Preferred Therapy Solutions

Vaccine Development and Testing: **An Overview**

- In the United States, vaccine development and testing follow a standard set of steps.
- The first stages are exploratory in nature. Regulation and oversight increase as the candidate vaccine makes its way through the process.

First Steps: Laboratory and Animal Studies

Exploratory Stage

- Involves basic laboratory research and often lasts 2-4 years
- Federally funded academic and governmental scientists identify natural or synthetic antigens that might help prevent or treat a disease.
    - These antigens could include virus-like particles, weakened viruses or bacteria, weakened bacterial toxins, or other substances derived from pathogens.

Pre-Clinical Stage

- The pre-clinical stages often lasts 1-2 years and usually involves researchers in private industry.
- Pre-clinical studies use tissue culture or cell-culture systems and animal testing to assess the safety of the candidate vaccine and its immunogenicity, or ability to provoke an immune response. Animal subjects may include mice and monkeys.
- These studies give researchers an idea of the cellular responses they might expect in humans. They may also suggest a safe starting dose for the next phase of research as well as a safe method of administering the vaccine.
- Researchers may adapt the candidate vaccine during the pre-clinical state to try to make it more effective. They may also do challenge studies with the animals, meaning that they vaccinate the animals and then try to infect them with the target pathogen.
    - Many candidate vaccines never progress beyond this stage because they fail to produce the desired immune response.

Investigational New Drug (IND) Application

- A sponsor, usually a private company, submits an application for an Investigational New Drug (IND) to the U.S. Food and Drug Administration.
- The sponsor describes the manufacturing and testing processes, summarizes the laboratory reports, and describes the proposed study.
- An institutional review board, representing an institution where the clinical trial will be conducted, must approve the clinical protocol.
- The FDA has 30 days to approve the application.

Once the IND application has been approved, the vaccine is subject to three phases of testing
Next Steps: Clinical Studies with Human Subjects

Phase I Vaccine Trials

- This first attempt to assess the candidate vaccine in humans involves a small group of adults, usually between 20-80 subjects.
- If the vaccine is intended for children, researchers will first test adults, and then gradually step down the age of the test subjects until they reach their target.
- Phase I trials may be non-blinded (also known as open-label in that the researchers and perhaps subjects know whether a vaccine or placebo is used).

Goals of Phase 1 testing

- Assess the safety of the candidate vaccine and to determine the type and extent of immune response that the vaccine provokes.
- In a small minority of Phase 1 vaccine trials, researchers may use the challenge model, attempting to infect participants with the pathogen after the experimental group has been vaccinated.

- The participants in these studies are carefully monitored and conditions are carefully controlled.
- In some cases, an attenuated, or modified, version of the pathogen is used for the challenge.

A promising Phase 1 trial will progress to the next stage

Phase II Vaccine Trials

- A larger group of several hundred individuals participates in Phase II testing.
- Some of the individuals may belong to groups at risk of acquiring the disease.
- These trials are randomized and well controlled, and include a placebo group.

Goals of Phase II testing

- Study the candidate vaccine's safety, immunogenicity, proposed doses, schedule of immunizations, and method of delivery.

Successful Phase II candidate vaccines move on to larger trials, involving thousands to tens of thousands of people

Phase III Vaccine Trials

- These Phase III tests are randomized and double blind and involve the experimental vaccine being tested against a placebo
  - the placebo may be a saline solution, a vaccine for another disease, or some other substance

Goal of Phase III trials:

- Assess vaccine safety in a large group of people.
- Certain rare side effects might not surface in the smaller groups of subjects tested in earlier phases.
  - For example, suppose that an adverse event related to a candidate vaccine might occur in 1 of every 10,000 people. To detect a significant difference for a low-frequency event, the trial would have to include 60,000 subjects, half of them in the control, or no vaccine, group (Plotkin SA et al. *Vaccines*, 5th ed. Philadelphia: Saunders, 2008).
- Vaccine efficacy is tested as well. These factors might include
  - Does the candidate vaccine prevent disease?
  - Does it prevent infection with the pathogen?
  - Does it lead to production of antibodies or other types of immune responses related to the pathogen?

Next Steps: Approval and Licensure

- After a successful Phase III trial, the vaccine developer will submit a Biologics License Application to the FDA.
- The FDA will inspect the factory where the vaccine will be made and approve the labeling of the vaccine.
- After licensure, the FDA will continue to monitor the production of the vaccine, including inspecting facilities and reviewing the manufacturer's tests of lots of vaccines for potency, safety and purity.
- The FDA has the right to conduct its own testing of manufacturers' vaccines.

Post-Licensure Monitoring of Vaccines

- A variety of systems monitor vaccines after they have been approved. They include Phase IV trials, the Vaccine Adverse Event Reporting System, and the Vaccine Safety Datalink.

Phase IV Trials

- Optional studies that drug companies may conduct after a vaccine is released.
- The manufacturer may continue to test the vaccine for safety, efficacy, and other potential uses.