Preclinical Testing

The diversity of biological products necessitates individualization of the preclinical evaluation, however, certain general principles apply. Prior to introduction of an investigational vaccine in human volunteers, investigators are required to provide evidence supporting the scientific rationale for a vaccine candidate, including immunogenicity, the quality (including purity) of the product, and preclinical safety information.

Animal models are useful for evaluating disease pathogenesis, immune response, toxicity, and, in some cases, efficacy against challenge with the infectious disease that the vaccine is intended to prevent. Animal studies are usually overseen by independent committees, often called animal use committees, to assure the humane conduct of studies and to avoid unnecessary testing and sacrifice of animals. Product quality is assessed by evaluating the manufacturing process, the materials used during production, and the final product. Specific descriptions of the manufacturing process, documentation of the source and quality of the materials used in manufacture, and in-process testing help to characterize the safety of the product (79). In addition, ICH has developed a wide range of guidance documents on quality assurance and in vitro and in vivo preclinical studies (77). Concerns about transmissible spongiform encephalopathies have highlighted the need to document the sources of bovine-derived materials and have led the United States to exclude materials for vaccine manufacture from countries in which bovine spongiform encephalopathy (BSE) or BSE risk exists (80–82).

Careful attention should be given to the design of preclinical toxicity studies, particularly when the investigational product consists of components not previously studied in humans such as new antigen delivery systems and novel adjuvants (83). Vaccines intended for administration to pregnant women or women of childbearing potential should be evaluated for teratogenicity and developmental toxicity (usually in several animal species) (84).

Additional laboratory testing may be warranted to evaluate particular products, for example, adventitious agent testing for vaccines produced in animal or human cell substrates (85), preclinical studies evaluating the potential for integration of plasmid DNA into the host genome for DNA vaccines (86,87), and demonstration of adequate attenuation for live, attenuated vaccines (88). Testing is required to document sterility, general safety, potency, and purity of the vaccine (89). Extra vigilance is necessary for novel vaccine technologies that require the development and standardization of new quality control measures. Laboratory evaluation of vaccine safety does not end when clinical studies begin or when a vaccine is licensed. Changes in the manufacturing process or components, the development of enhanced testing techniques, as well as new safety concerns identified in clinical studies or in post-marketing surveillance of a vaccine may prompt the investigator and/or manufacturer to consider reevaluation of the product's preclinical safety.

Clinical Pre-Licensure Studies

Clinical Studies and Human Subject Protections

Clinical studies must comply with accepted ethical principles guiding human participation in clinical trials, including informed consent, equitable selection of subjects, and appropriate scientific and ethical review of the proposed study. Evolution in thought regarding elements of ethical research, as well as the use of new vaccine technologies with uncertain risks, present new challenges for ensuring participant safety in clinical trials. Human subject protections are guided by ethical principles formalized in consensus documents such as the Belmont Report (90), various iterations of the Declaration of Helsinki (World Medical Association), and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (91). Similar concepts are codified in U.S. Department of Health and Human Services (DHHS) regulations as the ''Common Rule'' (92) adopted by 17 federal agencies that support or conduct research with human subjects, and FDA regulations that govern drug, biological, and device research (93). Centers that conduct human trials are required to have institutional review boards (IRBs), which independently review and approve the studies prior to any human testing. The IRBs also monitor the safety of human subjects during clinical trials. Investigators are usually required to have independent data monitoring committees (DMCs), also known as data and safety monitoring boards (DSMBs), to evaluate adverse events during the course of trials. DMCs or DSMBs consist of individuals with relevant expertise who provide ongoing review of data accumulated during clinical studies. Members of DMCs or DSMBs should be independent of the investigators and the study sponsors, and have no conflicts of interest with the product to be evaluated. Small, phase I, open studies may often have only a medical monitor to assess adverse events. The role of a DMC or DSMB is to advise the investigators and the sponsors on the safety of current study participants and the continuing validity and scientific merit of the study (94). A DMC or DSMB should have the ability to unmask the participants by a study group at any point during clinical trials to evaluate potential safety concerns. Draft guidance is available from the FDA to help determine when a DMC is needed and how such committees should operate.

Ethical and practical issues facing investigators with respect to pivotal studies include the choice of research design, the use of placebo controls, or the use of a comparison vaccine when evaluating a vaccine against a disease for which a licensed vaccine already exists (95,96). Conducting clinical studies in international settings presents additional challenges such as ensuring adequate local review and oversight, the need for studies to be relevant to the health needs of the host country, and the sustaining newly introduced health interventions once the trial is completed (97–99). Challenge studies to valuate vaccine efficacy, that is, inducing clinical infection in subjects to study the efficacy of an experimental vaccine, presents ethical issues for subject safety (100,101). When planning challenge studies, investigators should carefully consider the seriousness of the infectious disease, including sequelae, and the ability to treat the infection. Demonstrating efficacy when field efficacy trials or human challenge studies are not feasible or are unethical, for example, vaccines against agents of bioterrorism, is problematic. For products that reduce or prevent serious or life-threatening conditions where the product is expected to provide meaningful benefit over existing approaches, the FDA has regulations (the ''animal rule'') describing how animal efficacy data can be used to support licensure (102). In this setting, human clinical safety and immunogenicity data would still be required. The approval of new vaccines against anthrax and smallpox is an example of the development of new vaccines against agents where it is not possible to assess efficacy through field trials or individual challenge studies (103,104).