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An Overview of U.S. Food and Drug Administration Licensure of Vaccines

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INTRODUCTION

This chapter provides an overview of the regulatory authority for the licensure of biologics in the United States, as conveyed to the U.S. Food and Drug Administration (FDA). It includes a brief description of the statutory authority and implementation of this authority by the FDA. It describes the role of the FDA in product development, especially vaccines, and how the FDA responds to scientific advancements to ensure a state of the art, scientifically based regulatory approach to these products throughout their life cycle (pre-market, licensure, and post-market).

OVERVIEW OF FDA REGULATORY AUTHORITY

The licensure of biologics, including vaccines, is addressed in the U.S. federal laws as specified in the Public Health Service Act (PHS Act) section 351 (1) and the Food, Drug and Cosmetic Act (FD&C Act) (2). These Acts provide the statutory authority by which the FDA, through the Center for Biologics Evaluation and Research (CBER), Office of Vaccines Research and Review (OVRR), conducts its review and approval of vaccine license applications as well as post-licensure regulatory activities. The FDA implements these authorities through regulations, which are codified in the Code of Federal Regulations (CFR). Title 21 of the CFR, parts 600 through 680 (3), contains the regulations specific to the licensure of vaccines and other biological products. In addition to these specific regulations for vaccines, other sections of the CFR are fundamental to the manufacture and development of drugs and biologics. These include regulations on current Good Manufacturing Practice (cGMP) (21 CFR parts 210-211) (4) and the clinical development of investigational drugs (21 CFR part 312) (5). In the development of investigational vaccines in the United States, clinical evaluation must be conducted under the authority of the FDA through the submission of an Investigational New Drug (IND) application. The establishment of an IND allows for the FDA and the vaccine developer to communicate on all aspects of product and clinical development. 21 CFR 312.20 subpart B describes the requirements for an IND, the phases of investigations, the content and format of the IND, as well as the administrative requirements for submitting information to the FDA, including required periodic reporting.

To address the need for expediting public access to new drugs and biologics, the US Congress passed the Prescription Drug User Fee Act of 1992 (PDUFA), which permitted the FDA to collect fees to enhance the review process. PDUFA was reauthorized as part of the Food and Drug Administration Modernization Act of 1997 (PDUFA II), and the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PDUFA III), both of which amended the FD&C Act and the PHS Act. The implementation of the PDUFA has resulted in establishing timelines and performance goals for identified review activities conducted by the FDA, provided for additional guidelines for meeting with industry, as well as provided for fees (user fees) to support FDA's review of marketing applications. The implementation of these timelines and fees is intended to increase the transparency by which the FDA conducts its review and to facilitate the timeliness of product development and licensure.

CBER is committed to facilitating public access to safe and effective products. In fulfilling this commitment, CBER plays an active role in the scientific-based review during all stages of clinical development from IND through Biologics License Application (BLA). The stages of clinical development as outlined in 21 CFR 312.21 include phase 1 studies that evaluate primarily the safety of the product in a small number of subjects; phase 2 studies that evaluate the safety and sometimes preliminary effectiveness outcomes in a larger number of subjects; and phase 3 studies that are typically large-scale safety and efficacy studies needed to support licensure (5). Phase 4 studies are conducted post-licensure and are typically designed to gain additional safety data and occasionally to obtain additional efficacy data in broader populations than were studied in phase 3. Throughout all phases of clinical development, safety is a primary focus through the review of the manufacturing and testing, nonclinical toxicity data, as well as all previous human experience. Early in clinical development the data for supporting safety may be limited and therefore it is appropriate to limit the number of subjects in initial clinical testing. As clinical development progresses to phase 2 and especially phase 3, CBER reviewers increasingly focus their review on the robustness of chemistry, manufacturing, and controls (CMC) testing, the study design and objectives with regard to safety and effectiveness, as well as the statistical analysis plans for the proposed clinical protocols.