Vaccine Development – 101

The U.S. Food and Drug Administration (FDA) is the regulatory authority that has oversight of the safety, effectiveness and quality of vaccines that are used in the United States.

Vaccines to prevent infectious diseases are given to millions of babies, children, adolescents and adults and it is critical that they are demonstrated to be safe and effective. Vaccines have prevented countless cases of disease and disability and have saved millions of lives. Ensuring the safety and effectiveness of vaccines is one of FDA's top priorities.

FDA's Center for Biologics Evaluation and Research (CBER) ensures that FDA's rigorous scientific and regulatory processes are followed by those who pursue the development of vaccines. Vaccine development is a complex science. FDA's scientific and regulatory advice to vaccine developers, as well as FDA's evaluation to determine the safety and effectiveness of vaccines, are among the most robust in the world.

How Vaccines Work

Vaccines work by mimicking the infectious bacteria or viruses that cause disease. Vaccination stimulates the body's immune system to build up defenses against the infectious bacteria or virus (organism) without causing the disease. The parts of the infectious organism that the immune system recognizes are foreign to the body and are called antigens. Vaccination exposes the body to these antigens.

Some vaccines contain weakened versions of a bacteria or virus, other vaccines contain only part of the bacteria or virus. Some vaccines contain only the genetic material for a specific protein and direct the body to produce a small amount of that protein. The body's immune system reacts defensively once it detects this protein.

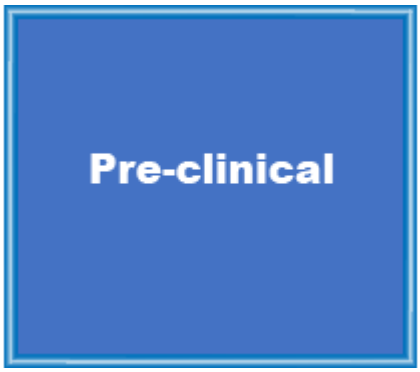
After vaccination, the immune system is prepared to respond quickly and forcefully when the body encounters the real disease-causing organism.

Below is the typical process that FDA expects vaccine developers to follow to generate the information it needs to assess the safety and effectiveness of a vaccine to prevent an infectious disease:

It Starts in a Lab

Scientists develop a rationale for a vaccine based on how the infectious organism causes disease. The scientists then conduct laboratory research to test their idea for a vaccine candidate; sometimes this testing occurs in animals. This is considered the *Research and Discovery Stage*. Once a scientific finding is thought to have practical applications, in that it may be feasible to develop a vaccine candidate based on that finding, the research moves forward.

Research Moves Forward



Before a vaccine can be tested in people, a company or researcher performs additional laboratory research and testing in animals to obtain information about how the vaccine works and whether it's likely to be safe and work well in humans. These tests are known as the *Preclinical* phase.

Testing the Vaccine in People

When the company/researcher is ready to begin studies in humans, they compile the results of their laboratory and other preclinical testing, as well as information pertaining to the manufacturing technology and the quality of the vaccine and submit these to FDA in the form of an Investigational New Drug application (IND). FDA evaluation includes an assessment of the preclinical data and a determination whether these tests were conducted according to Good Laboratory Practices. FDA also conducts an assessment of the product, its quality and safety, and the technology to manufacture it, to determine whether it is reasonably safe for testing of the vaccine to move forward in people. Studies conducted in people are known as the *Clinical Development* stage and typically cover three phases under the oversight of FDA.

Clinical trials are conducted according to plans that reflect FDA's considerable expertise in clinical trial design – these plans are called "protocols." Vaccines intended for children are generally tested first in adults, with a step-down clinical development program to children and infants.

The phases of the studies may progress sequentially, but it is also not uncommon for the phases of development to overlap.

Phase 1 - Emphasis during this phase is on safety and generally includes 20–100 volunteers who haven't been exposed to the disease being studied and who are generally otherwise healthy. These studies are used to determine whether there are adverse reactions with increasing doses and, if possible, to gain early information about how well the vaccine works to induce an immune response in people.

Phase 2 - In the absence of safety concerns from phase 1 studies, phase 2 studies include more people, where various dosages are tested on 100's of people with typically varying health statuses and from different demographic groups, in randomized-controlled studies. These studies provide additional safety information on common short-term side effects and risks, examine the relationship between the dose administered and the immune response, and provide initial information regarding the effectiveness of the vaccine in its ability to generate an immune response. Standardized and validated tests are used to evaluate the immune responses. These vaccine studies typically also include a control group consisting of people who may receive an FDA-approved vaccine, a placebo or another substance. People receiving the vaccine under study are compared to people in the control group.

Phase 3 - The vaccine is generally administered to thousands of people and the study generates critical information on effectiveness and additional important safety data. This phase includes additional information about immune response and compares those who receive the vaccine to those who receive a control, such as a placebo. For example, the number of cases of disease in the vaccinated group is compared to the number in the

control group to see whether the vaccine reduces the incidence of disease. These studies also provide information about the vaccine's safety including the identification of less common side effects.

Special Considerations - Public health emergencies and more information

- In public health emergencies, such as a pandemic, the development process may be atypical or expedited. For example, as demonstrated by the response to the COVID-19 pandemic, the U.S. government may coalesce government agencies, international counterparts, academia, nonprofit organizations and pharmaceutical companies to develop a coordinated strategy for prioritizing and speeding development of the most promising treatments and vaccines. In addition, the federal government may make investments in the necessary manufacturing capacity at its own risk, giving companies confidence that they can invest aggressively in development and allowing faster distribution of an eventual vaccine.
  Recognizing the urgent need for safe and effective vaccines FDA utilizes its various authorities and expertise to facilitate the expeditious development and availability of safe and effective vaccines. Early in a public health crisis, FDA provides clear communication to the pharmaceutical industry pertaining to the scientific data and information needed for safe and effective vaccines and works quickly to provide advice on their proposed development plans and assessment of the data that are generated. During a public health emergency, if certain criteria are met, manufacturers may submit a request for Emergency Use Authorization (/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization) (EUA) to FDA to facilitate the availability and use of their vaccine during this time.
- When evaluating the need for pre-clinical studies for a vaccine, FDA considers all data relevant to that vaccine and closely related vaccines, as well as the design of the specific clinical study for the vaccine in question. If FDA's evaluation of these data support initiating human studies of a candidate vaccine intended to prevent an infectious disease without first completing additional toxicology studies, then FDA would consider allowing such human studies to proceed.

- There is no predetermined timeline for vaccine development. Typically, the better the scientific understanding of a pathogen and the disease it causes, the more efficient vaccine development.
- Adaptive Trial Designs: These are clinical study designs which aim to expedite clinical trial decisions based on preliminary results derived from earlier trials and, in some cases, from the same trial. Using this approach can facilitate efficient clinical development. The goal of these designs is to reduce the size and duration of the trial and demonstrate an effect if one exists. These adaptations are performed with close attention to statistical rigor.

Assessment of Manufacturing is Also a Key Component

While the vaccine is being tested in people, FDA is also assessing information pertaining to the manufacturing of the vaccine and the facility where it will be made. Vaccine manufacturing is complex. The process of making the candidate vaccine for the phase 3 studies in batches called “lots” helps the manufacturer ramp up for commercial-scale manufacturing. FDA requires vaccine manufacturers to submit data to support manufacturing processes, facilities, product characterization, and demonstration of lot-to-lot consistency. FDA works with the manufacturer to develop a lot release protocol – a template of tests to be conducted on the vaccine- that will be used for each lot of vaccine post-approval. Experienced FDA-investigators carefully examine and evaluate the facility and operation for compliance with FDA regulations.

Once a manufacturing process is developed that ensures that the vaccine can be produced reliably and consistently, and the preclinical and clinical development programs have been successfully completed, companies submit a Biologics License Application (BLA) to the FDA. A BLA is a comprehensive submission that is submitted to the Agency. It includes preclinical and clinical data and information, as well as details of the manufacturing process and facility(ies).

Seeking Approval

By submitting a BLA to the FDA, a company is seeking permission to distribute and market a vaccine for use in the United States. FDA evaluates the data to determine whether the safety and effectiveness of the vaccine has been demonstrated and whether the manufacturing and facility information assure product quality and consistency. After its evaluation, FDA decides whether to approve (also known as to license) the vaccine for use in the United States. If FDA approves the vaccine, the company is permitted to market it in the United States for use in the population for which it is approved.

FDA makes its decisions based on its analysis of the benefits and risks for the intended population who will receive the vaccine, as well as the disease(s) to be prevented. FDA's scientific team works collaboratively to evaluate all of the scientific data and information included in the BLA and makes the determination whether to approve a vaccine. A typical FDA team is comprised of: physicians, chemists, statisticians, pharmacologists/toxicologists, microbiologists, experts in postmarketing safety, clinical study site inspectors, manufacturing and facility inspectors, and labeling and communications experts.

In some cases, FDA seeks the input of its Vaccines and Related Biological Products Advisory Committee (VRBPAC). This committee is comprised of a panel of outside, independent, technical experts from various scientific and public health disciplines that provide input on scientific data and its public health significance in a public forum. The FDA will consider, but is not bound by, the input received from the VRBPAC when determining whether to approve a vaccine.

Prescribing Information/Labeling

Prescribing information for a vaccine is based on scientific data that are submitted by the manufacturer in the BLA and determined by the FDA to be satisfactory to support the approved indication(s), usage, dosing, and administration. The prescribing information is updated as needed to include the most current information about the vaccine that is available to and reviewed by FDA. The prescribing information does not necessarily address all aspects of vaccine use, such as recommendations that are specific to disease outbreaks, vaccine shortages, and all subpopulations with underlying medical conditions.

FDA Oversight Continues After Approval

Monitoring of Safety and Effectiveness

It is important to note that a vaccine is a drug. Like any drug, vaccines have benefits and risks, and even when highly effective, no vaccine is 100 percent effective in preventing disease or 100 percent safe in all individuals. Most side effects of vaccines are usually minor and short-lived. For example, a person may feel soreness at the injection site or experience a mild fever. Serious vaccine reactions are extremely rare, but they can happen.

Although the vaccine development process and FDA's evaluation are rigorous and comprehensive, there is still a need for ongoing surveillance of vaccines after FDA-approval to identify uncommon adverse events or long-term complications that may occur, and

sometimes to monitor effectiveness. In certain cases, the FDA may require the manufacturer to conduct post-marketing studies to further assess known or potential serious risks. (These studies are sometimes called Phase 4 of development).

Vaccines are closely monitored using various surveillance systems, such as the Vaccine Adverse Event Reporting System (VAERS), the FDA BEST (Biologics Effectiveness and Safety) program and the FDA Sentinel Program, the FDA and Centers for Medicare & Medicaid Services (CMS) partnership, and the Centers for Disease Control and Prevention's (CDC) Vaccine Safety Datalink.

Lot Release

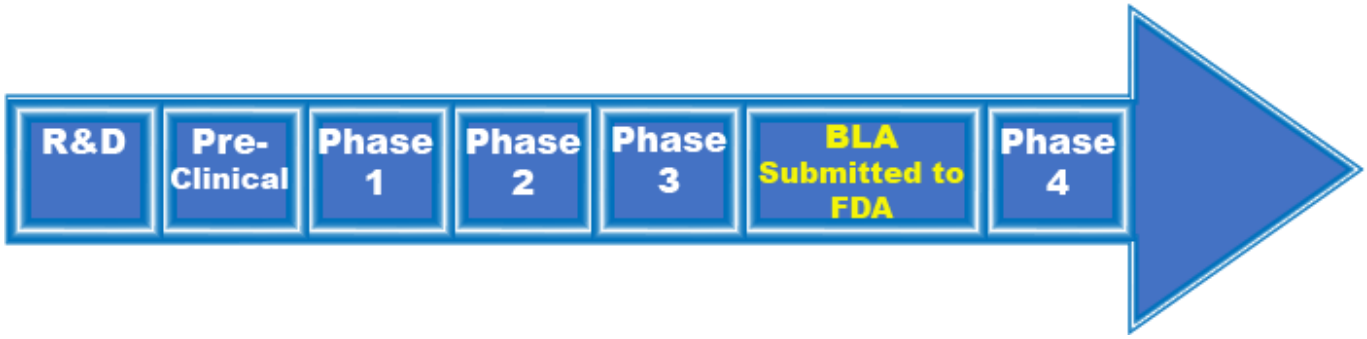
Lot release is a mechanism that provides FDA with a real-time system to continuously monitor product quality. As previously noted, vaccines are generally made in batches called lots. FDA requires vaccine manufacturers to submit data to support the demonstration of lot-to-lot consistency. After approval, the manufacturer must submit the following materials relating to that vaccine lot (or "batch")

- Protocols: contain the agreed-upon tests.
- Results: the results of the testing performed by the manufacturer. Testing typically includes assessment of purity, potency, identity and sterility.
- Samples: generally, the manufacturer must submit samples of the vaccine from the lot in question to permit FDA to perform confirmatory testing.

Manufacturers are not permitted to distribute a specific lot of vaccine until the FDA releases it.

FDA Research Provides a Unique Perspective

Research is fundamental to FDA's ability to provide effective scientific and regulatory evaluation of vaccines. FDA conducts its research activities in conjunction with its regulatory activities, which provides the Agency a unique perspective on both fronts. A wide variety of rapidly evolving technical and scientific issues concerning the safety, potency, and effectiveness of vaccines requires knowledge of new developments in basic research in the relevant biological disciplines. For this reason, FDA scientists conduct a variety of research that contributes to policy, risk assessments, new methods and standards, and changes to product labeling, including promoting new techniques for assessing vaccine safety and potency, as well as strategies for vaccine development.


R&D
Pre-Clinical
Phase 1
Phase 2
Phase 3
BLA Submitted to FDA
Phase 4