C. VACCINE TRIALS

INTRODUCTION

Vaccines are used to prevent infectious diseases. Successful vaccine trials have resulted in the development of safe and effective vaccines for polio, measles, rubella, hepatitis B, pneumococcal pneumonia, and other serious diseases. Currently, vaccines are being evaluated to prevent infectious diseases such as AIDS (or transmission of HIV), malaria, tuberculosis, trachoma, cytomegalovirus, herpes simplex, and influenza. Vaccines must undergo clinical testing prior to approval and licensure by the FDA. The regulations governing the conduct of clinical trials on investigational vaccines are the same as those governing the conduct of investigational new drug research [see Guidebook Chapter 5, Section B, "Drug Trials"]; however, the risks and benefits associated with vaccine trials may differ from those of drug trials.

A vaccine is a biologic; its use in trials involving human subjects is similar to the use of any drug. Vaccines do, however, differ from therapeutic drugs in two important ways. As used here, they are not designed to diagnose or cure disease in afflicted individuals; their purpose is to prevent a particular disease in healthy human beings. Vaccines are also used to protect people with a high statistical risk for contracting a particular disease or for suffering especially serious consequences from a disease. Vaccines trigger the body's normal immune response, producing antibodies that protect against future infection. Some vaccines (e.g., those containing active microorganisms or live-attenuated vaccines) have a small but real disease-producing capacity. Thus, one rare risk of a new vaccine is the possibility of infecting a healthy subject with the very disease researchers are seeking to prevent. More often, however, subjects involved in vaccine trials temporarily suffer from some of the symptoms and effects of the disease (e.g., polio, German measles) as they acquire immunity.

DEFINITIONS

- **Biologic**: Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of diseases or injuries.
- **Purity**: The relative absence of extraneous matter in a vaccine that may or may not be harmful to the recipient or deleterious to the product.
- **Sterility**: The absence of viable contaminating microorganisms; aseptic state.
- **Vaccine**: A biologic product generally made from an infectious agent or its components — a virus, bacterium or other microorganism — that is killed (inactive) or live-attenuated (active, although weakened). Vaccines may also be biochemically synthesized or made through recombinant DNA techniques.

IRB CONSIDERATIONS

The development of vaccines is of considerable benefit to society, especially in the case of devastating or highly infectious diseases. The direct benefit to the individual subject receiving a new vaccine is the possibility of immunity (i.e., protection against future disease). The benefits of such immunity will vary depending on: (1) the severity of the disease to be avoided; (2) the likelihood that the subject will be exposed to the infectious disease; and (3) in the case of certain diseases, the likelihood that the subject would suffer adverse consequences should he or she contract the disease. Some populations will be at greater risk of contracting an infectious disease than others, either because they are more likely to be exposed to the disease or because they have an increased susceptibility to it. Among those who contract an infectious disease, there may be some sub-groups that are particularly vulnerable to adverse consequences (e.g., children, persons of advanced age, or persons suffering from other illnesses).

For most diseases, participation in vaccine trials carries the generally small risk of contracting the disease. [In some vaccine trials (e.g., HIV) there is no such risk. In the case of HIV vaccine research, the lack of risk is due to the manner in which the vaccine is derived.] The risks of participating in a vaccine trial also include adverse effects.
unrelated to the disease in question (e.g., slight fever, headache, muscle soreness, or muscle aches). Such side effects are usually short-lived, tolerable, and not life-threatening. Again, the degree of risk associated with participating in a vaccine trial varies depending on the subjects' vulnerability to the adverse side effects of the vaccine. Some subjects may have an allergic or anaphylactic (i.e., a decrease rather than an increase in immunity) reaction to the vaccine. Anaphylactic reactions to vaccines cause the recipient to be hypersusceptible to the disease. Such reactions are generally unpredictable, and may be serious or potentially life-threatening.

The IRB should be aware of other risks associated with vaccine trials, including the possibility that vaccines produced synthetically or using recombinant DNA techniques may present risks as yet unknown, that groups often most likely to benefit from receiving a vaccine are often the most vulnerable to coercion (e.g., institutionalized persons or children), and that subjects in control groups may erroneously assume that they have been immunized.

When determining whether the risks are reasonable in relation to the benefits, IRBs should consider the severity of the disease, the risk of contracting the disease, and any special vulnerability of the subject population to the potential adverse effects of the vaccine. The most difficult cases are those in which the subjects most likely to benefit from participating in the vaccine trial are also the subjects at the greatest risk of suffering from the vaccine's potential adverse effects.

Some of the risks inherent in vaccine trials can be minimized. Before a vaccine is approved for testing with human subjects, IRBs should receive satisfactory evidence that animal trials and laboratory tests have, to the extent possible, demonstrated its safety. Since the sponsor must submit such information to the FDA as part of its investigational new drug application (IND), IRBs can readily obtain evidence of safety as well.

Mechanisms for protecting human subjects from some risks can be built into the vaccine study design. For example, with careful screening, investigators can avoid enrolling persons who may be susceptible to certain adverse reactions. Furthermore, trials can be designed to involve subjects who are most likely to be exposed to the infectious agent and who stand to benefit most from the protection afforded by the vaccine. Selecting subjects in this way avoids exposing those who may not be in need of its protective benefits to the risks of the vaccine. In many situations, however, Phase 1 trials should be designed to evaluate low risk subjects. For example, an effective hepatitis B vaccine already exists. It would therefore be appropriate to determine that an investigational vaccine for hepatitis B is immunogenic in humans prior to use in high risk subjects.

Vaccine trials require careful monitoring of human subjects for both immune status and adverse reactions. The monitoring reflects the dual goals of any trial to determine both the effectiveness and the safety of the investigational substance or device. Although subjects in vaccine trials should be advised beforehand of known or anticipated side effects, rare or unknown reactions may occur. FDA regulations require that subjects be provided with written instructions about whom to contact in the event of serious adverse reactions or research-related injury.

IRBs should also be aware that large-scale field trials of a vaccine may involve many thousands of subjects, making monitoring difficult. The IRB should make sure that the sponsor has made provisions for monitoring the progress of the research, the immune status of participants, and side effects reported. Maintaining careful records is important both for monitoring the safety and effectiveness of the vaccine and for locating subjects for follow-up. If a vaccine either does not immunize the subject or does so for too limited a time, subjects may erroneously assume they are protected and fail to seek necessary medical attention. In addition, members of a control group may (incorrectly) assume they are immune from the disease because they believe they have received an effective vaccine (which they have not). IRBs sometimes require that control group subjects be given the first opportunity to receive the vaccine once its safety and effectiveness have been established. If such arrangements are not part of the research design, at the end of the trial control subjects should be informed of both their status vis a vis the vaccine, and the outcome of the trial: e.g., that the vaccine was shown to be safe and effective, but that they either did not receive the vaccine or did not receive an effective dose of the vaccine.

For a discussion of ethical issues related to the clinical testing of AIDS vaccines, see Guidebook Chapter 5, Section F, "AIDS/HIV-Related Research."
POINTS TO CONSIDER

1. Has appropriate FDA clearance and an approved IND been obtained?

2. Is there evidence that the vaccine has been adequately tested in animal trials and in the laboratory?

3. Where appropriate, are subjects clearly told in the consent process that they might receive a placebo or ineffective dose of the vaccine, and thus may not be protected against the disease?

4. Does the protocol provide adequate plans to monitor all subjects for immune status and adverse reactions, respond to problems, and disseminate results?

5. Will subjects be informed about what to do and whom to contact in case of a serious adverse reaction or research-related injury?

APPLICABLE LAWS AND REGULATIONS

Federal Policy for the protection of human subjects

21 CFR 50 [FDA: Informed consent]
21 CFR 56 [FDA: IRB review and approval]
21 CFR 312 [FDA: Investigational new drug research]
21 CFR 600-800 [FDA: Standards for biological products]
21 CFR 630 [FDA: Standards for viral vaccines]