advisory committees. In the case of vaccines, CBER would request that the Vaccines and Related Biological Products Advisory Committee (VRBPAC) review the product and clinical data and provide comment on the adequacy of the safety and efficacy data submitted in the BLA. Based on the CBER reviews and the advice of the VRBPAC, CBER reaches a decision to approve the application based on demonstrated safety and effectiveness or to inform the applicant of the deficiencies found that preclude approval.

Post-Market

Once a product is approved, CBER continues product surveillance and oversight throughout the life of the product to ensure that the product continues to meet the standards for purity, potency and safety that were the basis for licensure. Key to this surveillance is the receipt of adverse event reporting through the Vaccine Adverse Event Reporting System (VAERS), a passive reporting system for capturing adverse events post-licensure. In addition, CBER may request that the applicant conduct phase 4 clinical studies to expand the safety database. Such phase 4 studies are agreed to prior to licensure and are considered post-marketing commitments.

CBER also obtains information on product performance through lot release information submitted to CBER and the conduct of biennial facilities inspections post-licensure. The review of lot release data and the conduct of CBER-generated confirmatory lot release testing allow for detection of changes in manufacturing performance that may impact the safety or efficacy of the product in distribution. Based on the data received, CBER may engage the manufacturer to better understand the trend and may also conduct an inspection of the facilities as a result of the data review. Changes observed relative to the product can be cross-checked against safety databases such as VAERS to determine whether there are safety or efficacy signals being observed during clinical use of the product.

Following licensure, CBER also monitors the distribution of product information to the public. Evaluation of the promotional labeling for a product is evaluated on a routine basis and is assessed for consistency with the product labeling approved by CBER. This surveillance is key to ensuring that accurate, substantiated information is being provided to the public.

Managed Review Process

To facilitate a rapid and efficient review environment, CBER has implemented a managed review process (MRP). The MRP allows for CBER staff to have a well-defined process for review throughout the life cycle of the product, starting before and extending through the IND and BLA phases of development and into the post-marketing phase. The MRP addresses all aspects of regulatory activities from public health–based research, management of exports, evaluation of biologics master files, emergency operations, prevention of product shortages, development of regulatory policy, as well as surveillance and enforcement activities (7). The MRP provides a framework by which each review team member can effectively and efficiently review and communicate their observations to CBER staff, as well as interact with sponsors.

Communication with CBER

A key component to facilitating product development is open and frequent communication with CBER. Communication with CBER can be through formal submissions to the IND or BLA in annual reports required by regulation. These annual reports provide the status of studies under IND or activities that have occurred relative to a licensed product, including the status of post-marketing commitments. In addition to this required reporting, sponsor/applicants can also seek CBER comment and guidance following submission of data and specific questions throughout the product life cycle. Responses to questions may be provided in writing or may be communicated through meeting with the sponsor/applicant.

RESPONDING TO A CHANGING SCIENTIFIC AND REGULATORY LANDSCAPE: CRITICAL PATH INITIATIVES

The FDA has recognized the challenges faced by pharmaceutical companies in sustaining a robust product pipeline for innovative medical therapies (8). In the face of new breakthroughs in biomedical science, the need for a greater leveraging of scientific innovation with product development is critical for moving therapies forward. New scientific discoveries need to be matched with new methods for assessing products to enhance the predictability and efficiency of the development pathway. In this regard, the FDA has launched a Critical Path Initiative, which is designed to provide new tools to enhance the product development pipeline. The list of opportunities for initiatives include expediting product development by advancing GMP initiatives, streamlining clinical trials, and developing better evaluation tools such as biomarkers for predicting adverse reactions. The complete Critical Path Opportunities List can be found at the FDA Web site (9). Several areas that may be important in stimulating vaccine product development are noted below.

Biomarkers for Vaccines

The demonstration of vaccine efficacy is required under Federal Law. The conduct of large-scale field trials with clinical disease endpoints has typically been the gold-standard for new vaccines. The cost and logistics of conducting such studies was recognized as an impediment to rapid evaluation of vaccine candidates. The Critical Path Opportunities List includes the development of surrogate markers of protection, such as immunogenicity, as an opportunity to improve the speed at which novel products are developed. In addition to efficacy endpoints, the analysis of critical path opportunities also noted that advancements in biomarkers as predictors for vaccine adverse reactions, as well as risks for developing enhanced disease, would also have a major impact on improving the critical path to vaccine development.

Manufacturing

Opportunities in the area of improving manufacturing capabilities include the availability of cell lines that are certified free from adventitious agents, which can be used as cell substrates for vaccine manufacture. Use of cell lines for manufacture may improve the consistency of manufacture, reduce adventitious agent testing requirements, and provide a more stable access than use of primary cells. In addition, the development of novel methods for measuring the physical characteristics of products, improved methods for detecting contamination in products, and development of new tools to predict and assess the effect of manufacturing changes on