# Vaccine Development: Steps to Approval of an Investigational Vaccine

*Emmanuel B. Walter, M. Anthony Moody*

**Development and licensure of a vaccine is a complex and highly regulated process starting with preclinical development and continuing with three phases of clinical investigation. Ensuring a safe, potent, and effective vaccine is of paramount importance. Following approval, vaccine safety is ensured through multiple well-established mechanisms.**

## Introduction

During the last century, vaccines were declared among the 10 great public health achievements, highlighted by the eradication of smallpox, elimination of the central nervous system virus poliomyelitis in the Americas, and improved control of other infectious diseases such as measles [1]. The first decades of the current century saw the development of new vaccines to combat rotavirus, human papillomavirus, and herpes zoster. Improved polysaccharide-protein conjugate vaccines for *Streptococcus pneumoniae* and *Neisseria meningitidis* were also produced. Novel adjuvants were added to some vaccines with the goal of enhancing the body's immune response. To reduce the "shot burden" on children, numerous combination vaccines were developed, facilitating administration of multiple vaccine antigens in a single syringe. In addition, vaccines to combat influenza were further advanced, including a live attenuated intranasal vaccine, a high-dose vaccine for older adults, and influenza vaccines manufactured using novel technologies. During their development, each new vaccine underwent rigorous testing, and on average took 8 to 17 years from the time of conceptualization to approval [2]. Herein, we describe steps in the development of a vaccine.

## Vaccine Candidate Development

Vaccine candidate development begins with the recognition of an infectious disease burden and the opportunity to prevent it through immunization. This can be facilitated by the identification of a protective response, usually found in persons who were infected, recovered, and were subsequently protected against reinfection. Basic science research takes this firm rationale for a new vaccine through the identification of antigens that can stimulate an immune response and leads to the development of a vaccine manufacture approach. These approaches include inactivated, live attenuated, subunit, viral vectored, and nucleic acid vaccine platforms. The approach used depends on a number of factors including the experience of the developer and the prospects for making a safe and effective vaccine for use in the target population.

In the United States, the development and approval process for a vaccine candidate is monitored by the Centers for Biologics Evaluation and Research (CBER) of the US Food and Drug Administration (FDA). Vaccines are unique as they are regulated as both a drug and as a biological product, or biologic. The FDA defines a drug as an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease [3]. Unlike drugs that are synthesized with a known chemical structure, biologics are complex mixtures composed of sugars, proteins, nucleic acids, or complex combinations of these substances, or they may be living entities such as cells and tissues [4]. Furthermore, as compared to drugs typically used to treat patients with diagnosed medical conditions, vaccines are given to large populations of healthy children and adults. Hence, to ensure safety, the development, approval, and post-approval process for vaccines is closely monitored and regulated.

## Vaccine Candidate Approval Process

As required by Title 21 of the Code of Federal Regulations, approved and licensed vaccines must meet standards to ensure they are safe, pure, potent, and effective. In the state of North Carolina, per Chapter 130A of North Carolina's General Statutes, only vaccine preparations that meet the standards of the FDA or its successor in licensing vaccines and are approved for use by the North Carolina Commission for Public Health may be used [5]. The initial step toward approval for a candidate vaccine is rigorous preclinical testing (Figure 1). Studies are conducted in animals to assess if there are any vaccine-induced toxicities that might preclude the vaccine from being administered to humans [6]. In particular, animal testing assesses reactions at the site of administration, as well as systemic reactions or laboratory

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Address correspondence to Emmanuel B. Walter, Duke Vaccine and Trials Unit, 2608 Erwin Rd, Suite 210, Durham, NC 27705 (chip.walter@duke.edu).

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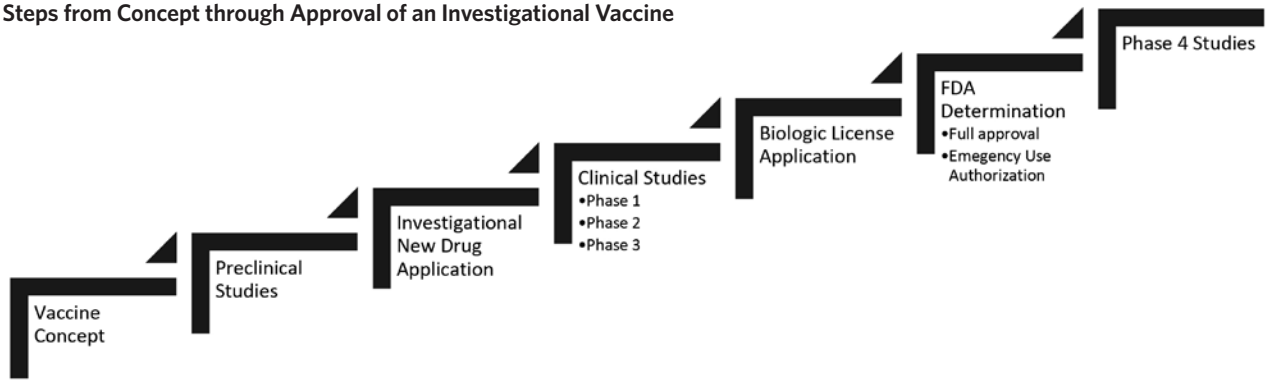
**FIGURE 1.**
**Steps from Concept through Approval of an Investigational Vaccine**




abnormalities. Animal studies also evaluate whether a candidate vaccine induces an immune response and, if animal models for disease exist, test how well vaccinated animals resist disease when challenged with the offending pathogen. Results from animal studies are used to predict a safe starting dose for the first-in-human trials. In addition, reproductive and developmental toxicity studies are performed if the vaccine is targeted for use in pregnant women.

If animal testing results are promising and a human clinical trial is planned, the vaccine developer and/or the sponsor must submit an investigational new drug (IND) application to the FDA. The IND describes the vaccine, its method of manufacture, and quality control tests for release [6]. Also included are preclinical data about the vaccine's safety and ability to elicit a protective immune response in animal testing, as well as the proposed investigational plan, including a clinical protocol for human studies. The plan must clearly outline study endpoints for evaluation of the vaccine candidate.

## Phased Testing

With FDA concurrence, a promising vaccine candidate generally proceeds through three successive phases of human trials (Table 1) [7]. Study phases may overlap, or in some cases multiple earlier phase trials may be needed, depending upon trial results. In each phase of investigation, human subject safety is considered of paramount importance. If at any time a vaccine is deemed unsafe, the pathway toward development is either terminated or the developmental course is significantly altered. Early phase vaccine investigations are commonly sponsored by academic investigators, small biotech companies, or the pharmaceutical industry. As investigations move along the developmental pathway, studies are more likely to be sponsored by larger pharmaceutical companies.

First-in-human testing of an investigational vaccine occurs in a Phase 1 study designed to assess whether it is safe, tolerable to the subject, and induces a satisfactory immune response. Phase 1 studies are small, including fewer than 100 subjects. Most Phase 1 studies are conducted in healthy adults even if adults are not the intended target population for the vaccine. These investigations frequently include a dose escalation study design in which the vaccine is tested at successively higher dosage levels, but only after the vaccine is deemed safe at the preceding lower doses. These studies provide early data on the side effect profile and immune response at different dose levels. Vaccine safety and tolerability are closely monitored in study participants and efforts are specifically targeted at identifying local and systemic side effects, monitoring clinical safety laboratory parameters, and following subjects for the occurrence of any unsolicited adverse events, serious adverse events, and adverse events of clinical interest.

Phase 2 investigations are typically larger and include several hundred participants from the target population for the vaccine. Phase 2 investigations further refine the optimal dosage and vaccination schedule. Like Phase 1 studies, these investigations assess both vaccine safety and immune response and may provide evidence of efficacy. In addition, the larger number of participants allows for better estimates of the proportions of individuals with common short-term side effects.

The last stage in the clinical development of a vaccine is a Phase 3 trial. These pivotal trials are used to make a final determination of the benefit versus risk of the vaccine upon which approval rests. These studies are designed to determine vaccine efficacy by measuring the occurrence of the disease of interest in persons randomized to either receive the vaccine or not. For diseases with which infection is infrequent and measuring vaccine efficacy is impractical, surrogate markers of vaccine efficacy may used. A surrogate marker is a measure of an immune response that from prior investigations has been established to correlate with protection [8]. Phase 3 investigations include several hundreds to tens of thousands of subjects. Like earlier-phase investigations, Phase 3 studies also monitor subject safety. Very large Phase 3 studies frequently include detailed assessments of vaccine side effects and immune response in defined substudy populations.

Late Phase 3 investigations also include evaluations of the consistency of investigational vaccine manufacture by comparing vaccine safety and immunogenicity (ability

**TABLE 1.**
**Phases of Clinical Evaluation of an Investigational Vaccine**

| Phase | Number and Type of Study Participants | Scientific Questions Asked |
|---|---|---|
| 1 | 20 to 100 healthy adults | • Is the vaccine safe? |
| | | • Is the vaccine tolerable? |
| | | • What are the vaccine side effects in relation to the dose administered? |
| | | • Does the vaccine cause the desired immune response? |
| 2 | Several hundred from target population | • What is the desired vaccine dose and dosing interval? |
| | | • Is the desired immune response to the vaccine achieved? |
| | | • What are the common short-term vaccine side effects observed? |
| 3 | Several hundred to tens of thousands from target population | • How effective and safe is the vaccine when comparing people who receive the vaccine to people who do not receive the vaccine? |
| | | • What are the most common side effects? |
| | | • Is the safety and immune response in study participants consistent across different lots of vaccine manufactures? |
| | | • What is the effect on safety and immune response when the vaccine is co-administered with other vaccines? |

Source. Adapted from: Centers for Disease Control and Prevention: Vaccines. Parents. CDC.gov website. https://www.cdc.gov/vaccines/parents/infographics/journey-of-child-vaccine-h.pdf. Updated July 2018. Accessed December 12, 2020.

of an antigen to provoke an immune response) in subjects receiving the vaccine from different manufacturing lots. Frequently, studies are also designed to evaluate the effects of coadministrating the investigational vaccine with other approved vaccines that are likely to be given at the same time in clinical practice. These studies assess the safety of vaccine coadministration as well as the effect on the immune response of both the investigational and coadministered vaccine antigens.

Ultimately, sponsors may request permission to introduce a biologic product into interstate commerce by filing a Biologics License Application (BLA) with the FDA. A BLA includes applicant information, product and manufacturing information, preclinical and clinical study data, and proposed product labeling information [9]. The efficacy and safety data from the trials provide information for the FDA review team to make a risk/benefit assessment. The product label includes information to assist health care providers with understanding the vaccine's proper use, including its potential benefits and risks. Simultaneously, the vaccine manufacturing plant undergoes a detailed inspection by the FDA to review the manufacturing process. After reviewing the BLA, the sponsor and the FDA may present their respective findings to the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). This non-FDA expert committee provides advice regarding the safety and efficacy of the vaccine for the proposed indication and assists the FDA with its determination for approval of the vaccine. Under section 564 of the Federal Food, Drug, and Cosmetic Act, the FDA may also authorize unapproved use of a vaccine in the event of a public health emergency.

## Distribution and Continued Evaluation

Once licensed by the FDA, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) provides advice as to how a vaccine is to be used in the civilian US population [10]. The committee advises the CDC on population groups and/or circumstances in which a vaccine is indicated in addition to making recommendations on contraindications and precautions for use of the vaccine. When making recommendations, ACIP considers several factors, including the safety, immunogenicity, and effectiveness of the vaccine at different ages; the severity of the disease; the number of people who get the disease if there is no vaccine; and the feasibility of implementing potential recommendations. ACIP frequently initiates discussions regarding potential vaccine recommendations for new vaccines during the FDA approval process so that recommendations for use occur in a timely manner.

After approval and distribution in the population, vaccine safety continues to be monitored. Through the vaccine approval process, the FDA may require the sponsor to conduct post-marketing Phase 4 studies to continue to evaluate the vaccine's safety, efficacy, or optimal use [11]. Additional commitments to maintain pharmacovigilence programs to assess the occurrence of adverse events of special interest, or to maintain a registry of women who receive the vaccine during pregnancy, may also be required. Vaccine manufacturers are also required to test each lot of a vaccine they produce to make sure it is safe, pure, and potent. Vaccine lots cannot be distributed until released by the FDA. Furthermore, the FDA continues to inspect manufacturing facilities every other year, and every year for those manufacturing influenza vaccines.

The safety of approved vaccine products is also monitored and studied through several well-established federally sponsored mechanisms [12]. The CDC and FDA co-manage the Vaccine Adverse Event Reporting System (VAERS), a passive reporting system for persons who experience adverse events following immunization (AEFI). VAERS is useful for detecting signals that might indicate a possible safety problem with a vaccine but is not useful for deter-

mining if a vaccine is causally related to an adverse event. In addition, the CDC's Vaccine Safety Datalink (VSD) uses electronic health data from nine health care organizations throughout the United States to both monitor vaccine safety and conduct studies about rare and serious adverse events following immunization. These studies are able to determine whether side effects are related to vaccination. Similarly, the FDA's Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system links data from health plans with data from state and city immunization registries to identify and analyze rare health outcomes that would otherwise be difficult to assess. Lastly, the CDC's Clinical Immunization Safety Assessment (CISA) project provides consultation on clinical vaccine safety issues in addition to conducting studies to identify risk factors and preventive strategies for AEFI, particularly in special populations.

In summary, the steps to FDA approval of a vaccine involve a regulated preclinical and clinical developmental process to assure its safety and efficacy. Once approved, numerous mechanisms are in place to ensure that a vaccine product remains safe, pure, and potent. Health care providers and the public should take comfort in the rigorous manner in which vaccine integrity is ensured. NCMJ

**Emmanuel B. Walter, MD, MPH** professor, Department of Pediatrics and chief medical officer, Duke Human Vaccine Institute, Duke University School of Medicine, Durham, North Carolina.
**M. Anthony Moody, MD** associate professor, Department of Pediatrics and research quality officer, Duke Human Vaccine Institute, Duke University School of Medicine, Durham, North Carolina.

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