not required, that is not identified in nature, severity, or frequency in the risk information described in the general investigational plan or elsewhere in the current application'' (21 CFR 312.32). As a general rule, many sponsors require investigators to report all adverse experiences even if the event is not apparently related to the vaccine. The investigator must keep a record to indicate the treatment and outcome of the adverse experience.

Regulatory Considerations in International Trials

International trials are of particular significance in vaccine development, in which the ultimate target population may be individuals in a country other than that in which the vaccine was manufactured. Such trials may reveal differences in safety, immunogenicity, and efficacy when the vaccine is studied in a new population. For example, a live oral cholera vaccine was less immunogenic when given to Thai adults than to U.S. adults (1), and oral polio vaccine was less immunogenic in children in developing countries (15). The experimental vaccine may or may not be studied under U.S. IND. If not, the vaccine must be manufactured outside the United States. Several provisions must be met for the U.S. FDA to accept data from an international trial. These include (*i*) the data must be applicable to U.S. populations; (*ii*) international investigators must be competent; (*iii*) the protocol must be reviewed for ethical considerations; and (*iv*) the site must be available for FDA inspection.

The same standards that apply to studies in the United States should be used in studies in foreign countries (16). The research should be developed in close collaboration with local investigators and other authorities in the country in which it will be performed (17). FDA does not require that case report forms or source documents be completed in English, but a translator may be required if the site or records are inspected. Local customs may affect several aspects of the trial, such as the means of obtaining and documenting informed consent and the recognition and reporting of the types of experiences that are considered adverse.

PROTOCOL DEVELOPMENT

General Considerations

The success of a vaccine trial in phase I or II is largely predicted by the quality of the protocol. According to the CFR, a protocol must contain the following components: (*i*) a statement of the purpose and objectives of the study; (*ii*) the name and address of the investigator, the name and address of the research facilities, and the name and address of the reviewing IRB; (*iii*) a statement of the number of participants and the inclusion and exclusion criteria for participating; (*iv*) the study design, including the type of control group, if any; (*v*) the dose to be given and method for determining the dose; (*vi*) a description of the outcomes to be measured; and (*vii*) a description of the measures to be taken to monitor the participants and to reduce risks.

In addition, many protocols contain a discussion of the scientific background and rationale to place the study in context. It is important to include information about the disease, its clinical nature and epidemiologic importance, and whatever is known about the elements of protective immunity. This is useful in justifying the need for the study and risk to volunteers.

The type of study, for example, controlled, double- or single-blinded, and the method of randomization, if any, should be included. Outcomes to be observed need to be clearly described; objective definitions of outcomes are highly desirable. Definitions of safety (e.g., degree of temperature that defines fever) and immunogenicity (e.g., definition of seroconversion) need to be clearly decided and documented during protocol development. A justification for the dosage should be provided. The means of monitoring patients and contingencies for handling side effects should be described.

Protocols include a section describing the statistical tests to be used to analyze the results and a section to justify the sample size chosen. In phase I studies, however, it is usually not possible to detect statistically significant differences between groups because of the small numbers of participants.

Considerations for Studies Involving Children and Infants

In designing a protocol to be carried out in children, additional considerations are required. In 1998, NIH issued a policy and guidelines on the inclusion of children as participants in research involving human subjects, providing guidance on inclusion of children and justification for exclusion of children in research funded by NIH. In considering the inclusion of children in vaccine studies, the first decision to be addressed is the age group to be vaccinated. The answer depends on the age at which children are at risk for the infection the vaccine is designed to prevent. For most pathogens, it is optimal to provide protection as early in life as possible. However, the presence of small amounts of maternal neutralizing antibody may inactivate some live viral vaccines, such as measles vaccine, requiring that immunization be postponed to a later age. Usually, pediatric vaccine development proceeds in older children, and progresses step-wise to younger children until the target age group is reached.

Early infancy is a time when children receive multiple routine vaccinations. An important issue is whether or not to give an experimental vaccine at the same visit with licensed vaccines. Frequently, phase I studies will dictate a four-week separation between the study vaccine and any other vaccinations, to avoid either confounding the safety data or inducing immune interference with simultaneously administered vaccines. To be logistically practical and economically feasible, new vaccines should eventually be incorporated into the routine vaccination schedule of infancy. Therefore, the effects on safety and immunogenicity of concurrent immunization should be evaluated in phase II studies. The number of doses of vaccine to be administered must also be determined. Two or more doses are often necessary to overcome maternal antibody or induce priming. This issue is most commonly addressed by giving two or three doses and measuring antibody levels before and after each immunization. The necessity, practicality, and ethics of including a placebo group should also be carefully weighed.

In designing a protocol for pediatric studies, one must carefully balance the need to be minimally invasive but to collect all necessary data. This sometimes requires compromises. The most difficult aspect of carrying out a successful pediatric vaccine trial is recruitment of sufficient numbers of children. Parents are protective of their children and will refuse to enroll their children or continue to participate in a study that they perceive is too invasive, or involves undue discomfort for their child. The number of times that specimens are sampled, therefore, should be kept to a minimum.