messenger to the home. Day care settings can be arranged for studies in which it is necessary to collect extensive clinical data or multiple specimens. The children are observed during the day by nursing staff, and they return home in the evening where the parents continue surveillance. This arrangement is sometimes optimal for phase I studies of live, attenuated vaccines.

REGULATORY ISSUES

History of the Regulation of Vaccine Development

The ancient Egyptians and Hebrews had strict meat handling laws, and later, ancient Greeks and Romans had regulations prohibiting the addition of water to wine. In the Middle Ages, grocers and druggists had trade guilds, which prohibited adulteration of drugs and spices. In the United States, there have been laws governing the size of a loaf of bread and prohibiting adulteration of bread; in 1785, the first comprehensive food adulteration law was enacted in the United States.

In 1938, the Federal Food, Drug, and Cosmetic (FD&C) Act was enacted in the United States in response to a number of deaths caused by the use of diethylene glycol (anti-freeze) as the vehicle for an elixir of sulfanilamide. This act required sponsors of investigational new drugs (IND) to submit safety data about the candidate product before premarket approval. The turning point for modern regulatory affairs was the passage in 1962 of the Kefauver-Harris amendments to the FD&C Act. The 1962 amendments required that efficacy data, as well as safety data, be submitted to support IND applications. These amendments followed shortly after the discovery that thalidomide caused birth defects. Although thalidomide was never approved in the United States, it was being used extensively in research. Before the 1962 amendments, there was no requirement that FDA be notified of the use of investigational drugs or regulate their use. Today, sponsors of new vaccines must submit both safety and efficacy data to support the application. Since these data are gathered through clinical investigations, all sponsors must secure an IND and follow a set of principles known as Good Clinical Practice (GCP).

GCP is the set of federal regulations and guidelines for clinical trials that will support an eventual application for licensure of a new vaccine or drug. GCP is designed to ensure the quality and integrity of clinical data and to protect the rights and safety of volunteers. GCP guidelines are described in detail in numerous Internet sites from various agencies, including the U.S. Department of Health and Human Services Office for Human Research Protection (OHRP), U.S. FDA, U.S. Army, U.S. Centers for Disease Control and Prevention, the International Conference on Harmonization (IHC), and others. These regulations are comprehensive, including protocol design and development, informed consent guidelines, record keeping, data reporting, adverse event reporting, etc.

In the United States, when Congress passes a law, the regulatory agency involved writes the regulation and is responsible for enforcing the law. The Code of Federal Regulations (CFR) contains these regulations. Title 21 of the CFR deals with food and drugs, and Title 45 part 46 deals with protection of human subjects. These regulations give specific directions for all individuals—sponsors, monitors, and investigators—involved in a vaccine trial. The following parts of Title 21 are relevant to clinical investigations of vaccines:

Part 50 (informed consent)
Part 56 (institutional review boards)
Part 312 (investigational new drug applications)
Part 601 (licensing)
Part 814 (pre-market approvals)

Elements of an Investigational New Drug Application

The components of an IND application are described in 21 CFR part 312. An IND is filed for a vaccine that has never been approved in the United States; for a new dose, route, or schedule of administration of an approved vaccine, or for a new indication of an approved vaccine. The application includes a completed and signed form FDA 1571, which is a master administrative document with a table of contents that serves as a checklist for the elements of the application. The signature of the sponsor indicates that he/she agrees to conduct the investigation in accordance with all applicable regulatory requirements, specifically, to wait for 30 days after the FDA receives the IND before beginning the study, not to conduct the study if the study is placed on ''clinical hold,'' and agree to the review and approval of the study by an institutional review board (IRB).

After the form 1571, there is an introductory statement about the vaccine's characteristics, a general investigational plan, an investigator's brochure, and the clinical protocol. Form FDA 1572 and the curricula vitae of the investigators are included. The form 1572 is a contract between the clinical investigator and the federal government to assure his/her compliance with 21 CFR 312, involving adherence to protocol, use of informed consent, record keeping, reporting, etc. Next are sections on chemistry, manufacturing and control information, pharmacology and toxicology information, and previous human experience. As the development of the vaccine progresses, the IND application is supplemented with protocol amendments, new protocols, new investigators, safety reports, information about microbiology or toxicology, and annual reports.

Obligations of Sponsors

The sponsor of a clinical investigation is the person who has assumed responsibility for compliance with the FD&C Act and FDA regulations and guidelines. The sponsor submits and maintains the IND application. Not until the IND has been prepared can the investigational product be shipped for the purpose of conducting clinical trials. A sponsor who both initiates and conducts a clinical investigation is called a ''sponsor-investigator.'' The specific legal responsibilities of the sponsor, contained in 21 CFR, include selecting investigators, providing adequate information to investigators, monitoring investigations, ensuring compliance with proper IND procedures, and informing FDA and the investigators of any adverse effects or risks of the product being studied. Sponsors may transfer all or part of their obligations to a contract research organization (CRO).

In 2004, the members of the International Committee of Medical Journal Editors issued a statement indicating that registration of clinical trials would be a requirement for subsequent publication of trial results (9). The purpose of registration is to provide results to study participants and to make public a list of all clinical trials. The Web site Clinicaltrials.gov is the information repository for posting information about clinical