CBER IMPLEMENTATION OF REGULATORY AUTHORITY

In executing its regulatory authority, CBER relies on the regulations as stated in the CFR as noted above. CBER's regulatory authority covers pre-marketing (investigational status), licensure, and post-marketing activities. A brief overview of CBER's regulatory activities in each of these areas is described below.

Pre-Market

In the United States, the clinical evaluation of a vaccine prior to licensure (i.e., an investigational vaccine) must be conducted under the authority and oversight of the FDA (21 CFR 312) through submission of an IND. The submission of an IND is required to allow the introduction of the investigational product into interstate commerce and its investigational use. In exercising this oversight authority, CBER is required to review the CMC information, nonclinical safety and activity testing, and any relevant clinical testing data regarding the investigational vaccine. The initial submission of the IND triggers the formation of a multidisciplinary review team, which evaluates product manufacturing and testing, nonclinical testing design and outcomes, clinical trial design, statistical design and analysis, as well as assessing the environment and the facility used to manufacture the product.

Throughout all stages of product development, safety of human subjects is paramount. Safety assessments are conducted based on CMC considerations, safety signals observed in nonclinical studies and lastly, by careful assessment of safety data being generated from clinical studies. With regard to CMC, CBER requires that sponsors submit adequate information as to the starting materials used in vaccine production, such as information on the microbiologic isolate used to generate the vaccine, all raw materials used, sourcing of animal derived raw materials, as well as adventitious agent testing and thorough characterization of cell substrates used in manufacturing. In addition to focusing on the materials used to produce the vaccine, CBER also requires that information on the manufacturing process, the facility and equipment used to manufacture the vaccine, as well as testing controls be submitted in order to demonstrate control of manufacture and to support the purity and potency of the vaccine. As investigational products reach advanced stages of product development, such as phase 3, additional information should be provided to demonstrate the robustness of the manufacturing process. Consistency of manufacture is a key component to support a licensing application and is critical to demonstrate in phase 3. Demonstration of manufacturing consistency in phase 3 allows CBER to adequately interpret clinical data generated in phase 3 for support of licensure.

Early signs of safety concerns may be apparent from nonclinical studies when toxicity is observed in animals. Nonclinical data can provide a safety signal, which can then be specifically monitored during clinical studies. Nonclinical studies may also be helpful in determining the initial dosage and regimen for phase 1 studies as well as support product formulation changes in order to enhance activity or stability of the product. Nonclinical animal studies are often required over the course of clinical development, especially to support the safe use of the product in special populations such as pregnant women or women of childbearing potential. Given the importance of the nonclinical data to support the safe use of the vaccine in humans, careful consideration is needed as to the choice of animal model and study design. It is important to discuss such aspects of any nonclinical study with CBER prior to study initiation to ensure that the study is adequately designed to support clinical use.

The clinical assessment of a vaccine occurs using a staged approach in which the initial phase 1 study is conducted in limited number of subjects to assess common events related to local and systemic reactogenicity. In phase 1, the study design may include a dose-ranging evaluation of the vaccine-induced immune response to provide a preliminary assessment of the immunogenicity of different dosages of vaccine administered according to the proposed immunization schedule. As clinical development moves to phase 2, larger numbers of subjects are studied to establish a better-defined safety profile for reactogenicity and adverse events. During phase 2, additional immunogenicity or effectiveness endpoints are studied, and these data are used to determine the most appropriate dosage and immunization schedule to take forward into a pivotal phase 3 study.

Phase 3 clinical development involves the design, conduct, and analysis of the pivotal study(ies) to support licensure. Given the critical nature of the phase 3 program, CBER encourages applicants to meet with CBER to discuss their proposed phase 3 study as well other aspects of the program, including status of manufacturing validation and consistency. In review of the study protocol, CBER gives careful attention to the sample size, statistical analysis plan, as well as primary and second-study endpoints. All aspects of the study need to be robust, including the laboratory testing to support efficacy endpoint determinations as well as the safety surveillance. Agreement on the phase 3 program status and study protocol is critical to facilitating the path to licensure, given that licensure of the vaccine for the requested indication will be based on the successful conclusion of the phase 3 study.

Upon completion of the phase 3 study, applicants often discuss their plans for BLA submission with CBER. This pre-BLA meeting is designed to advance the understanding between CBER and the applicant as to what data or information is to be submitted in the BLA, as well as the requirements for submitting the BLA either electronically or through paper documentation.

Licensure

The process by which CBER approves a product for market is through the issuance of a biologics license. The decision to approve a product is based on CBER's determination that the product is safe and effective, as demonstrated by the data submitted in the BLA, as well as inspection noted below. The regulations covering licensure of vaccines can be found in 21 CFR 600 (3). The BLA submission includes all CMC, nonclinical and clinical data necessary to determine that the product can be made consistently, is stable and meets the criteria for safety, purity and potency. Once the BLA is received, CBER assembles a multidisciplinary review team to review and evaluate all aspects of the application. In addition to reviewing the submission, CBER conducts both a facilities preapproval inspection (PAI) to assess compliance with Good Manufacturing Practices, as well as an inspection of clinical sites (Bioresearch Monitoring; BIMO) where the pivotal study was conducted to assess compliance with Good Clinical Practices (GCP) (6). As part of the CBER deliberations regarding an application, CBER may choose to seek the advice of their