

Food and Drug Administration Regulation and Evaluation of Vaccines

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KEY WORDS

vaccine, regulation, biologics licensing

ABBREVIATIONS

CBER—Center for Biologics Evaluation and Research

FDA—Food and Drug Administration

CFR—Code of Federal Regulations

CGMP—current good manufacturing practices

PDUFA—Prescription Drug User Fee Act

ICH—International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IND—investigational new drug

BLA—biologics license application

www.pediatrics.org/cgi/doi/10.1542/peds.2010-1722E

doi:10.1542/peds.2010-1722E

Accepted for publication Nov 29, 2010

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: *The author has indicated she has no financial relationships relevant to this article to disclose.*

abstract

The vaccine-approval process in the United States is regulated by the Center for Biologics Evaluation and Research of the US Food and Drug Administration. Throughout the life cycle of development, from preclinical studies to after licensure, vaccines are subject to rigorous testing and oversight. Manufacturers must adhere to good manufacturing practices and control procedures to ensure the quality of vaccines. As mandated by Title 21 of the Code of Regulations, licensed vaccines must meet stringent criteria for safety, efficacy, and potency. *Pediatrics* 2011;127:S23–S30

Vaccines are considered one of the most significant contributions to public health. No other medical countermeasures have been as effective in reducing or eliminating the incidence of infectious diseases such as measles, mumps, rubella, smallpox, and diphtheria.¹ The Center for Biologics Evaluation and Research (CBER) of the US Food and Drug Administration (FDA) is the federal regulatory agency charged with ensuring the safety, purity, and efficacy of vaccines in the United States. The review of vaccine applications occurs among the CBER's Office of Vaccines Research and Review, Office of Compliance and Biologics Quality, and Office of Biostatistics and Epidemiology. The development of vaccines is an intricate process, and every step in the life cycle from the testing of materials used for production to postlicensure lot-release testing is subject to stringent oversight by the CBER. After licensure, the CBER continues to oversee the production and performance of vaccines to ensure their continued safety and efficacy.

Vaccines are a unique class of pharmaceutical products that meet the statutory definition of both a drug and biological product.^{2,3} The Food, Drug, and Cosmetic 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 Prophylactic vaccines differ from many other drugs and biologicals primarily in how they are administered to a large population of young healthy people to prevent rather than treat disease, their mechanism of action, and 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.

This article provides an overview of the legislative history of biologicals regula-

tion and current FDA regulatory mechanisms that ensure the safety, purity, and potency of licensed vaccines.

REGULATIONS AND GUIDANCE DOCUMENTS

The CBER regulates, among other products, a broad class of vaccine products. Facilitating the development, approval, and availability of safe and effective medical products and technologies is part of the primary mission of the FDA. Federal oversight of biologicals dates back to 1902, when Congress enacted the Biologics Control Act, also known as the Virus-Toxin Law.⁴ This legislation was precipitated by the tragic deaths of 13 children who were administered tetanus-contaminated diphtheria antitoxin.⁵ The regulations under this act contained the primary concepts for regulation of biologicals, such as mandatory facility inspections and batch-certification guidelines.

The CBER derives its legal authority to regulate vaccines and other biologicals from §351 of the Public Health Service Act and the Food, Drug, and Cosmetic Act (Table 1).^{2,3} The Public Health Service Act is implemented through the Code of Federal Regulations (CFR),

which contains the general and permanent rules published in the *Federal Register* by the executive departments and agencies of the federal government. The regulations that apply specifically to licensure of vaccines and other biologicals are Title 21 CFR 600 through 680.⁶ Title 21 contains other relevant regulations applicable to vaccines including labeling, adequate and well-controlled clinical trials, institutional review boards, protection of human subjects, nonclinical laboratory studies, and current good manufacturing practices (CGMPs). CGMP regulations are codified in Title 21 CFR 210 and 211 and contain the minimum CGMPs for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to ensure its safety, quality, and purity.⁷ Adherence to CGMPs occurs primarily through well-defined written procedures for manufacturing processes, adequately controlled equipment and manufacturing environment, and well-trained employees.

Regulatory legislation has evolved over time to meet scientific advances in the pharmaceutical and biomedical industries. In the past 2 decades, these laws have afforded the CBER the authority to accelerate and improve its drug and biologicals review processes, ultimately to bring to market safe and effective drugs, vaccines, and other biological products.

The Prescription Drug User Fee Act

The Prescription Drug User Fee Act (PDUFA), first enacted in 1992, granted the FDA authority to collect user fees from manufacturers to expedite the review of drug and biological applications and postmarket drug-safety activities in accordance with performance goals developed by the FDA.⁸ The legislation was later reauthorized

TABLE 1 Acts and Regulations Pertinent to Vaccine Development

Public Health Service Act (42 USC 262-63) §351
Food, Drug, and Cosmetic Act (21 USC 301-392)
Title 21 CFR
21 CFR 600-680: biological product standards
21 CFR 314 (21 CFR 601.25[d][2], specific to biologicals): adequate and well-controlled trials
21 CFR 312: investigational new drug application
21 CFR 210-211: good manufacturing practices
21 CFR 58: good laboratory practices
21 CFR 56: institutional review boards
21 CFR 50: protection of human subjects
Prescription Drug User Fee Act (PDUFA) of 1992, 2002, and 2007
Food and Drug Agency Modernization Act (FDAMA) of 1997
Food and Drug Agency Amendments Act (FDAAM) of 2007

in 1997 (PDUFA II), 2002 (PDUFA III), and 2007 (PDUFA IV).

FDA Modernization Act of 1997

The FDA Modernization Act (FDAMA) of 1997 renewed PDUFA user fees and performance goals and provided additional funding to support drug premarket review activities.⁹ The FDAMA included measures to modernize the regulation of biological products by synchronizing their review process with that of drugs and eliminating the requirement for an establishment license for biologicals. Expedited approval mechanisms for life-threatening conditions were authorized as well as the use of surrogate end points in clinical trials. The FDAMA also included a pediatric exclusivity provision that granted 6 months of market exclusivity to sponsors who conduct pediatric studies on the active ingredients of their drugs at the request of the FDA. In 2002, the terms of this provision were reauthorized in the Best Pharmaceuticals for Children Act.¹⁰

Food and Drug Administration Amendments Act of 2007

The Food and Drug Administration Amendments Act (FDAAA) of 2007 provided significant reform to the regulation of drugs and biologicals.¹¹ In addition to reauthorizing and expanding the PDUFA, the new law provided the FDA with new funding to collect, develop, and review safety information and develop adverse-event-surveillance systems and analytic tools. The FDAAA also mandated that products for which a postapproval risk evaluation and mitigation strategy (REMS) is required have the REMS submitted to their license application. The law expanded pediatric research with the reauthorization of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, originally signed into law in December 2003.¹² Under the Pediatric Research Equity Act, a new

drug application or supplement must contain a pediatric assessment unless waived or deferred. If the assessment indicates that the treatment for the disease has a similar course in all adult and pediatric populations, the Secretary of Health and Human Services may conclude that data supporting pediatric effectiveness can be extrapolated from well-controlled studies, usually supplemented with other information obtained from pediatric subjects.

FDA Guidance Documents

The FDA periodically publishes guidance documents that contain the agency's "current thinking" on issues pertaining to the manufacture and clinical evaluation of drugs and biologicals. Select guidance documents that are applicable to vaccines are listed in Table 2. The agency's guidance documents are intended to clarify sections of the CFR and provide the CBER's interpretation of the regulations. These documents do not contain legal statutes but provide nonbinding recommendations to better facilitate many aspects of vaccine product development.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidance Documents

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a collaboration of regulators from the United States, Europe, and Japan. The goal of the ICH is to provide recommendations on methods to harmonize the interpretation and application of global regulatory requirements. The ICH has published a number of guidelines for pharmaceutical product development relating to quality, safety, efficacy, and multidisciplinary topics. Select ICH

TABLE 2 Select FDA and ICH Guidance Documents Relevant to Vaccine Development

Manufacturing, product testing, and CGMPs
FDA 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 ²²
FDA guidance for industry: development of preventive HIV vaccines for use in pediatric populations ³⁰
FDA guidance for industry: considerations for plasmid DNA vaccines for infectious disease indications ³¹
FDA guidance for industry: content and format of chemistry, manufacturing and controls information and establishment description information for a vaccine or related product ³²
ICH Q10 pharmaceutical quality system ³³
FDA draft guidance: process validation—general principles and practices ³⁴
Clinical studies
FDA guidance for industry: clinical data needed to support the licensure of pandemic influenza vaccines ³⁵
FDA guidance for industry: clinical data needed to support the licensure of seasonal inactivated influenza vaccines ³⁶
FDA guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials ³⁷
Toxicity assessments of vaccines
ICH S5a detection of toxicity to reproduction for medicinal products and toxicity to male fertility ³⁸
ICH S6 Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals ³⁹

documents relevant to vaccine development are listed in Table 2.

THE REGULATORY REVIEW PROCESS

Vaccine development and commercialization are complex processes. The CBER provides regulatory guidance to sponsors throughout vaccine development through a managed review process that encompasses the life cycle of development. Figure 1 provides a brief overview of the regulatory approval process. A multidisciplinary review team, comprising a regulatory project manager, clinical/medical officers, product reviewers, statisticians, phar-

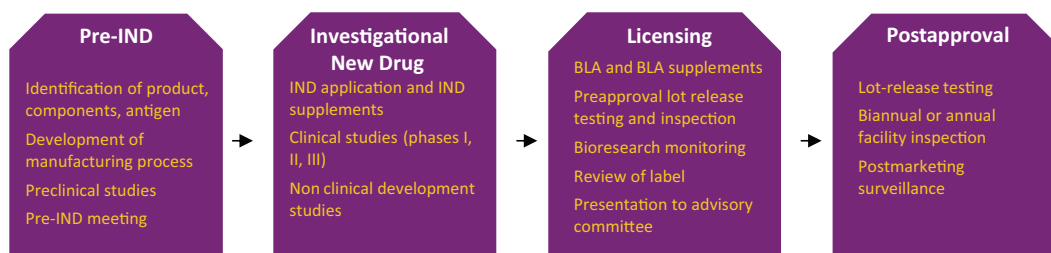


FIGURE 1
FDA regulatory review process.

macology/toxicology reviewers, and other scientific experts with various backgrounds in virology, bacteriology, immunology, and manufacturing technologies, reviews vaccine applications and other regulatory submissions in accordance with PDUFA time lines.

Preclinical Evaluation

Preclinical studies are generally conducted during the early stages of vaccine development and sometimes simultaneously with the clinical trial. Although limited at the beginning of clinical development, preclinical studies should be sufficient to rule out overt toxicity and identify potential toxic effects that might occur during the clinical trial. Nonclinical safety studies provide important safety data on the investigational product's effects in target organs as well as the reversibility of the toxicity. Toxicity studies should be conducted in compliance with good laboratory practices.¹⁵ These requirements help ensure the validity of toxicity test results by providing a well-controlled study environment. Adequate preclinical information must be provided to the CBER in the investigational new drug (IND) application to make a determination that it is reasonably safe to proceed with a clinical investigation.

More women of childbearing potential are participating in clinical trials, and more preventive and therapeutic vaccines are being developed for adolescents and adults. Consequently, there is increasing concern about the unin-

tentional exposure of an embryo/fetus before information is available about the risk versus benefit of a vaccine. The FDA published recommendations pertaining to the assessment of the developmental toxicity potential of preventive and therapeutic vaccines for infectious diseases indicated for females of childbearing potential and pregnant females.¹⁴

Considerations for preclinical studies are evaluated on a product-specific basis, and requirements may differ depending on the type of vaccine, the manufacturing process, and the mechanism of action. Dialogue with the CBER will help manufacturers or vaccine developers clarify what preclinical studies are needed, approaches to study design, and the extent of preclinical study documentation required before initiation of clinical trials. Requirements for preclinical toxicity studies depend on the vaccine's potential risk/benefit consideration, the target population, the available clinical data from the use of related products, product features, and the availability of animal models. As product development proceeds, the FDA may request additional preclinical studies.

Pre-IND Stage

The pre-IND stage primarily consists of laboratory development and testing of candidate vaccines and development of the manufacturing process. Sponsors are encouraged to meet with CBER reviewers for a pre-IND meeting to discuss preclinical studies, clinical

study design, data requirements, and other scientific issues that need resolution before the initiation of clinical trials. Procedures and policies for the conduct of meetings with the CBER are summarized in the FDA guidance document entitled "Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants."¹⁵

Investigational New Drug Stage

The clinical development of a new vaccine begins with the sponsor requesting permission to conduct a clinical study with an investigational product through the submission of an IND application. Title 21 CFR 312 describes the content of an original IND submission and the regulatory requirements for conduct of clinical trials under the IND regulations.¹⁶ Clinical studies are governed by good clinical practices. These regulations facilitate the protection and safety of human subjects and the scientific quality of clinical studies.¹⁷ Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. The IND submission is the means by which a sponsor obtains an exemption to this requirement. The IND submission describes the vaccine, its manufacture, control testing for release of the vaccine, the proposed scientific rationale, available preclinical animal safety testing results, and a proposed clinical study protocol. Review of the IND submission allows the FDA to monitor the safety of clinical trial subjects and en-

sure that the study design permits a thorough evaluation of the drug's effectiveness and safety.

Once an IND submission has been received by the FDA, the agency has 30 days to determine if the trial may proceed or be placed on clinical hold.¹⁸ Clinical hold is an order placed by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. Common reasons for clinical hold include safety issues with a candidate vaccine, unqualified investigators, inadequacy of the investigator's brochure, or insufficient information to assess risk. For larger phase II and III trials, clinical hold can be placed because of deficiency of the protocol design in meeting study objectives.

There are typically 3 successive phases in the clinical evaluation of vaccine products under the IND regulations.¹⁹ These phases can sometimes overlap, and the clinical evaluation may be highly iterative, because multiple phase I and II trials may be required as new data become available. The FDA rigorously oversees the clinical trial process. If data raise significant concerns about either safety or effectiveness, the FDA may request additional information or studies or may halt ongoing clinical studies. Phase I studies are designed to evaluate vaccine safety and tolerability and to generate preliminary immunogenicity data. Typically, phase I studies enroll between 20 and 80 subjects who are closely monitored throughout the duration of the trial. Phase II studies, which typically enroll several hundred subjects, evaluate the immunogenicity of the vaccine and provide preliminary estimates on rates of common adverse events. Phase II studies are often designed to generate data to inform the design of phase III studies. Sponsors are encouraged to meet with the CBER for an end-of-phase-II meeting to dis-

cuss their proposed phase III study. The phase III trial provides the critical documentation of the vaccine's safety and effectiveness needed to evaluate the risk/benefit relationship of the drug and to support licensure. Phase III trials are large and typically enroll from several hundred to several thousand subjects. Manufacturing reproducibility is typically addressed during the phase III trial by evaluation of lot consistency and ensuring process validation.

The general considerations for clinical studies to support vaccine licensure include safety, immunogenicity, and efficacy (immunogenicity may be sufficient in some cases). Ideally, efficacy should be demonstrated in randomized, double-blind, well-controlled studies. The end points will be product specific and may be clinical disease end points or immune response end points if efficacy against clinical disease has been established. The required number of study participants in efficacy trials for vaccines can range from thousands to tens of thousands of subjects. This broad range depends on variables such as study design and incidence of the disease to be prevented.

Licensing Stage

The licensing stage follows the IND stage when clinical studies are completed. The biologics license application (BLA) is a request for permission to introduce, or deliver for introduction, a biological product into interstate commerce. The regulations that pertain to the licensure and submission of a BLA can be found in 21 CFR 600 through 680.²⁰ Licensure of vaccines is based on demonstration of safety, purity, and potency as defined in Title 21 CFR 600²¹ and the ability to manufacture product in a consistent manner. A sponsor may apply for a license to manufacture and distribute a product

commercially by submitting a BLA to the director of the CBER Office of Vaccines Research and Review. A multidisciplinary CBER review team reviews the BLA to make a determination that a product is safe and effective for its intended use.

The BLA contains the data derived from nonclinical and clinical studies that demonstrate that a vaccine meets prescribed requirements for safety, purity, and potency. The submission must also contain a full description of manufacturing methods, compliance with CGMP requirements, data establishing stability of the product through the dating period, samples representative of the product for introduction into interstate commerce, and data describing the equipment and facility of each location involved in the manufacture. The BLA also includes the manufacturer's process for large-scale manufacturing of vaccine material. The chemistry, manufacturing, and controls information submitted to the FDA should include documentation of all raw materials used in the production of the master and working seeds, any cell substrates used in the production of the vaccine, and a description of the production of the seeds and cell banks used in vaccine production. The FDA requires that cell substrates and vaccine viral seeds used in production be tested and carefully characterized, because these components influence the safety and purity of the final product.²² Biological starting materials should be characterized to ensure that they are free from extraneous infectious organisms such as bacteria, fungi, mycobacteria, viruses, and other infectious agents.

In addition to review of the BLA submission, important regulatory review activities support vaccine licensure. These activities help ensure the quality and safety of licensed products. Vaccine lots are subject to prelicensure

lot-release testing. The preapproval inspection is designed as an in-depth review of the manufacturing facilities, the manufacturing process, and a sponsor's adherence to CGMPs. The conduct of the clinical study is evaluated by the CBER through a mechanism called bioresearch monitoring. Bioresearch monitoring involves inspection of clinical sites to ensure adherence to good clinical practices. Review of the proposed vaccine label is a significant part of the review process. Regulations that pertain to labeling can be found in Title 21 CFR 201 and 610.60-610.62.²³ Each statement of an approved biological must be carefully evaluated by the FDA to ensure that claims are supported by data.

During the CBER's review of the BLA, the agency may request that manufacturers present their data to the Vaccines and Related Biological Products Advisory Committee (VRBPAC). The VRBPAC is a standing FDA advisory committee composed of scientific experts and clinicians, consumer representatives, and a nonvoting member from industry. The VRBPAC and additional expert consultants, if needed, evaluate clinical data and comment on the adequacy of the data to support safety and efficacy in the target population. The committee's recommendations are strongly considered in the CBER's decision to license a vaccine. The committee may recommend that additional studies be performed before licensure. Once the CBER determines that the data support the safety and effectiveness of the vaccine and manufacturing consistency is demonstrated, the product may be licensed.

The CBER has developed a number of accelerated review mechanisms intended to expedite the review for vaccines against life-threatening conditions, including accelerated approval, fast track, and priority review. Designation of a drug under these mecha-

nisms does not alter the required scientific/medical standards, the quality of data necessary for approval, or the length of the clinical trial period.

The accelerated-approval regulation allows approval on the basis of a surrogate end point for drugs intended to treat serious diseases and that fill an unmet medical need. A surrogate end point is a marker (eg, a laboratory measurement or physical sign) used in clinical trials as an indirect or substitute measurement that represents a clinically meaningful outcome, such as survival or symptom improvement.²⁴ The use of surrogate end points may shorten the FDA approval time. Approval of a drug on the basis of such end points is given on the condition that postmarketing clinical trials verify the anticipated clinical benefit.

The fast-track mechanism is designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs (ie, providing a therapy when none exists).²⁵ Most drugs that are eligible for fast-track designation are likely to be considered appropriate to receive a priority-review designation. A priority-review designation is given to drugs that offer major advances in treatment or provide a treatment when no adequate therapy exists. A priority review reduces the FDA review time; the goal time for completing a priority review is 6 months.

The assessment of efficacy for some infectious-disease vaccine candidates cannot be ethically conducted under clinical trial, such as those for certain bioterrorism agents. 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.²⁶ This rule, referred to as

the "animal rule," provides that approval of certain new drug and biological products can be based on animal data when adequate and well-controlled efficacy studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human subjects. In these situations, certain new drug and biological products can be approved for marketing on the basis of evidence of effectiveness derived from appropriate studies in animals without adequate and well-controlled efficacy studies in humans. When assessing the sufficiency of animal data, the agency may take into account other data, including human data, available to the agency. Safety must be evaluated in humans as a prerequisite for approval.

Postapproval Stage

Lot-Release Testing and Facility Inspection

Vaccine production depends on living organisms, and there are many points during the manufacturing process at which to introduce contaminants. Regulatory requirements mandate that all licensed vaccines undergo appropriate lot testing before release, as listed in Table 3. Requirements for release testing of licensed biologicals can be found in Title 21 CFR 610.²⁷ The tests

TABLE 3 Lot-Release Testing

Sterility, purity: detects the presence of bacterial or fungal contaminants
General safety test: detects toxicity (conducted in small animal models)
Identity test: verifies that a product induces specific antibodies after vaccination (conducted in small animal models)
Potency: verifies immunogenicity, antigen content, or chemical composition (in vivo or in vitro)
Purity: verifies freedom from extraneous materials
Tests for removal of process contaminants
Pyrogenicity: detects the presence of fever-inducing substances

include those for bacterial and fungal sterility, general safety, purity, identity, suitability of constituent material, and potency. Depending on the product, additional testing (eg, to ensure adequate inactivation) may be required. In addition, constituent materials such as diluents and preservatives must meet standards for sterility.

After licensure, monitoring of the vaccine and production activities, including periodic facility inspections, must continue as long as the manufacturer holds a license for the product. Licensed establishments are inspected at least every 2 years except for those facilities that manufacture influenza vaccines; these establishments are inspected annually. The purpose of the inspection is to determine if licensed products are manufactured and tested as described in the license application and in accordance with applicable regulations. Manufacturers that fail to meet product standards or do not comply with CGMPs may have their licenses suspended or revoked, depending on the nature of the inspectional finding.

Postmarketing Surveillance

Postmarketing surveillance is a necessary component of vaccine-safety monitoring. Important objectives of postmarketing surveillance are to monitor increases in known reactions, to identify rare adverse reactions not detected during prelicensure studies, and to identify signals of possible adverse reactions that may warrant further study.²⁸ Manufacturers are re-

quired to provide ongoing reports of the safety of licensed vaccines. The Food and Drug Administration Amendments Act legislation gave the FDA increased authority to require postmarketing studies, to require sponsors to make safety labeling changes, and to develop and comply with risk-evaluation and -mitigation strategies. The CBER carefully considers a vaccine manufacturer's proposal for postlicensure surveillance through pharmacovigilance plans submitted with the BLA and has employed a multidisciplinary team including epidemiologists, clinical/product reviewers, compliance/manufacturing experts, and communications experts to evaluate vaccine safety.

The National Childhood Vaccine Injury Act, passed in 1986, requires health professionals and vaccine manufacturers to report to the US Department of Health and Human Services specific adverse events after the administration of particular vaccines.²⁹ In 1990, the Vaccine Adverse Event Reporting System (VAERS) was established under the joint administration of the Centers for Disease Control and Prevention (CDC) and the FDA to collect reports of suspected adverse events after administration of all US-licensed vaccines. The VAERS accepts reports of any adverse event that may be associated with US-licensed vaccines from health care providers, manufacturers, and the public. The FDA and CDC use VAERS data to monitor vaccine safety. Another important mechanism used by the CBER to monitor adverse events

from vaccines is the Vaccine Safety Datalink project, a collaborative effort between CDC's Immunization Safety Office and several large managed care organizations. The Vaccine Safety Datalink project was established in 1990 to monitor immunization safety and address gaps in scientific knowledge about rare and serious adverse events after immunization.

CONCLUSIONS

Vaccines are an important resource for protecting people and communities from the mortality and morbidity associated with many infectious diseases. The FDA provides regulatory oversight throughout the complex development process, which involves extensive laboratory characterization, preclinical testing, and clinical evaluation. Stringent regulatory prerequisites must be achieved throughout development for a vaccine to be considered for licensure. After licensure, vaccine safety is continually monitored through lot-release testing, inspections, and product surveillance. The FDA ensures the safety, effectiveness, and availability of licensed vaccines through its comprehensive and meticulous regulatory review mechanisms and its broad scientific research programs.

ACKNOWLEDGMENT

We thank Dr Theresa Finn for assistance in critically reviewing this article and providing constructive comments.

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