79 Regulation and Testing of Vaccines

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Vaccines are one of the most significant achievements of science and public health. As a result of successful vaccination programs and campaigns, many vaccine-preventable diseases are now uncommon in the United States. Vaccines for prevention of infectious diseases are regulated by the U.S. Food and Drug Administration (FDA) and the legal framework for regulation is derived from Section 351 of the Public Health Service Act and from certain sections of the federal Food, Drug, and Cosmetic Act (FD&C Act).[1,2] The FD&C Act defines drugs, in part, by their intended use as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease."[2] Thus, vaccines are a unique class of pharmaceutical products that meet the statutory definition of both a drug and biological product. Prophylactic vaccines differ from many other drugs and biologicals primarily in how they are administered to a large population, in particular, young healthy people to prevent rather than treat disease, their mechanism of action, and their risk/benefit profile. Although subject to the same regulations as other biological products, vaccines are inherently more difficult to develop, characterize, and manufacture than most pharmaceutical products. Current U.S. licensed vaccines are listed in Tables 79.1 and 79.2.

HISTORICAL PERSPECTIVE

Regulation of biologics has historically been initiated in response to issues of safety. Over time, legislative authorities have evolved to strengthen and modernize the regulation of vaccines and other biologics. Prior to 1902, manufacturing and product standards for biologics were not federally mandated. However, in 1902, the U.S. Congress passed an act to regulate the sale of viruses, serums, toxins, and analogous products (later referred to as the Biologics Control Act) following the deaths of 20 children who received contaminated products.[3] This Act authorized the Hygienic Laboratory of the Public Health and Marine Hospital Service to issue regulations that governed all aspects of commercial production of vaccines, serums, toxin, and antitoxins and similar products with the objective of ensuring their safety and purity. The regulations under this legislation contained the primary concepts for regulation of biologicals, such as labeling, mandatory facility inspections, and batch-certification guidelines. In 1930, the Hygienic Laboratory was reorganized, expanded, and renamed the National Institutes of Health (NIH).

In 1944, Congress recodified the 1902 Biologics Control Act as part of the U.S. Public Health Service Act (PHS Act) of 1944.[4] The PHS Act incorporated the 1902 Biologics Control Act into Section 351 of the PHS Act (42 U.S.C. 262). As with the 1902 Act, the 1944 PHS Act focused primarily on extensive control over manufacturing methods to ensure safety and purity. Unique to the 1944 PHS Act was Congress' explicit addition of the requirement that biologics manufacturers demonstrate potency as a measure of clinical usefulness. The PHS Act created the Laboratory of Biologics Control to facilitate testing and licensure of biologicals products and manufacturing establishments. After 1944, the authority of the Laboratory of Biologics Control was derived from Section 351 of the PHS Act and from certain sections of the 1938 FD&C Act. In 1948, the Laboratory of Biologics Control joined the NIH Division of Infectious Diseases and Division of Tropical Diseases to form the National Microbiological Institute (later renamed the National Institute of Allergy and Infectious Diseases). Administrative authority for regulation of biologics was originally granted to the National Microbiological Institute.

Although important regulations had been enacted to improve product safety, by the 1950s, the only legal requirement for vaccine licensing was submission of written protocols for vaccine production and safety testing to the Laboratory of Biologics Control. Regulations were dramatically expanded in 1955, when more than 200 cases of polio were attributed to incompletely inactivated polio vaccine manufactured by the Cutter Laboratories. As a result of the "Cutter Incident," administrative authority for the regulation of biologicals was transferred by Congress to the Division of Biologics Standards, a newly created division within the NIH. Regulations were strengthened that required more precise experimental testing to assess the safety of vaccines.

Congress passed the Consumer Safety Act of 1972 and transferred regulatory authority from NIH to FDA for the administration of the 1944 PHS Act. In 1972, the Division of Biologics Standards, which was charged with administering and enforcing Section 351 of the PHS Act, was transferred by the Secretary of Health, Education and Welfare to the FDA, and became the Bureau of Biologics. Once administrative responsibility for the regulation of biologicals was transferred from NIH to FDA, the FDA announced its intention to require that all new biologicals satisfy the additional standards of safety and efficacy mandated in the Drug Amendments Act of 1962. This resulted in the transfer of the regulations pertaining to biologics from Part 73 of Chapter I of Title 42 (USC §262) to Chapter I of Title 21 of the CFR. In 1982, the Bureau of Biologics was renamed the Office of Biologics Research and Review and combined with the Office of Drugs Research and Review to form the Center for Drugs and Biologics. In 1987, following a series of organizational changes within the FDA, the Bureau of Biologics was ultimately transformed into the Center for Biologics Evaluation and Research (CBER). A chronology of the development of the U.S. Biologicals Control Authority is summarized in Table 79.3 and outlined in Fig. 79.1.

FEDERAL LAWS AND REGULATIONS

Since its inception, the FD&C Act has been amended by Congress several times including the FDA Modernization Act (FDAMA) of 1997, the FDA Amendments Act (FDAAA) of 2007, and more recently, the FDA Safety and Innovation Act (FDASIA) of 2012.

Food and Drug Administration Modernization Act

Among other things, the FDAMA of 1997 included measures to modernize the regulation of biologics by synchronizing their review process with that of drugs and eliminating the requirement for an establishment license for biologics. Expedited approval mechanisms for life-threatening conditions also were authorized under FDAMA.[5]

TABLE 79.1 Bacterial Vaccines Currently Licensed in the United States

Vaccine	Manufacturer
Anthrax vaccine, adsorbed	Emergent Biodefense Operations Lansing, Inc.
BCG vaccine	Organon Teknika Corporation
Cholera vaccine, live, oral	Pax Vax Bermuda Ltd.
Diphtheria and tetanus toxoids adsorbed	Sanofi Pasteur, Inc.
Diphtheria and tetanus toxoids and acellular pertussis vaccine, adsorbed	Sanofi Pasteur, Inc.,[a] Sanofi Pasteur, Ltd., GlaxoSmithKline Biologicals
Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine combined	GlaxoSmithKline Biologicals
Diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine	Sanofi Pasteur, Ltd., GlaxoSmithKline Biologicals
Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *Haemophilus influenzae* type b conjugate (tetanus toxoid conjugate) vaccine	Sanofi Pasteur, Ltd.
Tetanus and diphtheria toxoids, adsorbed	Massachusetts Public Health Biological Laboratories
Tetanus and diphtheria toxoids, adsorbed for adult use	Sanofi Pasteur, Inc., Sanofi Pasteur, Ltd.
Tetanus toxoid	Sanofi Pasteur, Inc.
Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed	Sanofi Pasteur, Ltd., GlaxoSmithKline Biologicals
Haemophilus influenzae type b conjugate vaccine (meningococcal protein conjugate)	Merck Sharp and Dohme Corp.
Haemophilus influenzae type b conjugate vaccine (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine	Merck Co., Inc.
Haemophilus influenzae type b conjugate vaccine (tetanus toxoid conjugate)	GlaxoSmithKline Biologicals, Sanofi Pasteur S.A.
Meningococcal (groups A, C, Y, and W-135), oligosaccharide diphtheria CRM_{197} conjugate vaccine	Novartis Vaccines and Diagnostics, Inc.
Meningococcal group B vaccine	Wyeth Pharmaceuticals Inc., Novartis Vaccines and Diagnostics, Inc.
Meningococcal groups C and Y and *Haemophilus influenzae* type b tetanus toxoid conjugate vaccine	GlaxoSmithKline Biologicals
Meningococcal (groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine	Sanofi Pasteur, Inc.
Meningococcal polysaccharide vaccine, A, C, Y, W135 combined	Sanofi Pasteur, Inc.
Pneumococcal polysaccharide vaccine, polyvalent	Merck Co., Inc.
Pneumococcal 7-valent conjugate vaccine (diphtheria CRM_{197} protein)	Wyeth Pharmaceuticals Inc.
Pneumococcal 13-valent conjugate vaccine (diphtheria CRM_{197} protein)	Wyeth Pharmaceuticals Inc.
Typhoid vaccine, live oral, Ty21a	Berna Biotech
Typhoid Vi polysaccharide vaccine	Sanofi Pasteur S.A.

[a]License for the pertussis component of this product is held by the Research Foundation for Microbial Diseases of Osaka University (Aventis Pasteur Laboratories, Inc.).

Pediatric Research Equity Act

The Pediatric Research Equity Act (PREA) of 2003 amended the FD&C Act by adding Section 505(B) to address product development for pediatric subjects from birth to 16 years of age.[6] It requires that manufacturers submit a pediatric assessment with every application submitted under Section 505 of the FD&C Act or section 351 of the PHS Act for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration unless the applicant has obtained a waiver or deferral from the FDA. The pediatric assessment must contain data adequate to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations and data to support dosing and administration for each pediatric subpopulation for which the product is safe and effective.

Food and Drug Administration Amendments Act

The FDAAA of 2007 includes 11 titles that added many new provisions to the FD&C Act.[7] It reauthorized and amended several drug and medical device provisions, and provided the FDA with additional responsibilities and new authorities. The provisions of FDAAA that have had a significant impact on the regulations of vaccines and the review process are contained in Title IV, the PREA, and Title IX, Enhanced Authorities Regarding Postmarket Safety of Drugs. The FDAAA reauthorized and revised the PREA, primarily to enhance FDA oversight and applicant accountability for the agreed-upon

TABLE 79.2 Viral Vaccines Currently Licensed in the United States

Vaccine	Manufacturer[a]
Adenovirus type 4 and type 7 vaccine, live	Barr Labs Inc.
Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine combined	GlaxoSmithKline Biologicals
Diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine	Sanofi Pasteur, Ltd., GlaxoSmithKline Biologicals
Hepatitis A vaccine, inactivated	Merck & Co., Inc., GlaxoSmithKline Biologicals
Hepatitis B vaccine, recombinant	Merck & Co., Inc., GlaxoSmithKline Biologicals
Hepatitis A vaccine, inactivated and hepatitis B (recombinant) vaccine	GlaxoSmithKline Biologicals
Haemophilus influenzae type b conjugate vaccine (meningococcal protein conjugate) and hepatitis B recombinant vaccine	Merck & Co., Inc.
Human papillomavirus (types 6, 11, 16, 18) recombinant vaccine	Merck & Co., Inc.
Human papillomavirus bivalent (types 16 and 18) vaccine, recombinant	GlaxoSmithKline Biologicals
Human papillomavirus 9-valent vaccine, recombinant	Merck & Co., Inc.
Influenza virus vaccine, trivalent, types A and B	Sanofi Pasteur, Inc., Novartis Vaccines and Diagnostics Ltd., GlaxoSmithKline Biologicals, ID Biomedical Corporation of Quebec, CSL, Ltd., Protein Sciences Corporation
Influenza A (H1N1) 2009 monovalent	Sanofi Pasteur, Inc., Novartis Vaccines and Diagnostics Ltd., ID Biomedical Corporation of Quebec, MedImmune Vaccines, Inc., CSL, Ltd.
Influenza virus vaccine, H5N1 (for national stockpile)	Sanofi Pasteur, Inc.
Influenza A (H5N1) virus monovalent vaccine, adjuvanted	ID Biomedical Corporation of Quebec
Influenza vaccine, adjuvanted	Novartis Vaccines and Diagnostics
Influenza virus vaccine, quadrivalent, types A and B	Sanofi Pasteur, Inc., GlaxoSmithKline Biologicals, ID Biomedical Corporation of Quebec, MedImmune Vaccines, Inc.
Influenza virus vaccine, intranasal	MedImmune Vaccines, Inc.
Japanese encephalitis vaccine, inactivated	The Research Foundation for Microbial Diseases of Osaka University
Japanese encephalitis vaccine, inactivated, adsorbed	Valneva Austria GmbH
Measles, mumps, and rubella virus vaccine, live	Merck & Co., Inc.
Measles, mumps, rubella, and varicella vaccine, live	Merck & Co., Inc.
Poliovirus vaccine inactivated, monkey kidney cell	Sanofi Pasteur, S.A.
Rabies vaccine	Novartis Vaccines and Diagnostics Ltd., Sanofi Pasteur, S.A.
Rotavirus vaccine, live, oral	GlaxoSmithKline Biologicals
Rotavirus vaccine, live, oral, pentavalent	Merck & Co., Inc.
Rubella virus vaccine, live	Merck & Co., Inc.
Smallpox (vaccinia) vaccine, live	Sanofi Pasteur Biologics
Varicella virus vaccine live	Merck & Co., Inc.
Yellow fever vaccine	Sanofi Pasteur, Inc.
Zoster vaccine, live	Merck & Co., Inc.

[a]These are the names of the license holders. Company names may be different.

pediatric assessments.[8] Of note, a new provision directed the FDA to establish the Pediatric Review Committee (PeRC), an internal review committee with pediatric expertise. This committee is required to provide consultation to FDA review divisions on all pediatric plans and assessments and on all deferral and waiver requests. Thus, early in the application review process the review team must assess whether PREA applies. If PREA applies, then a pediatric assessment must be presented to the PeRC.

Section 901 of Title IX of the FDAAA authorizes the FDA to require certain postmarketing studies and clinical trials for prescription drug and biological products approved under Section 505 of the FD&C Act or Section 351 of the PHS Act (42 USC §262). Section 901 of the FDAAA also created new Sections 505–1 and 505(o)(4) of the FD&C Act, authorizing the FDA, under certain circumstances, to require risk evaluation and mitigation strategies and safety-related labeling changes, respectively. The FDAAA also specifies adverse event reporting requirements for products with labeling changes that are a result of a pediatric assessment. Specifically, during the 12 months from the date that such a labeling change is made, all adverse event reports are reviewed by the FDA Pediatric Advisory Committee. Following review, the Pediatric Advisory Committee makes recommendations regarding whether

TABLE 79.3 Chronology of the Development of Biologic Control Authority

Year	Legislation Enacted	Existing Organization
1902	Biologics Control Act (Virus, Serum, Toxin Law) of 1902	Public Health Hygienic Laboratory
1930		Hygienic Laboratory renamed National Institutes of Health (NIH)
1937		Laboratory of Biologics Control (LBC) formed within NIH
1944	Enactment of U.S. Public Health Service Act (42 USC §§262, 263)	
1948		LBC incorporated into the National Microbiological Institute (later renamed the National Institute of Allergy and Infectious Diseases)
1955		Establishment of the Division of Biologics Standards (DBS) by the Surgeon General
1972		DBS transferred to FDA to become Bureau of Biologics (BoB)
1982–1983		BoB renamed Office of Biologics Research and Review (OBRR); joined with Office of Drugs Research and Review (ODRR) to form the Center for Drugs and Biologics (CDB)
1987		OBRR renamed Center for Biologics Evaluation and Research (CBER)
1997	Food and Drug Administration Modernization Act of 1997	
2007	Food and Drug Administration Amendments Act (FDAAA)	
2012	Food and Drug Administration Safety and Innovation Act (FDASIA)	

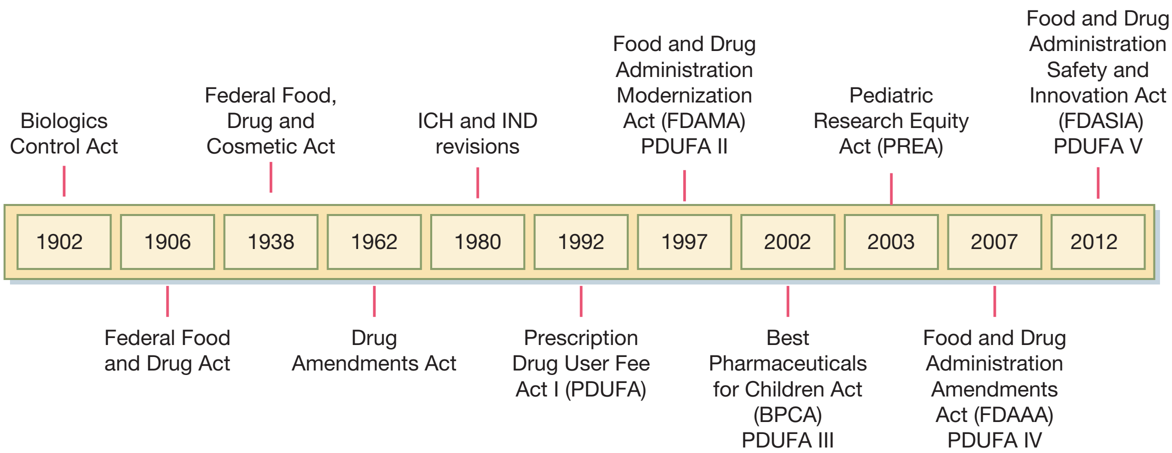

Figure 79.1. History of Food and Drug Law. ICH, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; IND, investigational new drug.

the FDA should take action in response to such reports and whether the current pharmacovigilance plan is adequate.

Food and Drug Administration Safety and Innovation Act

The FDASIA was signed into law in 2012 and expanded the FDA's authority by strengthening the agency's ability to safeguard and advance public health by promoting innovation, increasing stakeholder involvement in FDA processes, and enhancing the safety of the drug supply chain.[9] In addition to reauthorizing the prescription drug and medical device user fee programs, FDASIA established new user fee programs for generic drugs and biosimilar biological products. The provisions of FDASIA that impact the regulation of vaccines are contained in Pediatric Drugs and Devices (Title V) and Drug Approval and Patient Access (Title IX). Title IX expands the scope of products that qualify for accelerated approval and creates a new "breakthrough therapy" program, among other things (see below). FDASIA also revised PREA to include a provision that requires vaccine manufacturers to submit a Pediatric Study Plan early in the drug development process. This initial Pediatric Study Plan must contain an outline of the pediatric study or studies that the sponsor plans to conduct including, to the extent practicable, study objectives and design, age groups, relevant end points, and statistical approach, as well as any request for a deferral, partial waiver, or waiver. The FDA internal PeRC must be consulted for the review of the initial study plan, the agreed initial pediatric plan, and certain amendments to such plans. Both sponsors and the FDA must comply with prescribed timelines regarding submission, review, responses, and agreements reached regarding the Pediatric Study Plan, which are also described in applicable FDA guidance.[10]

Prescription Drug User Fee Act

Of note, these amendments to the FD&C Act also renewed the Prescription Drug User Fee Act (PDUFA) that was first enacted in 1992, and authorized the FDA to collect user fees from companies. These fees enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. In return for these additional resources, the FDA agreed to certain review performance goals, such as completing reviews of new drug applications and biologics license applications (BLAs) and taking regulatory actions on them in predictable timeframes. These changes revolutionized the drug approval process in the United States and enabled FDA to speed the application review process for new drugs and biologics without compromising the FDA's high standards for demonstration of safety, efficacy, and quality. The PDUFA program has been reauthorized every 5 years, 1997 (PDUFA II), 2002 (PDUFA III), 2007 (PDUFA IV), and 2012 (PDUFA V). It includes the 5-year review performance goals for drug and BLAs, supplements and resubmissions, meeting management goals, clinical holds, major dispute resolution, special protocol question assessment and agreement, electronic applications and submissions, discipline review, and complete response letters.

FEDERAL REGULATIONS AND FOOD AND DRUG ADMINISTRATION GUIDANCE

The FDA's CBER is the national regulatory authority in the United States charged with the regulation of biological products including vaccines. The review of vaccine applications occurs among CBER's Office of Vaccines Research and Review, Office of Compliance and Biologics Quality, and Office of Biostatistics and Epidemiology. CBER's current legal authority for the regulation of vaccines derives primarily from Section 351 of the PHS Act and from certain sections of the FD&C Act. The statutes of the PHS Act are implemented through regulations codified in the Code of Federal Regulations (CFR). The CFR is published annually and contains all changes in regulations that have occurred during the previous year that were published in the *Federal Register*. Regulations are adopted in conformity with the Administrative Procedure Act.[11] Thus, before a regulation can be established, repealed, or revised, it must be proposed and published in the *Federal Register* with an invitation to all interested individuals or parties to comment within a prescribed time, commonly a period of 1 to several months. Once comments are received, they are evaluated and considered by the FDA before publication of the final regulation in the *Federal Register*.

Title 21 of the CFR, parts 600 through 680, contains regulations specifically applicable to vaccines and other biologicals. In addition, because vaccines meet the legal definition of a drug under the FD&C Act, manufacturers must comply with regulations for Current Good Manufacturing Practices (CGMPs) (parts 210 and 211). Table 79.4 summarizes the regulations applicable to vaccines and other biological products. These regulations cover not only the methods and establishment standards pertaining to the manufacture of a biological product to assure that the product is safe and meets the quality and purity characteristics that are claimed by the manufacturer, but also requirements for performing clinical trials (i.e., 21 CFR §312).

A single set of basic regulatory requirements applies to all vaccines, regardless of the technology used to produce them. The regulatory approval criteria contained in Title 21 CFR also apply to vaccines, regardless of their indication or intended target population. Section 351 of the PHS Act (42 USC §262) states that a BLA can be approved based on a demonstration that "…(a) the biological product that is the subject of the application is safe, pure, and potent; and (b) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent…"

Some of the more pertinent operational definitions for biologics contained in the statutes and 21 CFR are as follows:

- Section 351 of the PHS Act defines a biological product as any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of diseases or conditions of human beings. Thus, vaccines clearly are regulated as biological products.
- Safety is defined as the relative freedom from harmful effect to people affected directly or indirectly by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the

TABLE 79.4 Regulations Applicable to the Development, Manufacture, Licensure, and Use of Vaccines[a]

Title 21, Code of Federal Regulations, Chapter 1: FDA, DHHS[a]	Subject
SUBCHAPTER F—BIOLOGICS[b]	
600	Biologic products, general, definitions Establishment standards Establishment inspection Adverse experience reporting
601	Licensing
610	General biologicals product standards
SUBCHAPTER C—DRUGS: GENERAL	
201	Labeling
202	Prescription drug advertising
210	Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs
211	Current good manufacturing practice for finished pharmaceuticals
SUBCHAPTER D—DRUGS FOR HUMAN USE	
312	New drugs for investigational use
314	Applications for FDA approval to market a new drug or an antibiotic drug
SUBCHAPTER A—GENERAL	
25	Environmental impact considerations
50	Protection of human subjects
56	Institutional review boards
58	Nonclinical laboratory studies, good laboratory practice regulations,[a] FDA, DHHS

[a]Food and Drug Administration, Department of Health and Human Services, Administration Code of Federal Regulations (CFR) Title 21. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

[b]Consists of Parts 600–680. Parts 606, 607, 640, 660 and 680 apply to blood, blood products, diagnostic test and allergenics.

DHHS, Department of Health and Human Services; FDA, Food and Drug Administration.

recipient at the time. Thus, the property of safety is relative and cannot be ensured in an absolute sense.

- Purity is defined as the relative freedom from extraneous matter, regardless of whether it is harmful to the recipient or deleterious to the product. Usually, the concepts of purity and safety coincide; purity most often relates to freedom from such materials as pyrogens, adventitious agents, and chemicals used in manufacture of the product.
- Potency is defined as the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through administration of the product in the manner intended, to effect a given result. Potency, as thus defined, is equivalent to the concept that the product must be able to perform as claimed, and, if possible, this must correspond with some measurable effect in the recipient or correlate with some quantitative laboratory finding.
- Standards mean specifications and procedures applicable to an establishment or to the manufacture or release of products that are designed to ensure the continued safety, purity, and potency of biological products. The word standard is also used with a secondary meaning, usually in the sense of a reference preparation, such as a bacterial or viral antigen that can be used in evaluating potency or, in some cases, safety and purity.
- The regulations regarding biological products, in addition, define effectiveness as the reasonable expectation that, in a significant proportion of the target population, pharmacologic or other effects of the biological product, when administered under adequate directions for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans.
- CGMPs define a quality system that manufacturers use as they build quality into their products. The regulations outline the minimum manufacturing, quality control, and quality assurance requirements for the preparation of a drug or biological product for commercial distribution. For example, approved products developed and produced according to CGMPs are safe, properly identified, of the correct strength, pure and of high quality.

The FDA also periodically publishes various guidelines and guidance documents with regard to the manufacture and clinical evaluation of biologicals. These documents published by the FDA do not have the force of law, but are intended to provide useful and timely recommendations; Table 79.5 lists those applicable to vaccines. Guidance documents are particularly useful as a means for the FDA to provide recommendations that are current with areas of rapidly progressing science, and for specifying a degree of detail beyond what is included in the regulations. In the past few years, several FDA regulations and guidance documents have had a direct impact on the review of vaccines for licensure by the FDA, such as the "Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics (2014)."[12] Some of these regulations and guidance documents evolved from an effort to streamline the regulatory process, while others—such as "Guidance for Industry: Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines (2007)", "Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines (2007)," "Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Material Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases (2010)," and "Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications (February 2006)"—were written to facilitate the development of new vaccines with new technologies.[13–16] These documents are available at CBER's website.[17]

COLLABORATIONS BETWEEN THE FOOD AND DRUG ADMINISTRATION AND NATIONAL AND INTERNATIONAL PARTNERS

The FDA's CBER regulatory review staff consists of an internal multidisciplinary team of scientists, medical officers, and regulatory and public health professionals. To stay current on scientific advances and biotechnologies, the team is involved in a dynamic exchange of information with the outside scientific community through laboratory research and collaborations, participation in workshops and seminars, and engagement with national partners. The FDA also relies on the expertise of formal advisory committees, which include experts in the fields of vaccinology, microbiology, infectious diseases, immunology, biostatistics, epidemiology, and clinical trial design. In addition, CBER works closely with its counterparts in other U.S. government agencies within the Department of Health and Human Services and the U.S. Public Health Service (PHS), such as the National Vaccine Program Office, the Centers for Disease Control and Prevention (CDC), the NIH, and the Health Resources and Services Administration. The CDC is responsible, among its other duties, for epidemiologic surveillance of disease and for support of immunization programs. Its Advisory Committee on Immunization Practices makes recommendations for vaccine use. The Director of the National Vaccine Program Office coordinates vaccine efforts throughout the PHS and other governmental agencies. The NIH is responsible for conducting and providing funds for a wide variety of biomedical research. The Health Resources and Services Administration is responsible for managing the National Vaccine Injury Compensation Program. Other important collaborators inside the U.S. government involved in vaccine activities include the U.S. Department of Defense, and the Department of Veterans Affairs. Additionally, CBER works closely with its multilateral partners, notably the Pan American Health Organization and the World Health Organization (WHO), to provide assistance in regulatory capacity building. CBER has been very active in supporting the WHO's Developing Countries' Vaccine Regulators Network and the WHO's African Regional Office-led African Vaccine Regulatory Forum. As a WHO Collaborating Center, CBER contributes to a range of activities, including establishment of physical and written standards, implementation of WHO international standards, strengthening global regulatory systems, and serving as the National Regulatory Authority (NRA) of reference for WHO's vaccine prequalification program. CBER experts also contribute as members of several WHO Advisory Committees including the Global Advisory Committee on Vaccine Safety, the Polio Research Committee, the HIV Vaccine Advisory Committee, and the Expert Committee on Biological Standardization. CBER is an Essential Regulatory Laboratory in WHO's Global Influenza Surveillance and Response System. In addition, the FDA has confidentiality arrangements with many NRAs around the globe, allowing it to share information as part of its regulatory processes. These arrangements have strengthened interactions between the regulatory authorities and have contributed to improving the promotion and protection of public health globally.

MANAGED REVIEW PROCESS

The regulatory review in CBER incorporates a managed and integrated regulatory process that is continuous from

TABLE 79.5 Guidance Documents Applicable to Development, Manufacture, Licensure, and Use of Vaccines[a]

Document	Date
GUIDANCE DOCUMENTS	
Draft Guidance for Industry: Formal Meetings between the FDA [Food and Drug Administration] and Sponsors or Applicants of PDUFA [Prescription Drug User Fee Act] Products	2015
Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics	2014
Providing Submissions in Electronic Format—Postmarketing Safety Reports for Vaccines: Draft Guidance for Industry 7/2014	2014
Guidance for Industry: General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases	2011
Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications	2010
Draft Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines	2009
Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccine	2007
Guidance for Industry: Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines	2007
Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	2007
Draft Guidance: Emergency Use Authorization of Medical Products	2007
Draft Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases	2006
Guidance for Industry: Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997	2006
Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format	2006
Draft Guidance for Industry: Labeling for Human Prescription Drug and Biological Products: Implementing the New Content and Format Requirements	2006
Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format	2006
Draft Guidance for Industry: INDs [investigational new drugs]—Approaches to Complying with CGMP [Current Good Manufacturing Practices] During Phase 1	2006
Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications	2006
Guidance for Industry: Fast Track Drug Development Programs—Designation, Development, and Application Review	2006
Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations	2006
Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format—Lot Release Protocols	2006
Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications	2005
Guidance for Industry: Development and Use of Risk Minimization Action Plans	2005
Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act	2005
Guidance for Industry: FDA Review of Vaccine Labeling Requirements for Warnings, Use Instructions, and Precautionary Information	2004
Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing Current Good Manufacturing Practice	2004
Draft Guidance for Industry: Vaccinia Virus—Developing Drugs to Mitigate Complications from Smallpox Vaccination	2004
Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines	2001
Draft Guidance for Industry on Recommendations for Complying with the Pediatric Rule	2000
Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products	2000
Guidance for Industry: Submitting and Reviewing Complete Responses to Clinical Holds	2000
Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information for a Vaccine or Related Product	1999
Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products	1998
Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products	1998
Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997—Elimination of Certain Labeling Requirements	1998
Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications	1998
Guidance for Industry for the Evaluation of Combination Vaccines for Preventable Diseases: Production, Testing and Clinical Studies	1997
Guidance for Industry: Changes to an Approved Application: Biological Products	1997
Guidance on Alternatives to Lot Release for Licensed Biological Products	1994

Continued on following page

TABLE 79.5 Guidance Documents Applicable to Development, Manufacture, Licensure, and Use of Vaccines[a] *(Continued)*

Document	Date
GUIDELINES	
Guidance for Industry: Process Validation: General Principles and Practice[a] Revision of the 1987 guidance General Principles of Process Validation.	2011
Guideline on General Principles of Process Validation	1987
Determination of Residual Moisture in Dried Biological Products	1990
POINTS TO CONSIDER	
Supplement: Nucleic Acid Characterization and Genetic Stability	1992
Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology	1985

[a]Guidance documents are available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm. They are also available at no charge from the Office of Communication, Training and Manufacturers Assistance, HFM-40, 1401 Rockville Pike, Rockville, MD 20852–1448.

discovery to postmarketing, and is designated as the Managed Review Process.[18] CBER's managed review process is designed to effectively review all regulatory submissions to reach informed evidence-based regulatory decisions to ensure safe and effective biological products. CBER uses a team-based approach with substantive involvement of discipline team leaders and management.

The Managed Review Process begins when a sponsor requests a pre–investigational new drug (IND) meeting that may result in the submission of an IND and, eventually, a BLA. The review process in CBER begins with an initial review of a submission for scientific content and compliance with the regulations. Members of a multidisciplinary review team are selected based on their expertise with the type of product and its method of manufacture. It is the responsibility of CBER's review component to evaluate submissions and recommend appropriate regulatory action to facilitate the approval of safe and effective biological products. The review includes an evaluation of chemistry, manufacturing, and controls information; the manufacturing facility and equipment; preclinical and clinical data on the safety, efficacy, pharmacology, and toxicology; the suitability of clinical trial design; and analysis of clinical data derived from such trials. In addition, reviewers monitor for conformance with FDA regulations in all phases of biological product development, including postmarketing. CBER scientists also perform research in the areas of statistical and epidemiologic analysis, clinical trial design, and chemistry, manufacturing and control specific to product issues, and contribute to policy development. Surveillance activities are performed to ensure that the safety of biological products is not compromised. These activities ensure the rapid availability and approval of safe and effective biological products.

MEETINGS WITH SPONSORS

The FDA encourages meetings with sponsors to the extent that they aid in the evaluation of the vaccine and in resolving scientific issues concerning the product. The general principle underlying the conduct of such meetings is that there should be free, full, and open communication about any scientific or medical question that may arise. Agreements reached at PDUFA meetings (e.g., pre-IND, IND, pre-BLA, and BLA meetings) are recorded in official minutes taken by FDA personnel and provided to the sponsor. They serve as a permanent record of any agreements reached. Detailed information on the conduct of regulatory meetings is described in 21 CFR §312.47.[19]

STAGES OF THE REGULATORY REVIEW OF VACCINE PRODUCTS

Premarketing Phase

The regulatory requirements for biological products cover the entire life-cycle of the product from the pre-IND stage, through the premarketing (consisting of the various IND phases and prelicensure) and postmarketing stages. The pre-IND stage consists of laboratory development, preclinical testing of candidate vaccines, and development of the manufacturing process. The clinical development of a new drug in the United States usually begins with a sponsor approaching the FDA for permission to conduct a clinical study with an investigational product through submission of an IND application form. These requirements can be found in the IND regulations.[20] Sponsors are encouraged to request a pre-IND meeting with FDA to discuss preclinical studies, clinical study design, and data requirements that require resolution prior to the initiation of clinical trials. In the application, the sponsor (a) describes the composition, source, and method of manufacture of the product and the methods used in testing its safety, purity, and potency; (b) provides a summary of all laboratory and preclinical animal testing; and (c) provides a description of the proposed clinical study and the names and qualifications of each clinical investigator. The FDA has a maximum of 30 days to review the original IND application and determine whether study participants will be exposed to any unacceptable risks. As part of the IND process, each clinical investigator files information describing the investigator's qualifications for performing clinical trials, details of the proposed study, and assurance that a number of conditions specified by the regulations will be met. A signed informed consent must be obtained from each study participant. Approval for the study must be obtained in advance from a local institutional review board. The regulations also cover the evaluation of the preclinical laboratory animal studies undertaken to support the use of the product in humans.

Investigational Phase

Only licensed vaccines may be shipped from one state to another; however, during the premarketing phase, interstate shipment of products for investigational use is allowed under the law and regulations. There are generally three separate phases in the clinical evaluation of experimental biologicals at the premarketing stage (Fig. 79.2). These phases may overlap, and the clinical testing may be highly iterative because

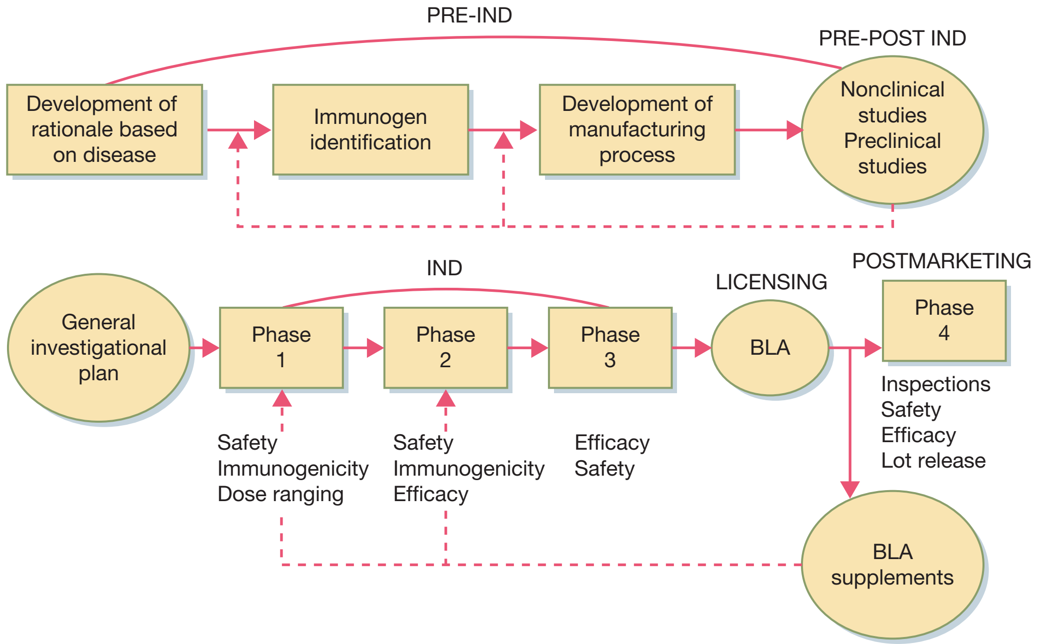

Figure 79.2. Sequence of key events in product development through the premarketing experimental investigational new drug (IND) and licensing phases and the postapproval marketing phase. Dashed lines indicate additional research/development submissions when significant changes are made in the product or its indications. BLA, biologics license application.

multiple Phase I or Phase II trials may be performed as new data are obtained. Phase I trials are intended primarily to provide a preliminary evaluation of safety and immunogenicity. These trials are typically conducted in a small number (e.g., 20 to 80) of closely monitored adult volunteers. If the ultimate target population for the vaccine is infants or young children, as is commonly the case, the product is usually evaluated in a stepwise progression from older to younger age groups down into the first year of life. Phase II studies can involve up to several hundred participants, are often randomized and well-controlled, and provide further information on safety and immunogenicity and optimal dose. In some cases, Phase II studies may provide preliminary data on the vaccine's activity against the infectious disease of interest. Phase III studies are large-scale trials to provide a more thorough assessment of safety as well as a definite assessment of efficacy.

The general considerations for clinical studies to support licensure of a vaccine include demonstration of safety, efficacy (immunogenicity may be sufficient in some cases), and evaluation of simultaneous administration with other licensed vaccines. Vaccine efficacy should be demonstrated, ideally in randomized, double-blind, well-controlled trials. The end points are product specific, and may be clinical disease end points or immune response end points if efficacy against clinical disease had been previously established and there are immune correlates or surrogates of that protection. In recent years, efficacy trials for various vaccines have involved a broad range in the number of study participants, from thousands to tens of thousands. This broad range is related to a number of interconnected variables such as study design and the incidence of the disease to be prevented. For example, clinical disease end point studies that are designed to demonstrate that a new vaccine is noninferior to an already existing product of the same type generally require larger numbers than one in which a new vaccine can be compared with a control that has no activity against the clinical disease. The incidence of the disease to be prevented in the study population is also important. As an example, a trial to show that pneumococcal seven-valent polysaccharide conjugate vaccine (PCV7) was successful in preventing a low incidence of invasive pneumococcal disease caused by the *Streptococcus pneumoniae* capsular serotypes included in the vaccine enrolled close to 40,000 children who were randomized equally to receive the pneumococcal conjugate vaccine or an unrelated control vaccine. In contrast, licensure of the pneumococcal 13-valent polysaccharide conjugate vaccine (PCV13) was based on noninferiority comparative studies to PCV7. Effectiveness of PCV13 was inferred from measuring anti-polysaccharide binding and functional opsonophagocytic antibodies because clinical end point disease efficacy studies were no longer feasible owing to the further decline of invasive pneumococcal disease as a result of introduction of PCV7 in the United States.

In some situations, human challenge studies have been conducted during early clinical development or in lieu of clinical trials in an endemic area. These studies served to demonstrate "proof of concept" of the vaccine early in clinical development (e.g., *Plasmodium falciparum* sporozoite challenge of malaria-naïve U.S. volunteers previously administered a candidate malaria vaccine). Human challenge studies may also be considered to demonstrate the efficacy of the vaccine. For example, the Agency convened the Vaccines and Related Biologics Products Advisory Committee (VRBPAC) to consider whether data from human challenge studies in U.S. subjects could be sufficient to demonstrate efficacy of a cholera vaccine in travelers to endemic areas who are at high risk for contracting the disease. In 1998, the VRBPAC agreed that human challenge studies could suffice to demonstrate efficacy of a cholera vaccine provided that studies were adequate and well-controlled and conducted under the provisions of good clinical practices.[21] In 2016, the FDA approved Vaxchora, a live, attenuated vaccine for the prevention of cholera in adults traveling to cholera-affected areas. Efficacy of Vaxchora was demonstrated in a controlled human challenge study in adult U.S. volunteers.

Safety is one of the most important considerations when evaluating new vaccines and modifications to currently licensed vaccines. The initial responsibility for determining vaccine safety starts with clinical investigators and vaccine manufacturers. The FDA is responsible for assuring that clinical trials are done under good clinical practices, a requirement essential for the evaluation of safety data intended to support a license application. In general, when evaluating safety, one must compare the risk of the vaccine-preventable disease with the risk of the adverse event(s) potentially associated with the vaccine, and these may change over time. As an example, the reported association between Rotashield (rotavirus vaccine, live, oral, tetravalent, manufactured by Wyeth) and intussusception resulted in the additional requirement for the evaluation of the safety of RotaTeq (live, oral pentavalent human-bovine reassortant rotavirus vaccine, manufactured by Merck) with respect to intussusception. This clinical trial enrolled more than 70,000 infants divided equally between RotaTeq and placebo. The primary safety hypothesis was that the oral RotaTeq would not increase the risk of intussusception relative to placebo within 42 days of any dose. The intended target population should be taken into consideration in assessing the adequacy of the safety database. For routinely administered childhood vaccines in the United States, the target population would be the birth cohort in the United States (approximately 4 million/year). This is generally a healthy population, and a government body (e.g., state or local governments) may mandate vaccination. Common reactions can be studied adequately in hundreds of individuals, but many thousands will be required to define low-incidence adverse reactions.

For vaccines evaluated in clinical end point efficacy trials, a large safety database likely will derive from a double-blind, randomized, well-controlled efficacy study. However, for vaccines evaluated in immunogenicity end point studies, additional studies likely will be needed to obtain an adequate safety database. Additional controlled safety studies are often requested when the numbers of subjects included in the efficacy studies are deemed insufficient to provide adequate safety data. Safety studies may be unblinded if the number of injections, route of administration, or schedule differs between groups, in particular when infants and young children are involved. Phase II safety studies should provide data on common local and systemic reactions to the study vaccine. Phase II clinical development also should include immunogenicity and preliminary safety data on the concurrent administration of the study vaccine with other vaccines, if relevant. Phase III safety studies are designed to evaluate less common reactions, may be unequally randomized, and may have a simplified trial design for assessing less-common adverse events in large trials. If a vaccine is recommended on the same schedule as other routinely recommended vaccines, safety and immunogenicity data should be obtained in prelicensure studies to support simultaneous administration.

Licensing Phase

Following completion of IND studies demonstrating the safety and efficacy of the vaccine for a specific use and population the sponsor can submit a BLA to obtain a license for a new vaccine under section 351 of the PHS Act for commercial manufacture and distribution of the product. Prior to the submission of a BLA, a pre-BLA meeting with the FDA is strongly encouraged to discuss the sponsor's product development plan. For the FDA to provide sponsors with advice regarding the adequacy of information to support a BLA, the following information in advance of the pre-BLA meeting should be submitted, depending on the type of meeting: (a) an executive summary of the clinical studies to be submitted in the application; (b) a proposed format for organizing the submission, including methods for presenting the data; (c) information on the status of needed or ongoing studies; and (d) any other information for discussion at the meeting. The primary purpose of this exchange is to uncover any major unresolved problems; identify those studies that the sponsor is relying on as adequate and well-controlled to establish the product's effectiveness; identify the status of ongoing studies; acquaint FDA reviewers with the general information to be submitted in the BLA (including technical information); review methods used in the statistical analysis of the data; and discuss the best approach for the presentation and formatting of data in the application.

At the time that an applicant submits a BLA to the Director of CBER's Office of Vaccines Research and Review precise production methods and procedures should be defined, and the manufacturing process should be standardized. Critical information to be contained in the BLA include data derived from nonclinical laboratory and clinical studies that demonstrate that the manufactured product meets prescribed requirements for safety, purity, and potency. The BLA should contain information that supports compliance with standards addressing requirements for (a) organization and personnel; (b) buildings and facilities; (c) equipment; (d) control of components, containers, and closures; (e) production and process controls; (f) packaging and labeling controls; (g) holding and distribution; (h) laboratory controls; and (i) records to be maintained. Furthermore, a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product for introduction or delivery for introduction into interstate commerce; summaries of test results performed on the lot(s) represented by the submitted sample(s); specimens of the labels, enclosures, and containers; and the address of each location involved in the manufacture of the biological product should be included in the BLA.

An application for a biologics license is not considered as filed (or accepted by the agency for review) until CBER determines that it has received all pertinent information and data from the applicant. In this regard, CBER can refuse to file a BLA if it deems the submission to be incomplete. Additionally, the manufacturing facility must be inspection-ready at the time the BLA is submitted. The applicant is also required to include either an environmental assessment or a claim for categorical exclusion from the requirement to submit an environmental assessment or an environmental impact statement. Other components of the BLA review include product labeling, which describes the indications for use, contraindications, dosage and possible adverse effects; protocols for the manufacturing and testing of the number of product lots specified to establish the consistency of the process; and confirmatory testing results within CBER of samples of in-process material or product in final containers and conformance to existing regulations.

An internal CBER multidisciplinary committee performs the scientific review of the BLA. This process occurs for each BLA or supplement to a BLA in which significant changes are proposed. During the review, there are discussions and exchanges of correspondence between the sponsor and the CBER review committee concerning issues that may arise. During the FDA review of the BLA an announced prior approval inspection (PAI) of the manufacturing facility is performed. This inspection is designed as an in-depth review of the facilities, records, total production process, methods, equipment, quality control procedures, and personnel. With the implementation of the BLA process, changes have occurred in the scope of issues reviewed during the PAI. Instead of the manufacturer submitting detailed records with the BLA regarding studies on cleaning validation, monitoring data for pharmaceutical-grade water, facility support systems (e.g., clean steam, compressed air, and building management systems), and other facility-related systems, a more detailed review of this type of data is done onsite during the PAI. PAIs tend to require longer periods of time for the FDA inspectors to be in the facility because of the increased scope of issues that are reviewed onsite. If licensure is denied following inspection for the original license application, reinspection will occur after receipt of assurance that all deficiencies that were the basis of the denial were corrected.

With the implementation of FDAAA (2007) and FDASIA (2012), in addition to completing the discipline reviews during the PDUFA V mandated timelines, the review committee must complete numerous additional tasks. These include, but are not limited to, review committee assignments, internal information exchange meetings, filing decisions, presentation of the application to the PeRC, midcycle review meetings and midcycle communication with the applicant, late-cycle meetings with the applicant, and presentation of planned or required postmarketing studies to an internal FDA safety committee.

After CBER reviews the entire package of information in the BLA, its advisory committee (the VRBPAC) and consultants, if needed, are asked to review and comment on the adequacy of the data to support safety and efficacy in the target population. The standards for safety and efficacy are relative; that is, the benefit-to-risk ratio of a biological product is considered. The VRBPAC's advice is considered in CBER's decision regarding licensure, and in developing recommendations for use to be given in the package insert. The committee may recommend additional studies to be performed either before or after approval. Once CBER determines that the data and information from the applicant are satisfactory and support the safety and efficacy of the product, the product is licensed.

Postmarketing Phase

If the manufacturer wishes to significantly modify the approved manufacturing process or directions for vaccine use, prior approval must be obtained from the FDA before these changes can be implemented. The applicant is required to submit an account of these changes to the appropriate license applications. Modifications to the manufacturing process may occur post licensure, such as scale-up or change in equipment to optimize the production process. Furthermore, clinical studies with the product also may be performed after licensure as the manufacturer seeks additional indications for product use (e.g., new target populations that would benefit from vaccination). For most new approvals, manufacturers may be asked to commit to completing specific postmarketing or so-called Phase IV studies, for example, to provide additional assessments of less-common or rare adverse events or further assess the duration of vaccine-induced immunity. These studies may also be designed to collect additional safety data in large numbers of vaccine recipients, as well as focus on issues that were identified during the prelicensure testing. Submission of status reports for certain postmarketing studies are required by regulation. In particular, this requirement for status reports pertains to postmarketing studies for clinical safety, efficacy and pharmacokinetics, and nonclinical toxicology to which an applicant committed in writing prior to licensure.[22]

Prior to FDAAA 2007, the FDA required postmarketing studies in the following situations (a) accelerated approvals for products approved under 505(b) of the FD&C Act or Section 351 of the PHS Act, respectively, which require postmarketing studies to demonstrate clinical benefit, (b) deferred pediatric studies, where studies are required under PREA, and (c) Animal Efficacy Rule approvals, where studies to demonstrate safety and efficacy in humans are required at the time of use. Under new Section 505(o) of the FD&C Act, the FDA is authorized to also require postmarketing studies or clinical trials at the time of approval or after approval if the FDA becomes aware of new safety information. Section 505(o)(3)(B) states that postmarketing studies and clinical trials may be required to (a) assess a known serious risk related to the use of the drug involved, (b) assess signals of serious risk related to the use of the drug, and (c) identify an unexpected serious risk when available data indicate the potential for a serious risk and when the adverse event reporting system is not adequate. The FDA has defined a clinical trial as any prospective investigation in which the sponsor or investigator determines the method of assigning treatment or other intervention to one or more human subjects. A study is all other investigations, such as investigations using humans, that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies, and laboratory experiments. The FDA has issued guidance for industry to describe the type of studies and clinical trials that are required (Post Marketing Requirement [PMR]) under the FDAAA 2007, and those that will remain agreed-upon postmarketing commitments. A PMR describes all required postmarketing studies or clinical trials including those required under Accelerated Approval, PREA, the Animal Rule, and FDAAA. Examples of required studies are pharmacoepidemiologic studies designed to assess a serious risk, trials with a primary safety end point, preclinical studies investigating specific end organ toxicities, as well as pharmacokinetic studies in the indicated population at potential risk for high drug exposure that could result in toxicity. Studies that generally would not be considered required postmarketing studies or clinical trials are agreed-upon studies (postmarketing commitments) and include biologic quality studies (such as manufacturing, stability, and immunogenicity studies that do not have a primary safety end point), trials in which the primary end point is related to further defining efficacy, and pharmacoepidemiologic studies designed to examine the natural history of disease or background rates for adverse events. Since passage of FDAAA 2007, several new vaccines have been approved with either PMRs or postmarketing commitments. The FDA has the authority to monitor the progress of postmarketing studies or trials by requiring the applicant to submit an annual status report. Applicants are required to provide a timetable for study completion, a periodic status report on the status of the study including whether enrollment has begun, the number of participants enrolled, the expected completion date, and whether any difficulties in completing the study have been encountered.

ADVERSE EVENT MONITORING (POSTLICENSURE FOLLOW-UP)

The FDA is responsible not only for approving vaccines but also for monitoring their safety postlicensure. Because of the relatively small size of most prelicensure trials, rare adverse events are unlikely to be detected. Consequently, postlicensure or postmarketing surveillance (i.e., the continued monitoring of vaccine safety in the general population after licensure) is critical for identifying and evaluating rare or uncommon adverse events.

An adverse event refers to any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. The Vaccine Adverse Event Reporting System (VAERS) is a national system for passive surveillance of adverse events following vaccination. Established in 1990 as a result of the National Childhood Vaccine Injury Act of 1986, VAERS is administered jointly by the FDA and the CDC and, in recent years, has received more than

30,000 reports per year. The purpose of VAERS is to detect possible signals of adverse events associated with vaccines to help ensure the safety of U.S.-licensed vaccines. VAERS collects and analyzes information from reports of adverse events that occur after the administration of U.S.-licensed vaccines. Reports are submitted by healthcare providers, vaccine recipients or their parents or guardians, vaccine manufacturers, and other interested parties. FDA medical officers review all serious reports (defined as events that are fatal, disabling, or life-threatening; require or prolong hospitalization; result in congenital anomalies; require medical intervention to prevent such outcomes; or are deemed to be other medically important conditions). The VAERS system is not limited to routinely recommended pediatric vaccines; voluntary reports of adverse events occurring after administration of any vaccine are also accepted. FDA and CDC continually monitor VAERS reports for any unexpected patterns of adverse events.

Another important mechanism used by CBER to monitor adverse events is the Vaccine Safety Datalink, a collaborative effort between CDC's Immunization Safety Office and nine healthcare organizations. The Vaccine Safety Datalink uses electronic health data from participating sites and conducts vaccine safety studies based on questions or concerns raised from the medical literature and VAERS reports. When there are new vaccines that have been recommended for use in the United States, or if there are changes in how a vaccine is recommended, the Vaccine Safety Datalink will monitor the safety of these vaccines.[23]

INNOVATIVE SYSTEMS FOR EVALUATING VACCINE SAFETY POSTMARKETING

The FDA's Sentinel Initiative was launched in 2008 in response to a Congressional mandate in the FDAAA of 2007. The Sentinel Initiative aims to develop and implement a proactive system that will complement existing systems that the FDA has in place to track reports of adverse events linked to the use of its regulated products. It is a national electronic system that is transforming the FDA's ability to track the safety of drugs, biologics, and medical devices once they reach the market.[24] The Post-Licensure Rapid Immunization Safety Monitoring system (PRISM), a component of the FDA's Sentinel Initiative dedicated to vaccines, uses the FDA's Sentinel Distributed Database, which includes a population exceeding 178 million. PRISM monitors the largest U.S. general population cohort designated for active surveillance of vaccine safety by linking data from health plans with data from state and city immunization registries. The FDA structured PRISM as a program that includes specific vaccine evaluations. For example, several vaccines including a human papillomavirus vaccine, Gardasil, and two rotavirus vaccines, RotaTeq and Rotarix, were chosen for surveillance because their evaluations would benefit most from PRISM's large cohort size.

Postlicensure Manufacturing Changes

In 1997, the FDA published a Final Rule, Changes to an Approved Application, which amended 21 CFR §201.12 and §314.70 to simplify and categorize manufacturing reporting requirements for changes in testing methods, equipment, facilities, or personnel.[25] Proposed changes in manufacturing methods that have a substantial potential to have an adverse effect on the safety or effectiveness of the product may not become effective until notification is given of CBER's approval. The changed created the following categories: (a) those sufficiently significant with regard to safety, purity, potency, and effectiveness of the product to require preapproval of a supplemental application before product distribution; (b) those of lesser importance for which the manufacturer must provide notification 30 days before distribution of product made using the change; and (c) changes for which the manufacturer need only notify the agency by submission of an annual report. The guidance document, "Changes to an Approved Application: Biological Products" (1997), provides examples of changes that fall into these categories.[26]

Following approval, there is continued surveillance of the product and of the manufacturer's production activities. For most licensed vaccines, samples are submitted along with protocols for each lot prepared by the firm that provide the details of production and a summary of test results. Although not required by law or regulation, CBER often performs selected laboratory tests. The type and extent of confirmatory testing performed by CBER depend on several factors, such as the newness of the product or the difficulties that may have arisen with manufacture or use of the product. Release or rejection is based on a review of all test results, including those done by the manufacturer and those performed by CBER. Alternatives to official lot release are allowable under the provisions outlined for extensively characterized products having a track record of continued safety, purity, and potency.[27] A manufacturer must be able to produce a vaccine that repeatedly meets the standards for potency, purity, and stability of bulk and final container material while using a consistent process. Important factors to be considered are the nature of the product with respect to correlation between the measure of potency and biological activity and effectiveness. Surveillance samples and protocols may be required to be submitted to CBER at predetermined intervals.

Licensed establishments are inspected at least every 2 years. The purpose of the inspection is to determine whether licensed products are manufactured and tested as described in the license application and in accordance with applicable regulations. Manufacturers who fail to meet product standards or who are not in compliance with CGMPs may have their licenses suspended or revoked, depending on the nature of the potential health hazards created. The major issues observed during inspections can be categorized in three major areas: (1) process-related issues, (2) quality unit-related issues, and (3) facility- and production environment–related issues. Some examples of process validation issues include lack of documentation of time limits for major steps in the production process, lack of validation of rework or reprocessing steps in the manufacturing process, and lack of data to support in-process specifications. Quality unit-related issues include the appropriate reporting of out-of-specification results and process deviations (including adequate investigations into causes), appropriate documentation of product release, and adequate training of personnel. Facility and production monitoring concerns include controlling production environments by appropriately monitoring heating, ventilation, and air conditioning (HVAC) system performance and microbial quality (e.g., pressure differentials, appropriate sampling sites, and frequency of sampling). Other concerns pertaining to the facility include adequate cleaning, sanitization, storage, and changeover procedures for multiproduct areas and equipment. If the inspection team finds CGMP deficiencies in an already licensed facility, the team may remain in the facility until they have achieved an audit that provides confidence in the ability of the firm to reproducibly manufacture a safe and potent product.

Accelerating Availability of Vaccines and Pathways to Licensure

Mechanisms for providing earlier access to vaccines to prevent or treat severe and life-threatening illness have been developed.

These include fast-track development and the breakthrough therapy designation. The fast track program (Section 506(b) of FD&C Act) was added by FDAMA (1997) and amended by FDASIA (2012). It is designed to facilitate the development and expedite the review of new drugs and biologicals that are intended to treat serious or life-threatening diseases or conditions and for which nonclinical or clinical data are available that demonstrate the *potential* of the product to address unmet medical needs. A designation of a vaccine as fast track program provides the opportunity for frequent interactions of the applicant with the review team. The breakthrough therapy program (Section 506(a) of FD&C Act) was added by FDASIA of 2012. It applies to products for the treatment of serious or life-threatening disease or conditions for which preliminary clinical evidence indicates that the product may demonstrate substantial improvement on a clinically significant end point over available therapies. A sponsor may request a designation as a breakthrough therapy concurrently with, or any time after, submission of an IND. This new designation assists drug developers to expedite the development and review of new drugs with preliminary clinical evidence that indicates the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases. Breakthrough therapy designation provides for increased interaction with FDA to expedite the development and review of the application. In contrast to Fast Track designation, a breakthrough therapy designation requires evidence of substantial improvement over current treatments.

Products regulated by CBER are eligible for priority review if they provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening disease. The FDA has 8 months to complete the review of a new BLA it designates as a priority, as opposed to 12 months for the completion of the review of a standard BLA submission.

Under the FDA's traditional approval pathway, a demonstration of vaccine effectiveness is based on a clinical disease end point (e.g., prevention of disease) or, alternatively, an accepted correlate of protection. In addition to these programs, the FDA's regulations provide for expedited pathways for licensure. Accelerated approval, 21 CFR §601.40, may be granted for certain biological products that have been studied for their safety and effectiveness in treating a serious or life-threatening disease or condition and that provide meaningful therapeutic benefit over existing treatments. Such an approval is based on adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate end point that is reasonably likely to predict clinical benefit or on a clinical end point that can be measured earlier than irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. Approval under this pathway is subject to the requirement that the sponsor study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate end point to clinical benefit. Of note, the FDASIA of 2012 provided that evidence to support an end point is reasonably likely to predict clinical benefit to include "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools." In other words, FDASIA expanded the scope of available end points that can be used to demonstrate that a product qualifies for accelerated approval, but do not affect the quantity and quality of evidence needed to demonstrate substantial evidence of effectiveness or safety.

Two vaccines to protect against meningococcal B diseases were licensed using the accelerated approval provisions and were designated breakthrough therapy. While the incidence of meningococcal serogroup B disease in the United States is low, outbreaks on several college campuses in the United States heightened concerns. Because of the diverse nature of meningococcal group B strains, as well as the low incidence of disease and the sporadic and unpredictable nature of an outbreak, clinical end point efficacy studies to support effectiveness of a serogroup B vaccine are not feasible. Given the public health concerns about meningococcal serogroup B disease in the United States, CBER agreed to provide breakthrough therapy designation and license two meningococcal group B vaccines, Trumenba and Bexsero, manufactured by Pfizer and GSK, respectively, under the accelerated approval regulations, 21 CFR §601 Subpart E. The Agency determined that it would be appropriate to use the accelerated approval pathway, basing approval on the ability of the vaccines to induce bactericidal antibodies, as measured by the human complement serum bactericidal assay, that are able to kill a panel of meningococcal group B strains that are representative of prevalent strains in the United States. The breadth of coverage of Trumenba and Bexsero against diverse meningococcal group B strains will be confirmed in subsequent clinical studies that examine the ability of the vaccine to induce bactericidal antibodies against a larger panel of meningococcal serogroup B strains representative of strains endemic in the United States.

In 2002, the FDA amended the biological products regulations to incorporate 21 CFR §601.90, Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible. This rule, referred to as the "Animal Rule," allows the use of animal efficacy data in lieu of human efficacy data when human challenge studies cannot be conducted ethically and field efficacy studies are not feasible because of infectious disease epidemiology (in the case of vaccines). In these situations, certain drug and biological products (e.g., vaccines) that are intended to reduce or prevent serious or life-threatening conditions caused by lethal or permanently disabling toxic chemical, biological, radiologic, or nuclear substances may be approved for marketing based on evidence of effectiveness derived from appropriate studies in animals and additional supporting data. Safety, pharmacokinetics, and immunogenicity data are still necessary in humans. Under the animal rule, the FDA licensure of a product for which safety has been established and the requirements of 21 CFR §601.60 have been met is based upon adequate and well-controlled animal trials, when results of these animal studies establish that the product is reasonably likely to provide clinical benefit to humans. The FDA can rely on the evidence from animal studies to provide substantial evidence of the efficacy of these products when:

1. There is a reasonably well-understood pathophysiological mechanism for toxicity of the chemical, biological, radiologic, or nuclear substance and its amelioration or prevention by the product.
2. The effect is demonstrated in more than one animal species that is expected to react with a response that is predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model (in other words, the model has been adequately evaluated for its responsiveness) in predicting the response in humans.
3. The animal end point is clearly related to the desired benefit in humans, which is generally the enhancement of survival or prevention of major morbidity.
4. The data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well understood to allow selection of an effective dose in humans, and it is reasonable to expect the efficacy of the

product in animals to be a reliable indicator of its efficacy in humans.

The animal rule does not apply if the product can be approved based on standards described elsewhere in FDA regulations (e.g., accelerated approval based on surrogate markers or clinical end points other than survival or irreversible morbidity).

Emergency use authorization (EUA) is another regulatory mechanism by which the FDA can accelerate the availability of vaccines and other pharmaceutical products. Under an EUA, the FDA can authorize the use of an unapproved product or the unapproved use of an approved product when an emergency or a potential emergency exists. Section 564(b)(1) of the Federal FD&C Act was amended by the Project BioShield Act of 2004 to allow the Secretary of Health and Human Services (Secretary) to authorize the introduction into interstate commerce of a drug, device, or biological product intended for use in an actual or potential emergency. Before an EUA may be issued by FDA, the Secretary must declare an emergency justifying the authorization based on:

- A determination by the Secretary of Homeland Security that there is a domestic emergency or a significant potential for an emergency that involves a heightened risk of attack with a specified biologic, chemical, radiological, or nuclear agent or agents; or
- A determination by the Secretary of Defense that there is a military emergency or a significant potential for an emergency that involves a heightened risk of attack with a specified biologic, chemical, radiological, or nuclear agent or agents; or
- A determination by the Secretary of Health and Human Services of a public health emergency under section 319 of the PHS Act that affects or has the significant potential to affect national security and that involves a specified biological, chemical, radiological or nuclear agent or agents or a specified disease or condition that may be attributable to such agent(s).

Once the Secretary declares an emergency, the FDA can authorize the emergency use of a particular product if the other statutory criteria and conditions are met. Based on the particular circumstances, the process for authorization can be expected to range in duration from hours to days. The Secretary has delegated the authority to issue an EUA under Section 564 of the FD&C Act to the FDA Commissioner.

Vaccine Testing

Vaccines are tested during both the prelicensure and the postlicensure phases. Testing procedures are developed with the goals of controlling and minimizing the potential for product-related adverse events by taking into consideration the experience gained from the same or related products. As an example, for inactivated vaccines, a clear understanding of the kinetics of inactivation is critical. For live vaccines, attenuation must be stable both to avoid reversion to virulence and to avoid the vaccine becoming over attenuated and, as a consequence, less potent. For example, during the first decade of its widespread use, Yellow Fever 17D vaccine virus was serially propagated in eggs, as required to meet demand. However, it soon became obvious that the level of attenuation of the vaccine from one passage to the next could vary considerably. Some lots were excessively neurovirulent, especially in infants and young children, whereas successive lots might by chance be overattenuated and, consequently, not immunogenic. The WHO formulated a solution to this problem, which was to adopt a "seed-lot system" wherein the vaccine is prepared from a master seed virus at a specified passage number in eggs. Working seed virus is prepared by one passage of the master seed and is, in turn, used to generate all production lots. All 17D vaccines and all other live virus vaccines now adhere to a seed-lot system for manufacture.

The FDA requires that cell substrates and vaccine viral seeds used in production be appropriately selected and tested to ensure that they do not introduce any unintended risks. Current cell substrates used to manufacture licensed vaccines are primary avian cells (embryonated eggs or chick embryo fibroblasts), diploid cells, continuous cell lines (Vero and Madin-Darby canine kidney [MDCK]), as well as yeast and insect cells. Table 79.6 lists the cell substrates used in current U.S.-licensed vaccines. In 2010, the FDA published the guidance, "Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases."[28] This document provides manufacturers of viral vaccines with guidance for the characterization and qualification of cell substrates, viral seeds, and other biological materials used for the production of viral vaccines for human use to assure that they meet the highest safety standards achievable using modern technology. Characterization of cell substrates should address certain general issues that might affect the safety and purity of vaccine products. For example, in the early 1960s, exogenous and endogenous contamination

TABLE 79.6 Cell Substrates Used in Current U.S.-Licensed Vaccines

		Vaccine	
Type	**Substrate**	**Live**	**Inactivated**
Animal tissues	Mouse brain Chicken eggs	 Influenza, yellow fever virus	Japanese encephalitis virus Influenza
Continuous cell lines (non-tumorigenic)	African green monkey cells (Vero)	Smallpox, rotavirus	Poliovirus, Japanese encephalitis virus
Diploid cells	Human MRC-5 cells Human WI-38 cells	Varicella, varicella-zoster Rubella, adenovirus types 4 and 7	Hepatitis A, rabies, poliovirus
Primary cell cultures	Chick embryo fibroblasts (CEFs) Madin-Darby canine kidney (MDCK) cells	Measles, mumps	Rabies Influenza vaccine
Insect cells	*Trichoplusia ni* *Spodoptera frugiperda*		Human papillomavirus Influenza vaccine
Yeast	*Saccharomyces cerevisiae*		Hepatitis B, human papillomavirus

of primary monkey kidney cells with simian virus 40 and chick embryo fibroblasts with avian leukosis virus were reported. Although chick embryo fibroblasts are still used for the production of viral vaccines, these cell substrates must be well-characterized and tested to assure absence of potentially infectious agents. Issues related to cell substrates have been discussed in a variety of forums.[29–31] Furthermore, if a vaccine is manufactured in a cell substrate that is derived from a tumor, or that has developed a tumorigenic phenotype through an unknown mechanism, it was considered to carry a higher theoretical risk of containing oncogenic substances such as oncogenic viruses and cellular DNA, derived from that cell substrate. This was the main reason tumorigenic cells or cells derived from human tumors had been considered unsuitable as cell substrates. However, at a 2012 meeting of the VRBPAC, experts recognized that cell lines derived from human tumor are an important tool for manufacturing of vaccines and could provide a wider repertoire of cell substrates for vaccine production.[30] They indicated that risk-mitigation strategies are the same for vaccines generated using human tumor-derived cell lines as for other cell substrates. A thorough characterization of the cell substrate with respect to adventitious viruses, which includes oncogenic viruses, should be done using new virus-detection technologies such as massively parallel sequencing, virus microarrays and broad-range polymerase chain reaction to complement existing assays. The manufacturing process should lower the amount and reduce the size of the DNA. Residual DNA for continuous nontumorigenic cells, such as low-passage Vero cells, should be limited to less than 10 ng/dose for parenteral inoculation and to less than 100 μg/dose for oral vaccines. Cells with tumorigenic phenotypes or other characteristics that give rise to special concerns may require more stringent limitation of residual DNA quantities and size to assure product safety.

The regulation of biologicals includes requirements for testing of licensed products (21 CFR §610). These tests include those for bacterial and fungal sterility, general safety, purity, identity, suitability of constituent materials and potency, thereby this specific testing performed may vary depending on the vaccine. For example, tests for potency may be based on studies of immunogenicity or, for some vaccines, protection from virulent challenge in laboratory animals. However, in vitro tests, including virus titration (e.g., live vaccines such as polio, measles, mumps, and rubella), antigen content (e.g., influenza and inactivated poliovirus vaccines), and biochemical and biophysical measurements (e.g., meningococcal conjugate vaccines) have been used.

Tests for purity are designed to determine that the product is free of extraneous material, except that which is unavoidable in the manufacturing process described in the approved license application. Tests for residual moisture and pyrogenic substances may also be included. Final-container material must be identified by a test specific for each product (e.g., neutralization of each of the components of live measles, mumps, and rubella vaccine with specific antisera). With regard to constituent materials, the manufacturer must ensure that all ingredients used in the product, such as diluents, preservatives, or adjuvants, meet generally accepted standards of purity. An adjuvant may not be used unless there is adequate proof that it does not adversely affect the safety or potency of the product.

Of note, the FDA periodically evaluates the appropriateness of testing requirements. An example is the general safety test (required under 21 CFR §610.11) used to detect extraneous toxic contaminants that may be present in the product in the final container from every final filling of each lot of the biological product. Technological advances have increased the ability of manufacturers to control and analyze the manufacture of many biotechnology-derived biological products. Thus, the FDA has published a final rule to remove this requirement.

In addition to the tests required by regulation, other tests tailored to the specific product may be required (e.g., neurovirulence testing and cell culture and animal tests for extraneous viruses). Once the product is licensed, the manufacturer's testing must be conducted according to the exact specifications in the manufacturer's license application, and the results of these tests must be within the specified prescribed limits.

Product Labeling and Advertising

Prescription drug labeling, also known as the package insert, package circular, or prescribing information, is the primary mechanism through which the FDA and drug manufacturers communicate essential, science-based prescribing information to healthcare professionals. Labeling provisions contained in 21 CFR §§201.57 and 201.56 require that prescribing information must summarize the essential information on the safe and effective use of the product; that information contained in the labeling must be accurate and not false and misleading; and that there must be no implied claims or suggestions for use if evidence of safety or effectiveness is lacking.[32] Whenever possible, data contained in labeling should be derived from human experience. In the United States, the FDA regulates the format and content of labels for product containers, cartons, and the package insert that accompanies the product. In January 2006, the FDA issued a final drug labeling rule, commonly referred to as the Physicians' Labeling Rule, amending the content and format of prescribing information for human drug and biologic products. The new format is intended to provide healthcare professionals with clear and concise prescribing information by reorganizing critical information into a streamlined format. Moreover, these revisions make it simpler for healthcare professionals to access, read, and use prescribing information, and enhance the safe and effective use of prescription drug products. New sections were added to the label, such as the Highlights section, which contains key benefit and risk information, and a table of contents for the full prescribing information. On December 3, 2014, the FDA issued the Pregnancy Lactation and Labeling Rule, which revises the content and format of the pregnancy subsection of labeling for prescription drugs and biologics (Sections 8.1 to 8.3 of the prescribing information). Previous regulations required that each product be classified under one of five pregnancy categories (A, B, C, D, or X) based on the risk of reproductive and developmental adverse effects or, for certain categories, such risk weighed against potential benefit. The most significant change proposed by the rule is the replacing of these letter risk categories with a narrative summary of the risks and benefits of using a drug during pregnancy, based on the available human and/or animal data and a discussion of the data. Additionally, the rule requires that prescription drug labeling include relevant clinical information to help healthcare providers make prescribing decisions and counsel women about the use of drugs during pregnancy and/or lactation.

The structured product labeling defines the content of human prescription drug labeling in XML format. It is a document markup standard approved by Health Level Seven and adopted by the FDA as a mechanism for exchanging product and facility information.[33] Structured product labeling documents contain both the content of labeling (all text, tables, and figures) for a product and additional machine-readable information (drug listing data elements). Drug listing data elements include information about the product (product and generic names, ingredients, ingredient strengths, dosage forms, routes of administration, appearance, Drug Enforcement Agency schedule) and the packaging (package quantity and type).

During the BLA review, the agency considers the draft labeling and clinical studies submitted by the manufacturer, and the proposed indication for the licensed product, which is based on clinical data submitted by the sponsor demonstrating the safety and effectiveness of the product for its intended use and target population. Subsequently, significant changes in labeling, including new indications for use, new dosage forms or regimens, expanded patient populations who receive the product and additional information regarding safety and effectiveness, require manufacturers to submit a supplemental filing for review and approval by CBER. Unlike other product labeling, the promotional labeling and advertising are not subject to preclearance; however, they are monitored for misleading claims. These documents must also meet the standard of fair balance, that is, claims of efficacy are balanced with information about the product's safety.

Labeling changes are usually initiated by the manufacturer but may be initiated by CBER. Historically, manufacturers have had to obtain prior approval from CBER before the labeling changes were made. The changes to 21 CFR §601.12, mentioned previously, also apply to labeling changes and allow exceptions for a change that adds or strengthens a contraindication, warning, precaution, or adverse reaction; adds or strengthens instructions about dosage and administration intended to increase safe use; or deletes false, misleading, or unsupported indications for use or effectiveness claims. Under this regulation, a manufacturer could effect such changes and, at the same time, submit them and the supporting data to CBER without preapproval.

As described earlier, the FDAAA amended the FD&C Act by adding new Section 505(o) authorizing FDA to require and, if necessary, *order* labeling changes if the FDA becomes aware of new safety information that the FDA believes should be included in the labeling of the drug. Section 505(o)(4) of the FD&C Act imposes timeframes for application holders to submit and for FDA staff to review such changes, and gives the FDA new enforcement tools to bring about timely and appropriate safety labeling changes.

SPECIAL CONSIDERATIONS

Adjuvants

Strategies and approaches for the development and delivery of vaccine antigens have expanded over the last several decades, leading to a broad range of novel products comprised of purified subunit antigens or subunit proteins. These antigens may require the presence of adjuvants to enhance the immune response to the vaccine antigens, reduce the dosing frequency, induce cross-protective effects, direct the immune response and/or achieve antigen sparing. The number of investigational vaccines containing novel adjuvants evaluated in clinical trials has increased in recent years and some vaccines containing novel adjuvants have been licensed by the FDA. For example, the human papillomavirus vaccine manufactured by GlaxoSmithKline, Cervarix, contains AS04, an adjuvant system comprised of an aluminum hydroxide and monophosphoryl lipid A. GlaxoSmithKline's pandemic influenza vaccine, Q-Pan, contains AS03, an adjuvant system comprised of an oil-in-water emulsion.

The CFR defines adjuvants, together with ingredients, preservatives, and diluents as constituent materials (21 CFR §610.15).[34] These regulations state, "All ingredients…shall meet generally accepted standards of purity and quality" and that, "An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not adversely affect the safety or potency of the product."

From a regulatory perspective, adjuvants are not considered active ingredients as defined in 21 CFR §210.3(b)(7) and vaccine adjuvants are not licensed separately.[35] It is the adjuvanted vaccine formulation, in toto, that is tested in nonclinical and clinical trials and licensed. There is a requirement that the adjuvanted vaccine formulation, as with any vaccine, must be both safe and effective, with its benefits outweighing the risks of adverse events that may occur. However, there is no explicit requirement for demonstrating the added safety and effectiveness of the adjuvanted vaccine formulation over that of the unadjuvanted vaccine formulation in comparative clinical trials.

The regulatory considerations for the nonclinical and clinical development of preventive vaccines, as well as pathways to licensure described elsewhere in this chapter, are largely also applicable to vaccines formulated with adjuvants. However, adjuvants can exhibit a range of properties that invoke complex immune responses, the mode of action is not always known or fully understood, and animal models that are relevant for evaluating both the safety and the efficacy of an adjuvant–antigen combination are frequently not available. Thus, there are some unique issues to be addressed during preclinical and clinical development of the adjuvanted vaccine formulation. A WHO guideline published in 2013 describes the nonclinical, quality, pharmacological, toxicological, and other information needed to support initiation of clinical trials with a vaccine combined with a novel adjuvant.[36]

In 2007, CBER published two guidance documents ("Guidance for Industry: Clinical Data Needed to Support Licensure of Pandemic Influenza Vaccines"[37] and "Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines"[38]). Each of these documents discusses the development of adjuvanted inactivated influenza vaccines and notes that "[d]ata to support the safety of the adjuvanted formulation and added benefit over the unadjuvanted formulation must be submitted in the BLA…"[37,38] Sponsors were advised that "at an early stage of development, clinical data supporting the value of adding the adjuvant should be provided…"[37,38] The seasonal influenza vaccine guidance notes further that "[i]f an adjuvant is added to a licensed seasonal vaccine without antigen sparing effects…the immune response elicited by the adjuvanted formulation should be substantially better than that elicited by the unadjuvanted vaccine…"[38] As the FDA's experience with novel adjuvants has grown, the agency continues to reexamine guidance and engages with sponsors and applicants regarding the clinical development of adjuvanted vaccines.

Vaccine manufacturers should provide a rationale for the use of an adjuvant in the vaccine. The "added benefit" of an adjuvant may be defined as evidence of enhanced immune response, antigen-sparing effect, dose sparing, increased breadth of immune response, or superior clinical efficacy. Information to support the "added benefit" of the adjuvant may be derived from preclinical studies, for example, in vitro assays and/or proof-of-concept studies in animal models conducted prior to the initiation of clinical trials or early phase clinical trials. There is no regulatory requirement to demonstrate the "added benefit" of an adjuvant in clinical comparative Phase III effectiveness trials unless the applicant plans to make a claim of superiority of the adjuvanted product over unadjuvanted product.

The benefits from incorporating or adding an adjuvant to any vaccine formulation need to be balanced with the risk of adverse reactions. Adjuvants have their own pharmacological activity, which may affect both the immunogenicity and the safety of vaccines. Adverse reactions may include local reactions such as pain, swelling, injection site necrosis, and granulomas. Systemic reactions may include nausea, fever, arthritis, as well as potential immunotoxic reactions. Unexpected, rare events may also occur. For example, during the H1N1 influenza pandemic in 2009–10, an increased risk of narcolepsy, a chronic neurological disorder caused by the brain's inability to regulate sleep–wake cycles normally, was observed in several European countries following vaccination with an AS03 adjuvanted, monovalent 2009 H1N1 influenza vaccine, Pandemrix.[39–43] The finding of narcolepsy in several European countries following vaccination with Pandemrix caused the European Medicines Agency to recommend restricting use of Pandemrix.[44]

Pandemrix was not licensed for use in the United States and no adjuvanted influenza vaccines were used in the United States during the influenza pandemic. The CDC published a study on a possible association between U.S.-licensed unadjuvanted 2009 H1N1 influenza vaccines, 2010–11 seasonal influenza vaccines, and narcolepsy.[45] The analysis included more than 650,000 people who received the pandemic influenza vaccine in 2009 and more than 870,000 people who received the seasonal influenza vaccine in 2010–11. The study found that neither vaccine was associated with an increased risk for narcolepsy. Additional studies including those conducted by the vaccine manufacturer will help discern whether this finding is attributable to the adjuvant, the H1N1 vaccine antigen, or both.

The safety of an adjuvanted vaccine formulation has to be demonstrated in adequate and well-controlled prelicensure safety studies. Safety information supporting licensure of an adjuvanted vaccine may include the safety experience obtained from domestic or foreign trials conducted using the adjuvanted vaccine formulation. In addition, safety experience with the same adjuvant formulated with other vaccine antigens may also contribute to the safety evaluation of the adjuvant. Early in clinical development (e.g., Phase I and Phase II clinical trials), supportive safety data may be derived by comparing the adjuvanted vaccine to a placebo or the unadjuvanted vaccine antigen, if feasible. Safety follow-up of human subjects administered vaccine with novel adjuvant is typically longer than for nonadjuvanted vaccines (e.g., 12 months rather than 6 months) and includes specific inquiries regarding symptoms consistent with autoimmune and neuro-inflammatory diseases. Furthermore, the safety database required to support licensure of a vaccine formulated with novel adjuvant may be larger than for unadjuvanted vaccines.

In summary, regulatory pathways supporting development and approval of vaccines formulated with novel adjuvants are similar to those for unadjuvanted vaccines. Efficient planning of the development pathway for any adjuvanted vaccine requires careful attention to preclinical testing, study design, dosing decisions, and safety monitoring. Although manufacturers are not required to demonstrate the "added benefit" of adjuvanted versus unadjuvanted vaccines in clinical comparative Phase III studies, manufacturers should provide a justification for including an adjuvant in the vaccine. Lastly, evaluation of safety of an adjuvanted vaccine needs to include special safety considerations.

Vaccines Against Global Infectious Diseases, Emerging Infectious Diseases, and Biothreat Agents

Immunization programs in the United States have been remarkably effective at reducing morbidity and mortality from the most common, naturally transmitted infectious diseases, such as polio, measles, and diphtheria. However, emerging infectious diseases (EIDs)—from pandemic influenza to novel pathogens like severe acute respiratory syndrome and Ebola, to biological threats that have the potential to be intentionally released into the general population by humans—also pose a threat to global public health. Vaccines will continue to be an important medical countermeasure against a broad range of infectious diseases from anthrax, smallpox, and influenza to newly emerging infectious diseases. Moreover, infectious diseases, such as tuberculosis and malaria present global public health challenges and increasing resistance to currently available treatments by common bacteria such as staphylococci, underscores the importance of the development of safe and effective vaccines.

The development of safe and effective vaccines to protect against global infectious diseases (e.g., tuberculosis, malaria, HIV/ AIDS), enteric diseases, and other neglected diseases of the developing world is of critical public health importance. Development and availability of such vaccines, particularly for use in the developing countries most affected by these diseases, will benefit U.S. and global health. In 2011, the FDA published a revised guidance document to assist sponsors in developing vaccines targeted against infectious diseases or conditions endemic in areas outside the United States. The FDAAA of 2007 revised the FD&C Act by adding Section 524, recognizing the importance of having products to treat and prevent tropical diseases that disproportionately affect poor and marginalized populations and for which there is no significant market in developed nations. Under Section 524, the Agency can grant priority review of applications under Section 505(b)(1) of the FD&C Act or Section 351 of the PHS Act for the treatment and prevention of specified tropical diseases, including tuberculosis, malaria, cholera, and "any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulation by the Secretary." Consequently, this guidance provides general recommendations for regulatory pathways to use in the development of vaccines to protect against global infectious diseases for U.S. licensure and clarifies applicable regulations: (a) the FDA can license vaccines to protect against infectious diseases or conditions that are not endemic or have not been reported to occur in the United States; (b) the regulatory pathways to U.S. licensure for the development of vaccines to protect against infectious diseases that are not endemic or have not been reported to occur in the United States are the same as for vaccines to protect against diseases that are endemic in the United States; (c) a sponsor may submit data from clinical trials conducted outside the United States to support product licensure, (d) noting that the accelerated approval regulations may be used in appropriate cases; and (e) that when pivotal studies are conducted outside the United States, in some instances, it may not be necessary to conduct studies in the United States. This guidance also responded to the congressional mandate in Section 740 of the fiscal year 2010 Appropriation Act (Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2010, Public Law 111-80) by requiring the FDA to make recommendations on appropriate preclinical, trial design, and regulatory paradigms to prevent, diagnose, and treat rare diseases and neglected diseases.

The U.S. military has implemented vaccination programs to protect troops against several biological threats; however, the risk-to-benefit ratio for protecting civilians against agents of bioterrorism is more difficult to assess. As of this writing, there is one licensed smallpox vaccine in the United States, Sanofi Pasteur Biologics' ACAM2000. New smallpox vaccines are being developed under IND applications, with the goal to seek licensure, and new vaccinia immunoglobulin preparations to treat certain complications of smallpox vaccination have been approved. There is one licensed anthrax vaccine in the United States, anthrax vaccine adsorbed (Emergent BioSolutions' BioThrax).

There are significant scientific and regulatory challenges associated with developing and testing new vaccines against EIDs and biothreat agents. Vaccines against EIDs are more likely to use novel technologies, and the science behind these technologies may be more complex; for example, use of novel cell substrates, the need to develop alternative potency assays, and the need to identify surrogate markers in humans or animals that predict vaccine effectiveness. To respond to this challenge, the FDA collaborates with interagency groups within the Department of Health and Human Services, such as the Biomedical Advanced Research and Development Authority, the CDC, and the NIH, as well as the Department of Defense and Department of Homeland Security to prepare for responding to an emergency. A committed, continuous investment in regulatory science is essential to producing medical countermeasures against public health threats. As noted in the *Public Health Emergency Medical Countermeasures Review*,[46] "Enhancement and ultimate application of updated regulatory science and scientific review capacity will help strengthen the MCM [medical countermeasure] regulatory process and thus streamline the MCM development process. [The] FDA will undertake a new initiative designed to focus on augmenting the tools used to assess the safety, efficacy, and quality of medical products, with a particular focus on MCMs, and to get them from concept through the approval process efficiently." An example of how the FDA's regulatory science efforts have assisted the agency in facilitating the licensure of vaccines against emerging diseases and biothreats is the successful public–private partnership during the 2009 H1N1 influenza pandemic, which resulted in the development and approval of safe and effective vaccines against the pandemic in record time. This included creating vaccine strains needed for vaccine manufacturing within weeks of the very first 2009 pandemic H1N1 influenza cases appearing, developing reagents and tests through international collaborations to measure the vaccine's potency, consulting the FDA's expert vaccine advisory committee to review the Agency's approach to approval of the 2009 H1N1 vaccine s as well as extensive in process quality control and product testing. Licensure of vaccines against the 2009 H1N1 influenza virus occurred in September 2009 based on the FDA's determination that standards to ensure the safety and potency of these vaccines had been met. In parallel to these efforts, NIH and vaccine manufacturers initiated clinical trials to determine the optimal vaccine dosage and number of doses needed to induce a protective immune response against pandemic 2009 H1N1 virus.

Another example illustrating collaboration both within the Department of Health and Human Services and between the Department and international partners is the response to the Ebola virus disease outbreak in West Africa in 2014–15 that caused more than 25,000 cases of Ebola virus disease and claimed the lives of more than 10,000 people, representing the most widespread epidemic of Ebola virus disease in history. To address this need, the FDA engaged with federal partners, sponsors of medical products, and international organizations to facilitate development of vaccines. To advance promising vaccine candidates to Phase I clinical trials to obtain preliminary human safety data, the FDA worked closely with manufacturers, clinical trial sponsors, and international regulators to rapidly assess product characterization data and protocols for these first human clinical trials and granted permission for the initiation of these Phase I studies in an expedited manner. Guidance provided by the FDA assured that these studies were conducted according to applicable regulations including the requirement for nonclinical testing and protection of human subjects. These efforts resulted in rapid availability of safety and immunogenicity data for the leading Ebola vaccine candidates, initiation of U.S. government–sponsored Phase III clinical studies to demonstrate the safety and effectiveness of these vaccines in individuals residing in outbreak areas, and collection of data supporting licensure of these products. To enable an initiation of these pivotal studies in an expedited manner, the FDA engaged in joint reviews with vaccine manufacturers, the WHO, regulatory agencies in Europe and Canada, and West African regulators to discuss study designs, ethical considerations, and required product information to reach international regulatory convergence, thus facilitating trial initiation. It is not always possible to test whether a vaccine or treatment will work against a new or emerging infectious disease, or against a biothreat, because the threat may be rare or even nonexistent at the time the vaccine or therapy needs to be developed. Moreover, many vaccines against EIDs and biothreats pose difficult challenges with regard to obtaining clinical efficacy data. For many of these infectious agents or toxins, human efficacy trials are not feasible because natural exposure no longer occurs (e.g., smallpox), occurs at a very low incidence, or occurs in an unpredictable manner. The animal rule described earlier (see "Accelerating Availability of Vaccines and Pathways to Licensure") is one regulatory mechanism that allows the FDA to address the challenges of obtaining clinical efficacy data for these products if the results of adequate and well-controlled animal studies establish that the product is reasonably likely to provide clinical benefits to humans.

Animal testing is often the only available option, but many diseases lack even good animal models, and animal studies are technically difficult to conduct and typically limited in size. Consequently, regulatory science is needed to develop and validate improved predictive models. Regulatory science can also support the identification and validation of surrogate measures of product efficacy. Biomarkers that predict efficacy are not yet available for most terrorism threats, emerging pathogens or major global infectious diseases. Efforts to develop, refine, and validate new biomarkers may lower development costs and improve and speed the development of safe and effective products for unmet public health needs.

In summary, for licensure, an EID vaccine product, just as for any product, must have an acceptable quality, safety, efficacy, and potency profile. Likewise, production and quality control also must be in compliance with CGMPs.

However, vaccines against EIDs and biothreats agents present unique issues for clinical development and evaluation by the FDA. Overall planning and coordination among the FDA and its national and international partners is necessary to move these products toward licensure and into distribution. FDA guidance and engagement with partners is critical to make sure these products can move from the future into the present.

CONCLUSION

The primary responsibility of NRAs is to ensure the quality, safety, and effectiveness of pharmaceutical products. The implementation of a strong regulatory system will facilitate these goals, which are especially critical for vaccines that are inherently more difficult to develop, characterize, and manufacture than most pharmaceutical products. The FDA has developed a managed review process that provides regulatory oversight through all phases of vaccine development. Advances across a wide range of scientific disciplines have enhanced the prospects of developing new and better vaccines. Novel vaccine approaches such as recombinant vaccines and novel adjuvants and delivery systems pose regulatory challenges for NRAs. However, NRAs should be dynamic and flexible entities, as they strive to develop regulatory requirements to address the evolving science. Further, NRAs must be prepared to address public health emergencies that will require expedited approval mechanisms, such as biological terrorist events, pandemic influenza, and other EIDs.

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References for this chapter are available at ExpertConsult.com.

REFERENCES

1. Food Drug and Cosmetic Act. 21 USC §321.
2. Public Health Service Act. ch 373, title III, §351, 58, Stat. 702, 42 USC §262 (1944).
3. Biologics Control Act. Public Law No. 57-244 (1902).
4. Public Health Service Act. July 1, 1944, Chap. 373, Title III, Sec. 351, 58 Stat. 702, currently codified at 42 USC §262.
5. Food and Drug Administration Modernization Act of 1997. Public Law No. 105-115 (1997).
6. Pediatric Research Equity Act of 2003. Public Law No: 108-155 (2003).
7. Food and Drug Administration Amendments Act of 2007. Public Law No. 110-85 (2007).
8. Gruber MF. US FDA review and regulation of preventive vaccines for infectious disease indications: impact of the FDA Amendments Act 2007. *Expert Rev Vaccines*. 2011;10(7):1011-1019.
9. U.S. Food and Drug Administration Safety and Innovation Act (FDASIA). Pub. L. No. 112-144, 126 Stat. 993 (2012).
10. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans. Guidance for Industry (March 2016). Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>.
11. 5 USC §551 et seq.
12. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014). Available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM358301.pdf>.
13. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (May 2007). Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091990.pdf>.
14. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines (May 2007). Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091985.pdf>.
15. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications (February 2010). Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM202439.pdf>.
16. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications (February 2006). Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm092170.pdf>.
17. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance, Compliance & Regulatory Information (Biologics). Available at: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>.
18. Sensabaugh SM. A primer on CBER's regulatory review structure and process. *Drug Inf J*. 1998;32:1011-1030.
19. Code of Federal Regulations. Title 21, Part 312.47. Washington, DC, Office of the Federal Register, National Archives & Records Administration; 2015.
20. Code of Federal Regulations. Title 21, Part 312. Washington, DC, Office of the Federal Register, National Archives & Records Administration; 2015.
21. Vaccines and Related Biological Product Committee (VRBPAC) Meeting Transcript, May 26-27. Available at: <http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3422t1.pdf>; 1998.
22. U.S. Food and Drug Administration. Postmarketing studies for approved human drugs and licensed biological products; status reports. *Fed Regist*. 2000;65:64607-64616.
23. Centers for Disease Control and Prevention (CDC). Vaccine Safety: Vaccine Safety Datalink (VSD). Available at: <https://www.cdc.gov/vaccinesafety/Activities/VSD.html>.
24. U.S. Food and Drug Administration. FDA's Sentinel Initiative. Available at: <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm>.
25. U.S. Food and Drug Administration. 21 CFR Parts 314, 600, 601, 610, and 640. Changes to an Approved Application. Final Rule. July 24, 1997. *Fed Regist*. 1997;62:39890.
26. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry: Changes to an Approved Application: Biological Products (July 1997). Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM170166.pdf>.
27. U.S. Food and Drug Administration. Guidance on alternatives to lot release for licensed biological products. *Fed Regist*. 1993;58:38771-38773.
28. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications (February 2010). Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM202439.pdf>.
29. Brown F, Esber EC, Williams MH, eds. Continuous Cell Lines—An International Workshop on Current Issues. *Dev Biol Stand*. 1992;76:1-368.
30. World Health Organization (WHO). Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks; 2010. Available at: <http://www.who.int/biologicals/Cell_Substrates_clean_version_18_April.pdf>.
31. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. Meeting of The Vaccines and Related Biological Products Advisory Committee (VRBPAC) (Transcript). September 19, 2012. Silver Spring, MD. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM326830.pdf>.
32. Code of Federal Regulations, Title 21, Part 201.56 and Part 201.57. Washington, DC, Office of the Federal Register, National Archives & Records Administration; 2015.
33. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Providing Regulatory Submissions in Electronic Format —Content of Labeling (April 2005). Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072331.pdf>.
34. Code of Federal Regulations, Title 21, Part 610.15, Washington, DC, Office of the Federal Register, National Archives and Records Administration.
35. Code of Federal Regulations, Title 21, Part 210.3, Washington, DC, Office of the Federal Register, National Archives and Records Administration.
36. World Health Organization (WHO). Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. Available at: <http://www.who.int/biologicals/areas/vaccines/ADJUVANTS_Post_ECBS_edited_clean_Guidelines_NCE_Adjuvant_Final_17122013_WEB.pdf>; 2013.
37. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Clinical Data Needed to Support Licensure of Pandemic Influenza Vaccines (May 2007). Available at: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074786.htm>.
38. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Clinical Data Needed to Support the Licensure

of Seasonal Inactivated Influenza Vaccines (May 2007). Available at: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074794.htm>.

39. Miller E, Andrews N, Stellitano L, et al. Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis. *BMJ*. 2013;346:f794.
40. Szakács A, Darin N, Hallböök T. Increased childhood incidence of narcolepsy in western Sweden after H1N1 influenza vaccination. *Neurology*. 2013;80(14):1315-1321.
41. Masoudi S, Ploen D, Kunz K, Hildt E. The adjuvant component α-tocopherol triggers via modulation of Nrf2 the expression and turnover of hypocretin in vitro and its implication to the development of narcolepsy. *Vaccine*. 2014;32(25):2980-2988.
42. Narcolepsy in association with pandemic influenza vaccination: a multi-country European epidemiological investigation. ECDC Technical Report, Stockholm, Sweden. Available at: <http://vaesco.net/vaesco/results/main/04/text_files/file/ECDC%202012%20VAESCO%20Narco%20report%20FULL.pdf>; 2012.
43. Nohynek H, Jokinen J, Partinen M, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. *PLoS ONE*. 2012;7(3):e33536.
44. European Medicines Agency recommends restricting use of Pandemrix, EMA/CHMP/568830. Press release. July 27, 2011. Available at: <http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109182.pdf>.
45. Duffy J, Weintraub E, Vellozzi C, et al; Vaccine Safety Datalink. Narcolepsy and influenza A(H1N1) pandemic 2009 vaccination in the United States. *Neurology*. 2014;83(20):1823-1830.
46. U.S. Department of Health and Human Services. The Public Health Emergency Medical Countermeasures Enterprise Review: Transforming the Enterprise to Meet Long-Range National Needs. Available at: <https://www.medicalcountermeasures.gov/media/1138/mcmreviewfinalcover-508.pdf>; 2010.