

## Vaccine Development in the United States

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### The History of Standardized Vaccine Development

With greater numbers of Americans receiving vaccinations in the early 20th century, unsafe immunizations became a threat to public health. Current laws and regulatory processes for immunizations in the United States are the federal government's direct response to public health crises caused by unsafe vaccines in the 20th century. After contaminated smallpox vaccines produced in St. Louis caused the deaths of nine children, in 1902 Congress passed what is now known as the Biologics Control Act. This was the federal government's first attempt to control the quality of all biological drugs. The act created a unit that was to become the National Institutes of Health and established the U.S. federal government's right to exercise control over entities that manufacture vaccines.

In the aftermath of World War II, the U.S. Public Service Act of 1944 was signed into law. It mandated that the federal government issue licenses for all biological products, including vaccines (PBS). The legislation was designed to consolidate and organize the health system in the United States.

In the spring of 1955, 200,000 children in the United States were vaccinated with a defective polio vaccine that still contained active poliovirus. Investigations revealed that Cutter Laboratories, which manufactured the defective vaccine in California, was responsible for 40,000 cases of polio. Two-hundred children suffered paralysis and 10 died (Fitzpatrick, 2006). The government's response was the forming of the Division of Biologics Standards, which has now become the Center for Biologics Evaluation and Research (CBER), which is a unit of the FDA. The United States's current vaccine approval process is based on this history, and its regulatory mechanisms seek to prevent future public health crises.

### Current Vaccine Development Process – Stages 1 and 2

The FDA's CBER has the mission of ensuring the safety and efficacy of vaccines. It achieves this through a well-regulated development process and post-approval inspections of manufacturers. The sponsor of a vaccine (i.e., a pharmaceutical company) can expect to spend \$200-500 million dollars, along with 10-15 years of research and development (Serdobova, 2006). Even with all of this investment of time and money, there is no guarantee that the candidate vaccine will be approved and licensed for sale.

The FDA has a two-part process for vaccine development. These parts cover the events that occur before the sponsor submits a new drug application (IND) to the FDA, and after the application is submitted. Also, after a vaccine is accepted and licensed for sale, the FDA still has controls to ensure the vaccine is safe and effective.

## Stage One

The first stage of vaccine development is the preclinical stage and can be broken down into three phases: (1) exploration, (2) animal testing, and (3) submission of an Investigational New Drug (IND) application to the FDA. The exploratory phase typically lasts 2-4 years and consists of basic lab research and the identification of natural or synthetic antigens, which alert the body to harmful pathogens (Bollmann).

If the vaccine shows promise in the exploratory phase, it moves on to the animal testing phase. This usually lasts 1-2 years and involves testing to first assess safety, and second, test immunogenicity (the ability of the vaccine to provoke an adequate immune response in the body). Animal testing typically is done on mice and monkeys, and at this phase researchers can start to experiment with finding safe doses and a method of delivery for the vaccine (Bollmann). Challenge studies, in which a subject is vaccinated and then purposely infected with the target pathogen to test vaccine effectiveness, is a form of animal testing done at this phase that for ethical reasons is not done on humans. Researchers often use this phase to make adjustments to the candidate vaccine in order to get a desired level of immunogenicity. Many candidate vaccines fail to reach a substantial level of immunogenicity and fail to show enough promise to be considered for an IND application (Bollmann).

The last phase in the preclinical stage is the submission of an IND application to the FDA for review. Its purpose is to describe the manufacturing and testing processes, summarize the lab reports, and, in detail, describe the proposed clinical studies that will validate the safety and efficacy of the vaccine. An institutional review board of experts must approve the clinical protocol. The FDA has 30 days from the time of submission of the application to approve or deny it.

## Stage Two

The second stage of vaccine development comprises clinical trials in humans, which is broken into three phases that mirror the FDA's process for approving pharmaceuticals. Finally, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) reviews data gathered in phases 1-3 and recommends to the CDC director the federal government's recommendations for safe use of the vaccine. The stages of clinical trials are formally referred to as phases.

The goals of a phase 1 clinical trial are to assess safety in humans and determine the type and extent of the immunogenicity the vaccine provokes. A phase 1 clinical trial typically involves 20-80 adults and can be non-blind, meaning the researchers know whether or not the vaccine or placebo is being administered.

The goals of a phase 2 clinical trial are, in addition to studying safety and immunogenicity, determining the proposed dosage, immunization schedule, and method of administering the vaccine. A phase 2 clinical trial involves more research subjects than phase 1, normally several hundred, and the trials are randomized, well controlled, and include placebo control groups.

The goals of a phase 3 clinical trial are to assess safety in a large group of people, determine when rare side effects have a better chance of occurring, and ascertain vaccine efficacy. Phase 3 can involve tens of

thousands of individuals. At any phase of clinical trials, the FDA may request more information or further studies, or even halt ongoing studies if there are significant concerns over safety or effectiveness.

## Licensing and After

Assuming the candidate vaccine has achieved success in the clinical trials and the FDA has not halted its progress, the vaccine's sponsor can next submit a Biologics License Application (BLA), to the FDA for approval. The FDA will then inspect the manufacturer of the vaccine and approve labeling for the vaccine. Subsequently, the sponsor presents the findings of the years of testing the vaccine has undergone to the Vaccines and Related Biological Products Advisory Committee (VRBPAC), a non-FDA panel of experts that reviews the findings and either supports or opposes licensing of the vaccine to the FDA. The FDA then decides whether or not to grant the license. If the Office of Vaccines Research and Review in CBER approves the vaccine, the sponsor receives a vaccine approval letter. If they are denied, the office will send a complete response letter, which goes into detail about how the vaccine in its present form cannot be approved.

After the FDA approves a vaccine, ACIP recommends the vaccine to the CDC director, who makes the final decision as to whether the vaccine can be marketed. Using the data gathered during testing, ACIP, a panel of 15 experts, decides the appropriate age, doses, frequency of administering, and labeling information about the vaccine. The final ACIP recommendations are published in the CDC's Morbidity and Mortality Weekly Report (MMWR). ACIP has functioned in this role since 1964 and continues to be transparent in its operations, even allowing the public to sit in on its tri-annual meetings in Atlanta, GA (Smith, 2010). The phases of the approval process are meant to operate as redundant mechanisms to ensure vaccine safety.

After licensing, the FDA continues to monitor the vaccine's production and efficacy in many ways. First, the FDA ensures vaccine purity and safety through periodic facility inspections of the manufacturing plant and requesting the results of the manufacturers tests for potency and purity. Manufacturers are also required to submit samples of each vaccine lot to the FDA for testing (Bollmann).

The drug company that produces the vaccine can also conduct what are called phase 4 trials. These trials study the vaccine while it is on the market and help to determine if the vaccine is effective in the general population. The FDA can require a company to conduct a phase 4 trial, or the company can take the initiative for competitive reasons, such as to find new markets for the vaccine. Phase 4 also allows for a way to discover rare, long-term effects that can possibly occur and may not have surfaced in phases 1-3.

## The Vaccine Adverse Event Reporting System (VAERS)

After the vaccine is rolled out, there is continuous monitoring. One element of this system is the Vaccine Adverse Event Reporting System (VAERS). VAERS was cofounded by the CDC and FDA in 1990 and is a voluntary reporting system to which anyone can submit a report and which was designed to allow the CDC to investigate cases of potential problems with vaccines (Bollmann). It allows regulators to detect

rare, new adverse effects as well as monitor increases in known adverse effects, identify potential risk factors for adverse events, identify bad vaccine lots, and assess the safety of newly licensed vaccines.

The drawbacks associated with the system are that while 30,000 events are flagged each year (with 10-15% of them serious), it is likely that less serious events, such as swelling at the injection site, are underreported, while more serious events that coincidentally occur around the same time as the vaccination are overreported. The VAERS system collects reports of adverse events that are not vetted by experts, which can make it difficult for the CDC to get all the facts it needs to make an informed decision about the cause of the adverse event. Also, since anyone in the general public can submit alerts, reports often lack important medical information, such as lab results. Regardless, the CDC investigates the adverse events to determine the probable causes (Bollmann).

The CDC established the Vaccine Safety Datalink (VSD) in 1990, to collect information about vaccinations from databases maintained by nine managed care organizations (MCOs), such as the Group Health Cooperative in Seattle, WA, and the Colorado based Kaiser Permanente (“Vaccine safety datalink,” 2013). These medical groups serve huge numbers of people in the U.S. The VSD is a collection of these managed care organizations linked databases. Some problems with this data source are that it is not representative of the population as a whole: for example, there are very few completely unvaccinated children in the databases, which is not representative of the U.S. population of children as a whole. Also, the nature of the information gathered poses challenges to researchers studying it. Unlike normal studies, which are randomized and controlled, primary medical sources cannot be controlled, making it harder to determine factors effecting medical problems (“Vaccine history”, 2011).

Rapid Cycle Analysis (RCA) was launched in 2005 to monitor real time data and compare rates of adverse events in recently vaccinated people with the rates among unvaccinated people. RCA allows the CDC to be alerted to problems as they happen, so that they can notify the public as soon as possible. RCA uses data from the MCO’s that is updated weekly. The VSD team uses this data to compare the rates of a particular adverse event in people who have been vaccinated with a specific vaccine to the rate of the adverse event in a similar group of people that did not receive the vaccine. If the rate of the adverse event is greater in the vaccinated group, the adverse event may be associated with that vaccine. A formal epidemiological study would then be conducted to confirm or deny the association (“Rapid Cycle Analysis,”). The RCA system is used mainly to monitor newly licensed vaccines and allow the VSD to respond accordingly (Bollmann).

## Further Reading

More information on VAERS can be found on the Virginia Tech Vaccination Research Group website. Please click here to read the [“Vaccine Adverse Event Reporting System”](#) information sheet and [“How an Adverse Report Following Vaccination Is Assessed”](#) flowchart.

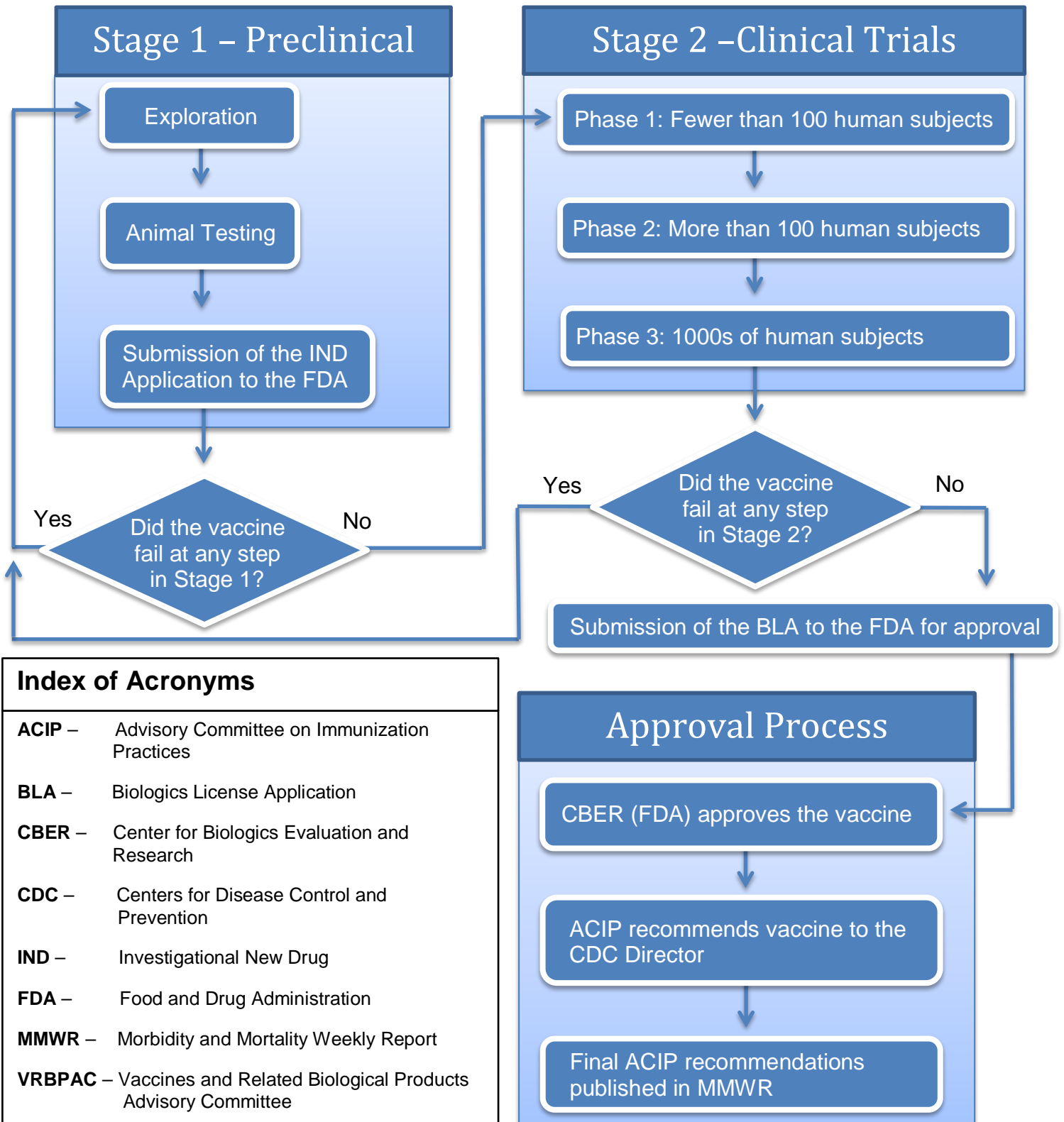
To see a flowchart of the stages and phases described above, please see the appendix to this information sheet.

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**Appendix – Vaccine Development Flowchart**



Index of Acronyms	
<b>ACIP</b>	Advisory Committee on Immunization Practices
<b>BLA</b>	Biologics License Application
<b>CBER</b>	Center for Biologics Evaluation and Research
<b>CDC</b>	Centers for Disease Control and Prevention
<b>IND</b>	Investigational New Drug
<b>FDA</b>	Food and Drug Administration
<b>MMWR</b>	Morbidity and Mortality Weekly Report
<b>VRBPAC</b>	Vaccines and Related Biological Products Advisory Committee