*The quality management of vaccines by the Food & Drug Administration (FDA) is vital to the success of any vaccine and the health of the U.S. population. While it is up to other companies to research, create, and test each vaccine themselves, these companies rely on approval from the FDA before they can realistically mass produce, ship, and provide their vaccines to the general public. Since these vaccines deal with highly contagious and often deadly viruses that have historically plagued the human population with death and long-term injuries, it is crucial that these vaccines be monitored and controlled to ensure the health and safety of the individuals who receive each vaccine. Before FDA approval can even be considered, companies must conduct thorough research and development (R&D), begin and complete multiple phases of clinical trials, and maintain rigorous documentation of the effects experienced by the recipients of vaccines during testing. Once a vaccine receives FDA approval, the vaccine must then be closely monitored for quality, safety, and efficacy, often by the use of algorithms and data collected over long-term studies. In the midst of the COVID-19 pandemic, the control and monitoring of vaccine quality management is crucial to combating the virus, as recipients must feel as though they can trust the FDA's judgement on the safety and efficacy of a vaccine produced on an accelerated timeline. Transparency in the FDA's quality management of the vaccine is also helpful in reassuring the public during the declared state of emergency by providing as much clarification as possible regarding the efficacy and potential long-term side effects as research in to the COVID-19 vaccine continues. Overall, the FDA relies heavily on the clinical trials to research and monitor the short-term and long-term efficacy and side effects of vaccines. These results provide the basis for the FDA's quality management for the approval process as well as the control and monitoring of vaccines once they are made available to the public.*

Keywords: Quality Management, Vaccines

## Background Information

The process of developing a vaccine in general is a long and rigorous process involving research and development, testing, and regulation, and can take place over the course of up to 10-15 years without mitigating circumstances [1]. However, historically the regulation portion of the

process began as vaccine development progressed, rather than occurring with the first several vaccines. In the early stages of vaccine development, there were no production regulations in place to ensure quality management and monitor the effects. It was not until 1902 that the United States Congress pass the Biologics Control Act as an effort to control the quality of drugs (and vaccines) produced and distributed [1]. By 1944, the United States Public Service Act was passed, requiring federal licenses for vaccines and, after an accident involving the poliovirus vaccine occurred in 1954, the Division of Biologics Standards (DBS) was formed and later known as the Bureau of Biologics as part of the Food & Drug Administration (FDA) [1]. The FDA is currently the United States' primary source of vaccine approvals due to their continued role of monitoring and controlling the quality of vaccines and their side effects. Outside of the United States, a committee known as the World Health Organizations is relied on internationally for vaccine guidance [1].

The research and production of vaccines is rooted in how vaccines function to prevent diseases. Once fully developed and introduced into the body, the vaccine mimics the virus of a particular disease, enabling the body's immune system to respond against the virus without the recipient technically contracting the disease [2]. Whether the vaccine used contains a weakened version of the virus or merely a portion of the virus, the outcome is the same: the body is exposed to the infection, or antigen, and learns to combat the true virus and prevent the disease from being contracted in the future [2].

In the early stages of vaccine development, the focus is on research, or research and development (R&D) [2]. This research is often federally funded, and laboratory based, lasting around 2-4 years, during which time scientists look for antigens that appear to prevent or combat against certain diseases [1]. Once the scientists find an antigen that shows significant potential, the research transitions to a pre-clinical stage involving testing the immune response in animals. This stage usually last at least 1-2 years and are supported by private companies, but most potential vaccines never progress beyond this stage due to a lack of positive results [1]. If the potential vaccine, or candidate vaccine does show promising results, the company sponsoring the vaccine applies to the FDA for an Investigational New Drug (IND) status. Once approved, the vaccine may then begin being used in a clinical trial [1]. The individual phases of a standard clinical trial are explained further in the next section.

**FDA Quality Management**

Vaccines are regulated similarly to other drugs, however the monitoring process which ensures quality can differ from non-vaccine drugs. The current monitoring system was developed during the 20th Century as procedures and regulation became more standardized [1]. In order for a vaccine to be approved by the U.S. Food and Drug Administration (FDA), several stages and trials have to be completed. In the United States, vaccines are required to undergo an exploratory stage and a pre-clinical stage. As stated previously, many potential vaccines never make it past the two-step stage process due to poor quality responses. However, if the experimental results and responses from the stage process are approved, the vaccine is subject to a sponsorship, which is usually a private company, and applied to the Investigational New Drug (IND) and FDA [3, 1]. This application is essentially documentation of the vaccine processes and protocols during the two-step stage process. If the application is approved, the vaccine can then move forward to the three phases of a clinical trial, which are used to access the safety, immunization scheduling, and method of delivery. During Phase I, this is the first attempt to assess the candidate vaccine in humans and involves a small group of adults, usually between 20-80 subjects, to determine the type and extent of immune response that the vaccine provokes [3, 1]. Phase II includes a larger group of testing participants who are considered to be more at risk, which is more of a study of the vaccine injection to analyze dosage amounts and delivery methods. If the vaccine reaches Phase III, which includes an even larger testing group (tens of thousands of people), overall safety is assessed. During this phase, a testing method is considered, and the trial size must consider any adverse event taking place relating to a candidate vaccine may occur. For example, if 1 of every 10,000 people are adversely affected, the trial would have to include 60,000 subjects, half of whom would be part of the control (or no vaccine) group, in order to adequately determine if the adverse effect may be considered a "low-frequency" event [3, 1]. Phase III not only tests a vaccine's safety, but the vaccine's efficacy as well, including factors such as disease prevention, immunity, and antibodies.

If the vaccine successfully passes Phase III, it can now submit a Biologics License Application to the FDA, which enables the labeling and mass production of the vaccine upon FDA approval [1]. Vaccine efficacy is dependent on the particular vaccine and is measured during the Phase III process. Particularly, a vaccine's efficacy is measured in a controlled clinical trial and is based on how many of the individuals who were vaccinated developed the 'outcome of interest' (usually disease) compared with how many people who received the placebo (or "dummy" vaccine)

developed the same outcome [4]. To monitor side effects of approved vaccines, the FDA and CDC established The Vaccine Adverse Event Reporting System (VAERS). VAERS is a voluntary reporting system used to determine if any adverse effects were caused by the vaccination. This is critical to the management of vaccine effects which effects how safe it is. While there are not many equations that are involved in the management of vaccines, algorithms are a tool used to determine who may receive initial access to the vaccine. However, just like the vaccine itself, the algorithms can vary from the federal, state, and local levels.

As part of the development process, scientists will use the Centers for Disease Control's (CDC's) Vaccine Safety Datalink (VSD). The VSD allows these scientists to determine if side effects detected during the clinical trials are, in fact, a result of the vaccination itself [5]. The VSD is not a specific organization or algorithm, but rather it is a network consisting of eight separate organizations within the United States [5]. Scientists working on the candidate vaccine use VSD in two ways, the first being the monitoring the possible correlation a patient's medical history and the side effect. The second method these scientists may use consist of a method known as Rapid Cycle Analysis (RCA), which continuously monitors the data provided to the VSD, which may also provide insight into possible correlations between patients with certain commonalities in their medical profile and the likelihood of experiencing the side effect [5]. Both methods have the same goal in mind in terms of monitoring the quality of candidate vaccines, but the RCA is a newer method which provides potentially faster results based on calculated data analysis [5].

**Relevance to Today**

These algorithms and how vaccines are approved or monitored today are particularly of interest given the past year and half in the world effected by the COVID-19 disease. The three current approved vaccines in the USA include the Pfizer, Moderna, and Johnson & Johnson (J&J). However, only the Pfizer is currently FDA approved. The Moderna and J&J versions of the vaccine were issued Emergency Use Authorizations (EUA) due to the disease creating public health emergency pressure. EUA can be issued when there is secretary clearance that there is a public health emergency. FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases [6]. The COVID-19 vaccine was deemed an exception because it was subject to the state of emergency approval.

However, on August 23, 2021, the Pfizer became the first FDA approved vaccine against COVID-19. For the Pfizer vaccine to be approved, the clinical trial participants needed to continue being monitored for safety and side effects for a longer period of time: 6 months after completing the two-dose series [7]. The company needed to provide additional clinical data, manufacturing process and quality assurance details, and have their manufacturing facilities undergo an FDA inspection [7]. This approval process can often help inspire confidence the COVID-19 vaccine's safety and effectiveness, especially for those individuals who are apprehensive of getting the vaccine. This apprehension is largely due to the EUAs being issued, which can directly affect the management of the COVID-19 vaccine because of the accelerated production rate of vaccines under an EUA. Vaccine development experience, project management processes, and governmental regulations all need to be considered when managing a project that needs to be delivered on a global scale and unprecedented speed. Management responsibilities include how its approved for production, how the vaccine is manufactured, packaged, stored, and shipped, all while ensuring the product is adheres to government-regulated quality standards. The safety of the vaccine is paramount, with regular assessments and post-approval clinical studies to report on its safety and effectiveness [8]. In order to successfully produce a COVID-19 vaccine on a global scale, the higher authorities of the management team need to have an understanding in vaccine development and government contracting. The vaccine development process continues to support the validity of monitoring the safety of vaccines, while government involvement usually centers around FDA decision-making for control and quality management.

## Conclusion

The United States Food and Drug Administration regularly monitors and controls the quality of vaccines which are approved to ensure safety and efficacy for the recipients of the vaccine. Prior to even being considered for FDA approval for mass production and distribution of a vaccine, the FDA requires each vaccine undergo thorough research and development, testing prior to clinical trials, the phases of the clinical trial themselves, and data analysis that all conclusively prove the vaccine to have minimal harmful side effects for the general population. Even once a vaccine receives FDA approval and becomes widely used, the FDA continues to monitor the health of the recipients for potential long-term side effects and will even recall a

vaccine if these long-term side effects prove to be too harmful to be outweighed by the benefits of the vaccine. The priority placed on safety and efficacy of vaccines by the FDA is consistent during emergency conditions as well, though the timeline for trials and distribution may be accelerated. Since the beginning of the standardized regulation of biologics such as vaccines, the FDA has continuously developed and progressed the methods in which the vaccine data has been collected and analyzed, ensuring that the quality management of all vaccines remains a complex, multi-level, and perpetual process.

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