

FEDERAL REGULATION, SURVEILLANCE AND EVALUATION OF VACCINES

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Vaccine Licensure

The regulation of vaccines begins with the extremely lengthy and rigorous process of vaccine licensure. The Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) is the United States agency that is responsible for regulating and licensing vaccines.¹ CBER reviews applications for licensure of vaccines, biologicals and blood products as well as evaluates the establishments that produce these products, enforces compliance with FDA standards and conducts post-marketing product surveillance.

However, vaccine regulation requires the coordination and assistance of many government agencies. CBER works with many organizations to fulfill these responsibilities. The chart below describes the roles that the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH) and the National Vaccine Program Office (NVPO) play in this process.³

Organization	Role
Centers for Disease Control and Prevention (CDC)	Responsible for disease surveillance and for support of immunization programs
National Institutes of Health (NIH)	Conducts and funds biomedical research
National Vaccine Program Office (NVPO)	Coordinates the vaccine efforts of the US Public Health Service and the Interagency Vaccine Group (IAVG). IAVG consists of the following organizations: <ul style="list-style-type: none"> • Agency for International Development (USAID) • Centers for Disease Control and Prevention (CDC) • Department of Defense (DoD) • Food and Drug Administration (FDA) • Centers for Medicare and Medicaid Services (CMS) • National Institutes of Health (NIH) • Office of the General Counsel (OGC)

The diagram on page 18 illustrates the process a vaccine sponsor must go through to license a vaccine for public use. Licensure is a long and expensive process. Fulfilling the licensure requirements of CBER takes between 5 and 10 years and costs between \$300 and \$500 million.² Even if the vaccine is licensed, federal oversight continues for as long as the vaccine remains licensed in the United States.

Investigational New Drug (IND) Application

The process of vaccine licensure begins when a vaccine sponsor files an Investigational New Drug (IND) application. This application sets into motion a systematic and in-depth evaluation of the safety and efficacy of the vaccine that may or may not result in licensure of the vaccine for use in the US. The IND application must meet FDA's strict review criteria before clinical studies can begin on the candidate vaccine. The IND application must explain the scientific rationale for the vaccine, describe the vaccine and the manufacturing process required to produce it, describe all pre-clinical study data, and propose a plan for a Phase I clinical trial. Pre-clinical study data must demonstrate that the vaccine has passed a series of tests for purity (laboratory tests) and safety (studies in animals). Information contained within the

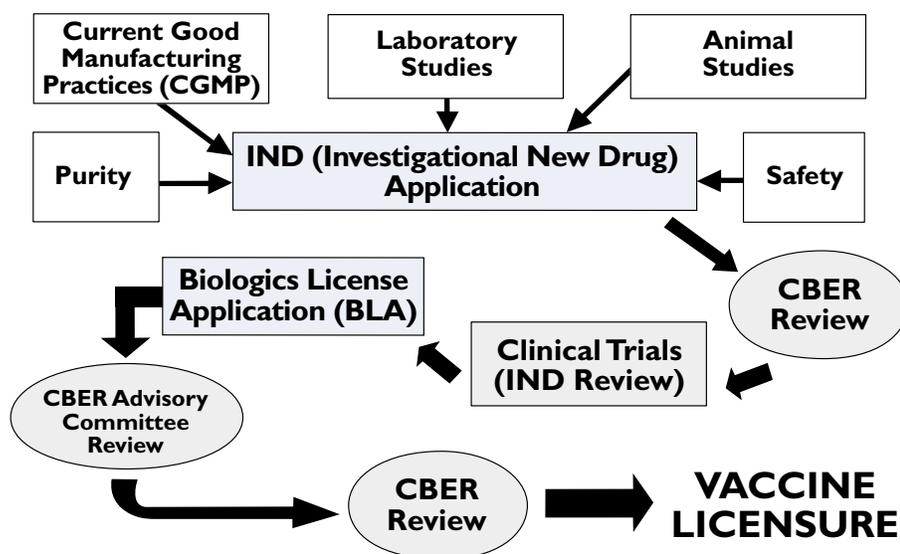
GLOSSARY TERMS

Adverse events	Influenza
Advisory Committee on Immunization Practices (ACIP)	Intussusception
Allergy	Measles
Anthrax	Meningococcal disease
Association	Mumps
Attributable risk	Pertussis
Autism	Pneumococcal disease
Bias	Pneumococcal polysaccharide
Cases	Poliomyelitis
Clinical trial	Polysaccharide
Compulsory immunization laws	Polysaccharide vaccine
Contraindications	Pre-clinical study
Controls	Registry
Coverage	Risk
Current Good Manufacturing Practices	Rotavirus vaccine
Diabetes	Rubella
Diphtheria	Safety assessment
Disease	Seizure
Efficacy	Smallpox
Epidemic	Tetanus
Epidemiologic studies	Thimerosal
Excise taxes	Vaccination registry
Guillain-Barré syndrome	Vaccine
<i>Haemophilus influenzae</i> type b	Vaccine Identification Standards Initiative
Hepatitis	Vaccine Information Statement
Hepatitis A	Vaccine Injury Compensation Program
Hepatitis B	Vaccine Safety Datalink Project
Immunization	Vaccine schedule
Inflammatory bowel disease	Vaccine sponsor
	Varicella
	Virus

ACRONYMS

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research (FDA)
CDC	Centers for Disease Control and Prevention
CGMP	Current Good Manufacturing Practices
CISA	Clinical Immunization Safety Assessment
CMS	Centers for Medicare and Medicaid Services
COID	Committee on Infectious Diseases (AAP)
DHHS	United States Department of Health and Human Services
DoD	Department of Defense
DTaP	Diphtheria, tetanus, acellular pertussis vaccine
FDA	Food and Drug Administration
Hib	<i>Haemophilus influenzae</i> type b
HMO	Health maintenance organization
HRSA	Health Resources and Services Administration
IAVG	Interagency Vaccine Group
IND	Investigational New Drug
IOM	Institute of Medicine
IPV	Inactivated poliovirus
IRB	Institutional Review Board
MMR	Measles, mumps, rubella
MSAEFI	Monitoring System for Adverse Events Following Immunization
NIH	National Institutes of Health

(continued)



IND application must, according to the Code of Federal Regulations, demonstrate compliance with the minimum standards for Current Good Manufacturing Practices (CGMP), which are federally mandated regulations that define requirements for the manufacturing process, quality control, documentation, testing and facilities.^{4,5} The FDA may require that additional studies be conducted or that alterations be made throughout the manufacturing process.³

CBER has 30 days to complete the initial review after the complete IND application has been received. At the end of this time, a decision is made either to approve the application (and allow the vaccine to enter clinical trials) or to request additional information from the sponsor. However, even if approved, CBER review continues until the vaccine is licensed. Routine inspections and reviews are ongoing and a vaccine can be placed on “clinical hold” at any time during this process if, for example, CBER requests that further studies be done or requires that alterations be made to the manufacturing process.⁵

Institutional Review Board (IRB)

In addition to receiving IND application approval, a local, outside body of experts known as an Institutional Review Board (IRB) must also approve the study before the candidate vaccine can enter clinical trials. An IRB is a committee established by the agency, institution or corporation conducting the clinical trial to review all aspects of the study. Such committees typically include scientists, physicians and other professionals as well as individuals from the community. One crucial role of the IRB is to oversee the development and use of informed consent forms that must be signed by vaccine study participants. The FDA requires that all clinical studies provide study participants with information on the types of tests/procedures they will be subject to under the study, why these tests are being conducted and what known risks, if any, are involved in taking part in the research study. After this information is provided, individuals must sign consent forms to provide documentation that they understand and agree to the terms of participation in the study and have been made aware of the risks involved.³

Clinical Studies

After both CBER and the study’s IRB have given the vaccine sponsor permission to move forward with clinical studies, the vaccine can enter a Phase I clinical study. Clinical studies required for licensure must move through Phase I, II and III studies as described on pages 13–14. IRB approval must be given prior not only to the initiation of Phase I studies but also to Phase II, Phase III and Phase IV studies. These trials are constantly monitored and reviewed by CBER and can be halted,

NVAC	National Vaccine Advisory Committee
OGC	Office of the General Counsel
PHS	Public Health Service
USAID	United States Agency for International Development
VAERS	Vaccine Adverse Events Reporting System
VICP	Vaccine Injury Compensation Program
VIS	Vaccine information statement
VISI	Vaccine Identification Standards Initiative
VNPO	National Vaccine Program Office
VRBPAC	Vaccines and Related Biological Products Advisory Committee (CBER)
VSD	Vaccine Safety Datalink Project

WEB RESOURCES

FEDERAL VACCINE REGULATION:

Center for Biologics Evaluation and Research (CBER)

<http://www.fda.gov/cber/index.html>

Centers for Disease Control and Prevention

<http://www.cdc.gov/nip/vaccine/develop-approval.htm>

Executive Summary of the Task Force on Safer Childhood Vaccines

<http://www.niaid.nih.gov/publications/vaccine/safervacc.htm>

Food and Drug Administration (FDA)

<http://www.fda.gov>

National Vaccine Program Office (NVPO)

<http://www.cdc.gov/od/nvpo>

Vaccine Information Statements (VIS)

<http://www.cdc.gov/nip/publications/VIS/default.htm>

Vaccines and Related Biological Products Advisory Committee

<http://www.fda.gov/cber/advisory/vrbp/vrbpmain.htm>

NATIONAL VACCINE PROGRAM INTERAGENCY GROUP:

Agency for International Development (USAID)

<http://www.usaid.gov>

Centers for Disease Control and Prevention (CDC)

<http://www.cdc.gov>

National Immunization Program

<http://www.cdc.gov/nip>

National Center for Infectious Diseases

<http://www.cdc.gov/ncidod/index.htm>

Centers for Medicare and Medicaid Services (CMS)

<http://cms.hhs.gov>

Department of Defense (DOD)

<http://www.defenselink.mil>

Health Resources and Services Administration (HRSA)

<http://www.hrsa.gov>

National Vaccine Injury Compensation Program (NVICP)

<http://bhpr.hrsa.gov/vicp>

National Institutes of Health (NIH)

<http://www.nih.gov>

National Institute for Allergy and Infectious Diseases (NIAID)

<http://www.niaid.nih.gov/default.htm>

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temporarily or permanently, at any time if vaccine production does not meet FDA standards for CGMP, if there are concerns about the safety of the vaccine or if there is evidence of a lack of efficacy.

Licensure

All clinical studies conducted within the IND review process must be close to completion or have been completed before the vaccine sponsor can begin the final vaccine licensure application. In addition, all production techniques must be developed per regulatory guidelines and all manufacturing processes must be standardized. When the vaccine sponsor determines that all of these criteria have been met, the sponsor will apply for a license to manufacture and distribute the vaccine to the public by submitting a Biologics License Application (BLA).

In the BLA, the vaccine sponsor must include: (1) a complete description of all manufacturing and testing methods for the vaccine; (2) results of all laboratory tests performed on a specific number of vaccine production lots that are intended for distribution to the public [this includes the production of at least six large lots of vaccines, each containing tens of thousands of doses, to demonstrate that the manufacturing process is consistent and reliable⁶]; (3) a summary of the results of all clinical studies; and (4) proposed labeling, including the indications, directions and contraindications for use of the vaccine. Information submitted in the BLA must demonstrate compliance with standards for all production materials, facilities, personnel, equipment and packaging. Sponsors must also show that labeling, holding, distribution and record maintenance meet FDA standards.³

Scientific review of the BLA is conducted internally by CBER's Vaccines and Related Biological Products Advisory Committee (VRBPAC). This advisory committee reviews the data supporting the safety, purity and potency of the vaccine, and provides recommendations on whether the product should be approved. VRBPAC includes representatives of CBER, a representative from the CDC, professors and leaders from leading US universities and representatives of other organizations.^{5,7} During the BLA review, discussions and correspondence between the vaccine sponsor and VRBPAC are ongoing and sometimes outside consultants and advisors are brought in to further review the application.³

When the application process is near completion and vaccine production has begun, an announced inspection of the production facility is conducted. This inspection provides an in-depth review of the production facilities, records, process, methods, equipment, quality control procedures and personnel. The committee presents all data and recommendations to CBER, and if CBER determines that the data and information are satisfactory, the vaccine is licensed.³

Advisory Committees

After a new vaccine is approved by the FDA, advisory committees made up of immunization experts facilitate the incorporation of the vaccine into public health programs. These advisory committees decide whether to recommend the vaccine for the general population, how the vaccine should be incorporated into established vaccination schedules and how the vaccine should be incorporated into various health

service delivery systems. In addition, experts review and update recommendations on existing vaccines and immunization programs.⁷ These advisory committees have an even broader mandate than the FDA. Besides evaluating the available safety and immunogenicity data, advisory committees must take into account societal perspectives, the systems in place for delivery of vaccines, cost-effectiveness and cost-benefit



VACCINE ADVISORY COMMITTEE:

Advisory Committee on Immunization Practices (ACIP)

<http://www.cdc.gov/nip/acip/default.htm>

American Academy of Family Physicians (AAFP)

<http://www.aafp.org>

American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID)

<http://www.aap.org>

National Vaccine Advisory Committee (NVAC)

<http://www.cdc.gov/od/nvpo/committee.htm#nvac>

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

<http://www.fda.gov/cber/advisory/vrbp/vrbpmembers.htm>

SURVEILLANCE MECHANISMS:

Institute of Medicine

<http://www.iom.edu>

Institute of Medicine Immunization Safety Review Committee

<http://www.iom.edu/imsafety>

National Childhood Vaccine Injury Act

<http://www.cdc.gov/nip/vacsafe/default.htm#ncvia>

VAERS Information and Reporting Form

<http://www.vaers.org>

Vaccine Injury Compensation Program

<http://www.cdc.gov/nip/vacsafe/default.htm#vicp>

Vaccine Injury Table

<http://www.bhpr.hrsa.gov/vicp/table.htm>

Vaccine Safety Datalink Project

<http://www.cdc.gov/nip/vacsafe/default.htm#vsd>

REGISTRY INFORMATION:

National Partnership for Immunization

<http://www.partnersforimmunization.org/immregistry.html>

Immunization Registry Clearinghouse of the National Immunization Program

<http://www.cdc.gov/nip/registry/>

Every Child by Two

<http://www.echt.org/immreg.html>

All Kids Count

<http://www.allkidscount.org>

analyses, expert opinion based on similar vaccines and the impact of the new vaccine on child, adolescent and adult immunization schedules.⁸

The following expert advisory committees guide the formulation of government policies:

- **Advisory Committee on Immunization Practices (ACIP)** consists of 15 experts selected by the Secretary of the US Department of Health and Human Services (DHHS) for their expertise in vaccination, infectious diseases and public health. This committee advises the Secretary, the Assistant Secretary for Health and the CDC on the most effective means to prevent vaccine-preventable diseases. ACIP develops written recommendations for the routine administration of vaccines to the public as well as schedules that note the appropriate periodicity, dosage and contraindications for each vaccine.⁹

The background work leading to vaccination recommendations is done by ACIP working groups. Working groups are composed of ACIP members, representatives of professional societies and other federal agencies and organizations (including industry) with an interest in immunization. Academic researchers and representatives from vaccine manufacturers may serve as consultants to working groups. Working groups consider and summarize data for presentation to the full ACIP.

The process of developing ACIP recommendations includes: (1) a review of labeling and package inserts for each vaccine; (2) a thorough review of published and unpublished studies on the safety, efficacy, acceptability and effectiveness of the vaccine, with consideration of the relevance, quality and quantity of this data; (3) a cost-effectiveness analysis; (4) a review of the morbidity and mortality associated with the disease both in the general population and in specific risk groups; (5) a review of the recommendations of other groups; and (6) a consideration of the feasibility of incorporating the vaccine into existing child and adult immunization programs. Feasibility issues include acceptability to patients, parents and the community; vaccine distribution and storage; access to vaccine and vaccine administration; impact on health care delivery systems; and social, legal and ethical concerns.

The final stage of the ACIP vaccine recommendation process is adoption of the working group's recommendations by committee vote. Adoption requires approval by a majority of committee members. In situations where a quorum of members is not present at the meeting or cannot vote because of potential conflicts of interest, *ex officio* members may be authorized to vote.¹⁰ ACIP recommendations are referred to CDC and then to the Secretary of DHHS who may accept or reject the recommendations. If accepted, the recommendations become part of the national immunization policy.

- **National Vaccine Advisory Committee (NVAC)** makes recommendations on vaccine policy, programs and delivery for the entire country. These recommendations are given to the Director of the National Vaccine Program Office (NVPO) of the US Department of Health and Human Services (DHHS) who then reports all proceedings to the US Surgeon General. NVPO was established by DHHS to achieve optimal prevention of human infectious diseases through immunization and to

achieve optimal prevention of adverse events associated with vaccine use.¹¹ NVPO helps to coordinate the vaccine efforts of the US Public Health Service and NVPO's Interagency Vaccine Group (IAVG).

- **Office of Emergency Preparedness (OEP)** is located within DHHS and is responsible for managing and coordinating federal health, medical and health-related social services and recovery from major emergencies and federally declared disasters such as natural disasters, technological disasters, major transportation accidents and terrorism. This agency plays a major role in the development of policies for the use and distribution of vaccines that help prevent diseases caused by certain potential bioterrorism agents.
- **Advisory Commission on Childhood Vaccines (ACCV)** gives the Secretary of Health and Human Services advice regarding the National Vaccine Injury Compensation Program (VICP) (see page 24). Such advice includes recommendations on VICP implementation, on changes to the list of adverse events for which this program provides compensation, on the provision and use of childhood vaccines with few or no significant adverse reactions, on obtaining and using credible data on the frequency and severity of adverse reactions associated with childhood vaccines and on research to be conducted.

The following professional organizations provide information and perspectives during the process of federal vaccine policy development and guide the implementation of these policies by conveying them to their constituents:

- **American Academy of Pediatrics (AAP)**, a professional organization of pediatricians, has established the Committee on Infectious Diseases (COID) that monitors developments in the prevention, diagnosis and treatment of infectious diseases and reports these to AAP members with pertinent recommendations. The Committee regularly updates the Red Book: Report of the Committee on Infectious Diseases and develops and reviews policy recommendations on the use of vaccines.¹²
- **American Academy of Family Physicians (AAFP)**, a professional organization for doctors specializing in family medicine, provides recommendations and policy statements to its members on vaccine use and delivery.¹³

Vaccine Information Statements

Vaccine Information Statements (VISs) are information sheets on the recommended vaccines that are produced by the Centers for Disease Control and Prevention (CDC). Federal law requires that this information be given to vaccine recipients, their parents or their legal representatives whenever certain vaccinations are given (prior to each dose of these vaccines). VISs provide general information about a particular vaccine and the diseases that the vaccine helps to prevent and explain both the benefits and risks of the vaccine. VISs are available for the following vaccines: diphtheria, tetanus, acellular pertussis (DTaP); hepatitis A; hepatitis B; *Haemophilus influenzae* type b (Hib); influenza; measles, mumps, rubella (MMR); meningococcal; pneumococcal conjugate; pneumococcal polysaccharide; tetanus/diphtheria; varicella; and anthrax. These forms are now available in over 26 different languages and can be downloaded from the Immunization Action Coalition Web site at www.immunize.org/vis.

State Requirements



Individual states are responsible for implementing all vaccine requirements, including school immunization requirements. In 1809, Massachusetts passed the first immunization law, requiring its population to be vaccinated against smallpox.¹⁴ States' rights to pass compulsory immunization laws were confirmed by the Supreme Court in 1905 and upheld in 1922 in a case involving required vaccination for school entry. Modern school immunization laws began with efforts to eliminate measles in the US in the 1960s and 1970s.¹⁴ The usefulness of these laws was revealed by early data showing a 40% to 51% lower rate of measles in states with school immunization laws compared with those without such laws.¹⁵ Immunization mandates during measles outbreaks in Alaska in 1976¹⁶ and in Los Angeles in 1977¹⁷ proved to be very effective in preventing and eliminating the spread of measles.

Today, states make decisions based on the recommendations of the vaccine advisory committees, recognizing the need to prevent disease epidemics and to reduce disease burdens. State mandates exist for childhood and adolescent immunizations but do not include adult immunizations. All 50 states have both school immunization laws as well as medical criteria for exemption from mandated immunizations. Forty-eight states allow exemptions to immunization based on religious beliefs, and 15 states also allow for philosophical exemptions from mandated immunizations.¹⁸

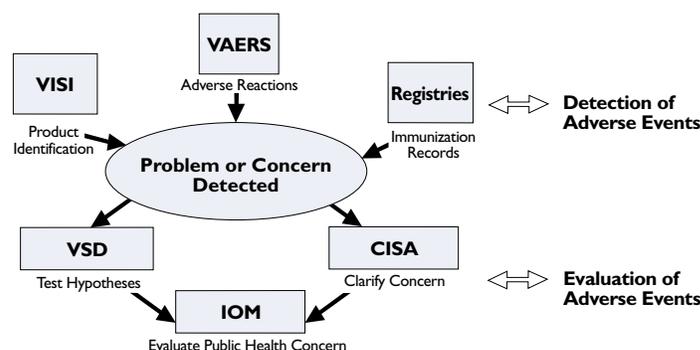
Vaccine Financing

Programs have been established to finance the purchase of vaccines for low-income, uninsured and underinsured children. Currently, almost 60% of pediatric vaccines are purchased either by the federal government or by state and local governments through documented federal contracts. Most federally purchased vaccines are supplied through the Vaccines for Children (VFC) program, providing free vaccines for administration to eligible persons from birth through 18 years of age. Funds are also appropriated under a grant program established by Section 317 of the Public Health Service Act. These funds are distributed by CDC to state and local immunization programs to support vaccination in public clinics and, in some states, by private providers. Costs of influenza and pneumococcal vaccination for persons over 65 years old are covered by Medicare part B.¹⁹

Vaccine Surveillance Mechanisms

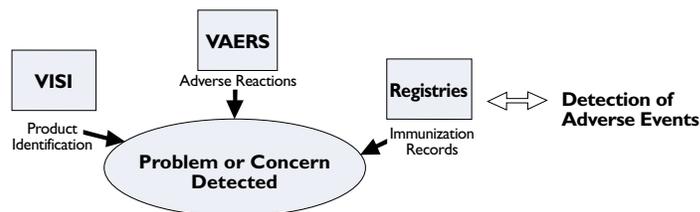
Government monitoring and interest in vaccine use does not stop once a vaccine is licensed and is made available to the general public. National detection and evaluation systems are in place to

continually assess the safety and efficacy of vaccines that are widely used in the US.



Detection of Adverse Events

At least three mechanisms exist within the immunization system to help detect adverse events in a timely and accurate fashion.



(1) Vaccine Identification Standards Initiative (VISI)

Currently being incorporated into the manufacturing process of vaccines, the Vaccine Identification Standards Initiative (VISI) requires the placing of a bar-coded sticker on each vaccine. Health professionals can peel off the sticker and place it on the immunization record of the person being vaccinated, allowing health officials to directly link reports of adverse events to specific products and lots while increasing the accuracy and availability of information contained in individual immunization records.

(2) Immunization Registries

Immunization registries are confidential, computerized systems that contain information about an individual's immunization record and their compliance with the vaccine schedules. Besides identifying vaccine coverage, registries help programs assess safety by confirming who has received which vaccine as well as where and when the vaccine was administered. Registries can also generate reminder or recall notices to patients when revaccination is needed or when new vaccines are introduced.

Cost analyses have shown that registries can save enormous amounts of money.²⁰ Sixteen vaccination registry projects have estimated costs for the average child to participate in a registry to be \$3.91 or \$78 million for all children aged 0-5. But once established nationwide, registries would save health care and education systems \$280 million annually.²¹

(3) Vaccine Adverse Event Reporting System (VAERS)

Adverse events are undesirable experiences occurring after immunization that may or may not be related to the vaccine.

Adverse events can range from mild reactions such as pain at the vaccine injection site to more severe reactions such as seizures. Although most vaccine manufacturers encourage the reporting of adverse events to them, Congress recognized the importance of establishing an independent reporting program to ensure scientific independence when evaluating vaccine safety. Therefore, in 1986, Congress created the Vaccine Adverse Event Reporting System (VAERS) under the National Childhood Vaccine Injury Act²² to serve as the mechanism by which information about adverse events following immunization may be reported, analyzed and made available to the public.²³ VAERS replaced the Monitoring System for Adverse Events Following Immunization (MSAEFI) established in 1978 by the Centers for Disease Control and Prevention (CDC), which required the distribution of an information leaflet to all recipients of vaccines. The leaflet contained a statement requesting that vaccine recipients notify a doctor that they had recently been vaccinated should they require medical care within four weeks of vaccination. VAERS expands upon this program by accepting reports directly from lay persons, distributing report forms to all physicians, providing a list of events mandated for reporting and establishing a 24-hour toll-free help line.²⁴

In addition, the National Childhood Vaccine Injury Act mandated that before administering each vaccine, health care providers must give each person who is to be vaccinated or their guardian a copy of the corresponding vaccine information statement (VIS). Available since April 1992, these statements outline the benefits and risks of vaccination and give information on how to report the occurrence of an adverse event to VAERS.²⁵

VAERS serves both as a national registry of adverse events following immunizations and as a tool used by the Food and Drug Administration (FDA) and CDC to generate hypotheses regarding potential associations between mild and serious events and vaccine administration. VAERS attempts to detect previously unrecognized vaccine-related reactions, unusual increases in previously reported events, pre-existing conditions that may be associated with certain reactions and contraindicate additional doses of the vaccine as well as to identify specific vaccine lots associated with reported events.²⁶ Both the FDA and CDC review data reported to VAERS. The FDA surveys individual reports to update product labeling, to perform comprehensive review of recently licensed vaccines, and to monitor trends for individual vaccine manufacturers and lots. The CDC reviews collective reports to detect and analyze epidemiological trends and associations.²⁷

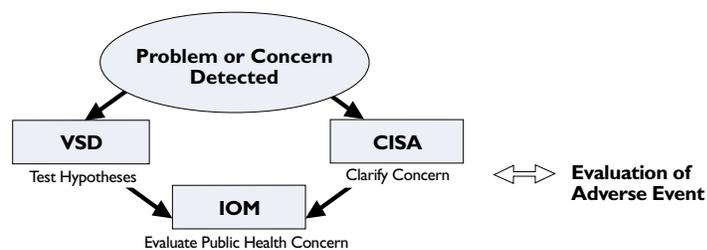
To accomplish its objectives, VAERS report forms are mailed directly to approximately 200,000 primary care physicians, emergency room directors and state health departments each year. A report form can also be found in the Physician's Desk Reference, in the American Academy of Pediatrics' Red Book: Report of the Committee on Infectious Diseases and can be accessed through the Internet (see Web Resources). Reporters to VAERS receive letters acknowledging that their report was received. While reporters are generally encouraged to send in reports as soon as possible, vaccine manufacturers are required to send in serious adverse event reports within 15 days of receiving those reports.²⁶

The strengths of VAERS lie in its national scope, its timeliness in gathering information about adverse events and its relatively

cost-effective implementation. Because VAERS is a passive or voluntary reporting system, the database is subject to under-reporting, biased reporting, inadequate report quality, differences in reporting rates between the public and private sector and increased reporting when a vaccine is first licensed, or following the appearance of media stories questioning the safety or importance of a vaccine, etc.²⁷ Interpretation of VAERS data is also difficult due to the mixing of multiple exposures and outcomes, difficulty in detecting new and changing adverse events and mixing of potentially causal and coincidental events. The lack of denominators, i.e., information on the total number of people receiving the vaccine of interest, and control groups creates difficulty in applying information from VAERS to the general population. Although unable to address potential vaccine-adverse event causality, the usefulness of VAERS is due to the ability to use the data to propose hypotheses about potential causal relationships that can be tested and verified by other mechanisms.²⁸

VAERS data have been extensively utilized. The Institute of Medicine (IOM) Vaccine Safety Committee used VAERS to assess various relationships between childhood vaccines and adverse events in 1994.²⁹ The Advisory Committee on Immunization Practices (ACIP) has documented possible adverse events and adverse events related to vaccination and developed recommendations for precautions and contraindications to vaccination through review of VAERS data. CDC and FDA have used VAERS to screen for and detect previously unrecognized reactions to current and future vaccines. For example, investigations of VAERS reports by the FDA have shown that the hepatitis B vaccine is safe for use in infants.³⁰ Similar investigations have been conducted for hepatitis A³¹ and varicella vaccines.³² VAERS data were used to compare the safety record for diphtheria, tetanus, acellular pertussis (DTaP) vaccine³³ and inactivated poliovirus (IPV) vaccine³⁴ with the vaccines they replaced (diphtheria, pertussis, whole cellular pertussis vaccine and oral poliovirus vaccine, respectively). VAERS detected influenza vaccine-associated increased rates of Guillain-Barré syndrome from 1992-1993 to 1993-1994,³⁵ and increased rates of intussusception associated with the rotavirus vaccine in 1999.³⁶ These surveillance data led to further research into potential associations between each vaccine and the corresponding reported diseases and resulted in the withdrawal from use of the rotavirus vaccine.^{37,38}

Evaluation of Adverse Events



The Vaccine Safety Datalink Project (VSD) and the Clinical Immunization Safety Assessment (CISA) Centers are two systems created to evaluate and clarify hypotheses generated from information gathered from the three reporting mechanisms described above.²⁸ Committees of the IOM also review these hypotheses as well as various immunization research studies to provide research and policy recommendations.

(1) Vaccine Safety Datalink (VSD) Project

This collaboration between CDC and several health maintenance organizations (HMOs) began in 1991 and is aimed at testing the hypotheses raised by adverse events reports. Today, over 7.5 million people (approximately 2.5% of the United States population) are involved through eight participating HMOs. The VSD database is able to combine information on patient vaccination records, health outcomes (from hospital, emergency room and out-patient department records) and patient characteristics (birth certificate and census information) to test such hypotheses. Additional information on socioeconomic status is obtained by linking the zip codes and street addresses of the patients with their respective census tract blocks.

Initially, data were only obtained for infants and children up to six years of age, but now VSD incorporates information on older children, adolescents and adults. To maintain patient confidentiality, participants have unique identification numbers that can be used to link data on their medical services within the HMO. Each site sends its encoded data to the CDC for merging and analysis. Routine data quality checks for each of the databases are conducted periodically using a random 2% sample of the study population to review the automated vaccination and diagnostic data entry.

The VSD acts as a large cohort for post-licensure surveillance and is useful for accurate risk-benefit assessment by both the public and policymakers.³⁹ The project provides information to calculate incidence rates, attributable risks and background rates of illness in the absence of vaccination in a more timely and efficient manner than an ad hoc epidemiological study. Follow-up diagnosis validation is also possible for specific adverse events. However, only short-term follow-up information may be available for persons who have either just entered or have left one of the participating HMOs. The VSD population has become more geographically diverse and representative of the US population as a whole with each addition of a new HMO. However, the population remains skewed towards the middle class and few unvaccinated controls are available because of the high vaccination coverage attained within participating HMOs. Some patient characteristic information can take about one year to obtain and prepare for incorporation, making the project more costly than basic passive surveillance. Despite the large number of persons included in this surveillance system, VSD is not sufficiently large or diverse to test certain hypotheses regarding very rare events (such as the postulated relationship between the influenza vaccine and Guillain-Barré syndrome or the safety concern of vaccines containing thimerosal). Studies of adverse events with delayed onset, e.g. autism, are difficult for VSD,²⁸ and inferences that can be made about vaccine-disease causality are limited.

VSD studies have been published on such topics as vaccine coverage, disease incidence, methodology, vaccine safety and cost-effectiveness. Completed studies have informed the public about immunization issues in the US such as the recommended age to administer the second dose of measles, mumps, rubella (MMR) vaccine and revaccination with pneumococcal polysaccharide vaccine, and have increased public knowledge about proposed associations between vaccines and diseases such as autism,

diabetes and inflammatory bowel disease.³⁹⁻⁴² Both the number and the size of the VSD studies continue to grow. This monitoring system is vital in order to observe a vaccine's effect on a large population and to maintain public confidence in vaccines.³⁹

(2) Clinical Immunization Safety Assessment (CISA) Centers

The Clinical Immunization Safety Assessment (CISA) network, funded in October of 2001, is comprised of academic centers with clinical expertise in adverse events following immunization. In partnership with the Centers for Disease Control and Prevention (CDC), the network seeks to improve the scientific understanding of vaccine safety at the individual "patient" level. The purpose of CISA centers is to serve as an intermediate step between passive reporting of individual cases of adverse events with no or minimal follow-up and more rigorous vaccine safety epidemiological investigations.

Once fully established, CISA center staff will systematically evaluate cases of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS) or referred to them by health care providers. Selected cases will undergo enhanced follow up and targeted clinical evaluation to better understand the mechanism(s) and risk factors for their particular adverse event. The results of these evaluations will be used to develop clinical evaluation protocols or patient management guidelines that can be used by all health care providers.²⁸ The first group of CISA centers was funded in October 2001 and includes Johns Hopkins University partnering with specialists at the University of Maryland, in Baltimore; Northern California Kaiser with collaborators at Stanford University in San Francisco, California; Vanderbilt University in Nashville, Tennessee; Boston University Medical Center in Boston, Massachusetts; and Columbia Presbyterian Hospital in New York City, New York.

(3) Institute of Medicine (IOM)

Funded by Congress, the mission of this independent body is to advance and disseminate scientific knowledge to improve human health. The IOM provides objective, timely, authoritative information and advice to the federal government concerning health and safety policy. IOM studies have been conducted on vaccine safety, childhood immunization, immunization policy, vaccines and the military, and vaccine research and development.⁴³ In order to evaluate current immunization programs and vaccine recommendations, the National Childhood Vaccine Injury Act of 1986 (see Vaccine Injury Compensation Program below) established a committee of the IOM to comprehensively review the medical literature on vaccine-related adverse events.⁷

In 1991 and 1993, two reports from this committee showed that inadequate or no data existed to either accept or reject 50 (66%) of the 76 potential vaccine adverse events that were evaluated. The study stated that "many gaps" exist in both current knowledge and research capacity. These gaps included inadequate understanding of the relevant biological mechanisms, insufficient/inconsistent information from case reports, inadequate size or follow-up of many epidemiologic studies, limited surveillance to assess causation and few experimental studies performed to assess the causes of adverse events.²⁹

Recently, the CDC and the National Institutes of Health (NIH) commissioned the IOM to establish an Immunization Safety Review Committee, a body of independent experts charged with reviewing hypotheses regarding vaccine safety. This Committee will meet three times each year over the course of its three-year study period (2001-2004). Each meeting will focus on specific hypothesized concerns about vaccine safety. A report assessing biologic plausibility and identifying competing hypotheses and available scientific evidence is to be issued following each meeting. When appropriate, the committee will make specific recommendations to policy-makers.⁴⁴

The Committee held its first meeting in January, 2001 and has since evaluated several vaccine safety issues. All issues evaluated by this committee have been addressed in the *Vaccine Safety Issues* section. Other Committee information, including its schedule, is available through the IOM Immunization Safety Review Committee Web site (see Web Resources).

Vaccine Injury Compensation Program (VICP)

Established by Congress under the 1986 National Childhood Vaccine Injury Act, this program provides compensation to children who have been injured from a vaccine administered as part of the routine childhood immunization schedule. Funding for VICP comes from excise taxes imposed on vaccine manufacturers. Prior to this program, drug manufacturers and health care providers paid millions of dollars to the families of children allegedly injured by adverse events attributed to childhood immunizations. Because of escalating costs associated with litigation and settlements, the cost of immunizations to providers increased dramatically, and some producers withdrew from the market to reduce liability costs. To help solve this problem, Congress established the VICP no-fault compensation system that went into effect on October 1, 1988.

In order to receive compensation from this program, persons must file a claim against the Secretary of the US Department of Health and Human Services (DHHS) within three years of injury or two years of death. Persons injured before the effective

date of the Act may pursue compensation through state law or through this federal program. Persons filing claims to VICP may not sue either the manufacturer or anyone involved with vaccine administration until the claim against DHHS has been resolved. Claimants have 60 days to accept—or reject—a judgement or award. The decision is irrevocable. If claimants accept compensation under the Act, they will not be able to pursue further compensation. However, claimants who reject a judgement can bring civil action for damages against the manufacturer of the vaccine, the person who administered the vaccine, or both; the findings of the VICP are not admissible in the civil action.

This federal program qualifies more vaccine-injured children for compensation than would have been possible under the former tort system. State civil action requires that plaintiffs show both that the wrong actually caused the injury and that the party against whom they are seeking compensation did something wrong. More vaccine-injured children qualify for compensation under VICP because claimants must only show that they were injured by the vaccine to succeed in their claim against DHHS. Injury criteria acceptable for compensation are detailed on the Vaccine Injury Table (see Web Resources). Children whose injuries do not appear in the Vaccine Injury Table may also recover damages under the Act, but only if they can prove that the immunization actually caused their injuries. The less complex set of requirements is a benefit for claimants not only because it makes it much more likely that they will qualify for compensation but also because it streamlines the proceedings, requiring less legal involvement and permitting more rapid compensation.

Claimants are entitled to damages limited to the actual costs of care for treatment and rehabilitation not covered by public or private insurance. Monetary caps limit damages for pain and suffering and for wrongful death to \$250,000 each. Finally, certain types of damages, including punitive damages and so-called derivative claims by family members for loss of companionship, are not permitted under the Act. Claimants may recover attorneys' fees under the Act even when they are not awarded compensation so long as their claim was "brought in good faith and there was a reasonable basis for the claim."^{45,46}

REFERENCES:

1. Chen R, Rastogi S, Mullen J, et al. The vaccine adverse event reporting system (VAERS). *Vaccine* 1994;12(6):542-50.
2. Macartney KK and Offit PA. How vaccine safety is monitored before and after licensure. *Pediatric Annals* 2001;30(7):392-9.
3. Parkman P, Hardegree M. Regulation and testing of vaccines. In: *Vaccines*, 3rd ed. Plotkin S, Orenstein W, editors. Philadelphia: WB Saunders Company; 1999.
4. Pharmaceutical Research and Manufacturers of America. *Safety first, last and foremost*. Washington, DC; 1999.
5. Davenport L. Regulatory considerations in vaccine design. In: *Vaccine design: The subunit and adjuvant approach*. Powell M, Newman M, editors. New York: Plenum Press; 1995.
6. Macartney KK, Offit PA. How vaccine safety is monitored before and after licensure. *Pediatric Annals* 2001;30(7):392-9.
7. National Network for Immunization Information. *Communicating with patients about immunization*. Nashville, TN: National Network for Immunization Information; 2000.
8. Halsey N. Lecture—"Process for Developing AAP Guidelines". Baltimore, MD; 1999.
9. Centers for Disease Control and Prevention. <http://www.cdc.gov/nip/acip/default.htm>; August 1, 2002.
10. Schwartz B, Orenstein WA. Vaccination policies and programs: the federal government's role in making the system work. *Primary Care* 2001;28(4):697-711
11. Department of Health and Human Services. *Charter, National Vaccine Advisory Committee*. Atlanta, GA: Centers for Disease Control and Prevention; 1999.
12. American Academy of Pediatrics. <http://www.aap.org>; August 1, 2002.
13. American Academy of Family Physicians. <http://www.aafp.org>; August 1, 2002.
14. Orenstein W, Hinman A. The immunization system in the United States: The role of school immunization laws. *Vaccine* 1999;17(suppl 3):S19-S24.

15. Centers for Disease Control and Prevention. Measles - United States. *Morbidity and Mortality Weekly Report* 1977;26:11-109.
16. Middaugh J, Zyla L. Enforcement of school immunization law in Alaska. *Journal of the American Medical Association* 1978;239:2128-30.
17. Orenstein W, Hinman A, Williams W. The impact of legislation on immunization in the United States. Paper presented at: Proceedings of the Second National Immunization Conference, Public Health Association of Australia; May 27-29, 1992; Canberra, Australia.
18. Edwards K. State mandates and childhood immunization. *Journal of the American Medical Association* 2000;284(24).
19. Schwartz B, Orenstein WA. Vaccination policies and programs: The federal government's role in making the system work. *Primary Care* 2001;28(4):697-711.
20. Horne PR, Saarlans KN, Hinman AR. Update on immunization registries. *American Journal of Preventive Medicine* 2001;20(2):174.
21. Horne PR, Saarlans KN, Hinman AR. Costs of immunization registries: Experience from the All Kids Count II projects. *American Journal of Preventive Medicine* 2000;19(2):94-8.
22. The National Childhood Vaccine Injury Act of 1986, at Section 2125 of the Public Health Service Act as codified at 42 USC. 300 aa-(Suppl. 1987).
23. Vaccine Adverse Event Reporting System: Introduction. <http://www.vaers.org>; August 1, 2002.
24. Miller E, Waight P, Farrington P. Safety assessment post-licensure. In: *Developments of biological standardization*. Plotkin S, Brown F, Haoraud F, editors. New York: Karger; 1998. p. 235-43.
25. Chen R, Rastogi S, Mullen J. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12(6):542-50.
26. Singleton J, Lloyd J, Mootrey G, et al. An overview of the Vaccine Adverse Event Reporting System (VAERS) as a surveillance system. *Vaccine* 1999;17:2908-17.
27. Macartney KK and Offit PA. How vaccine safety is monitored before and after licensure. *Pediatric Annals* 2001;30(7):392-9.
28. Chen R. "Lecture—Current(+future) vaccine safety data sources." Washington, DC: Institute of Medicine;2001.
29. Stratton K, Johnston R. *Adverse events associated with childhood vaccines*. Washington, DC: National Academy Press;1994.
30. Niu M, Davis D, Ellenberg S. Recombinant hepatitis B vaccination of neonates and infants: Emerging safety data from the Vaccine Adverse Events Reporting System (VAERS). *Pediatric Infectious Disease Journal* 1996;15:771-6.
31. Niu M, Salive M, Krueger C, Ellenberg S. Two-year review of hepatitis A vaccine safety: Data from the Vaccine Adverse Event Reporting System (VAERS). *Clinical Infectious Diseases* 1998;26:1475-6.
32. Wise R. Safety surveillance for varicella virus vaccine [abstract]. Paper presented at the 31st National Immunization Conference, 1997; Detroit, Michigan.
33. Rosenthal S, Chen C, Hadler S. The safety of acellular pertussis vaccine vs. whole-cell pertussis vaccine. A post-marketing assessment. *Archives of Pediatric and Adolescent Medicine* 1996;150:457-60.
34. Wattigney W, Terracian G, Chen R. Enhanced surveillance of inactivated poliovirus vaccine in infants: The Vaccine Adverse Events Reporting System [Abstract]. Paper presented at the 32nd National Immunization Conference, 1998; Atlanta, GA.
35. Durry E, Haber P, Rhodes P, et al. Planning for retrospective study of a possible association between Guillain-Barré syndrome and 1993-94 influenza vaccination. *Pharmacoepidemiology Drug Safety* 1995;4:S41.
36. Centers for Disease Control and Prevention. Intussusception among recipients of rotavirus vaccine - United States, 1998-1999. *Morbidity and Mortality Weekly Report* 1999;48:577-81.
37. Lasky T, Terracciano G, Magder L, et al. The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *New England Journal of Medicine* 1998;339(25):1797-801.
38. Murphy T, Gargiullo P, Massoudi M, et al. Intussusception among infants given an oral rotavirus vaccine. *New England Journal of Medicine* 2001;344(8):564-72.
39. Chen R, DeStefano F, Davis R, et al. The Vaccine Safety Datalink: Immunization research in health maintenance organizations in the USA. *Bulletin of the World Health Organization* 2000;78(2):186-94.
40. Jackson L, Benson P, Sneller V, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. *Journal of the American Medical Association* 1999;281(3):243-8.
41. Davis R, Marcuse E, Black S, et al. MMR2 at 4-5 years and 10-11 years of age. A comparison of adverse event rates in Vaccine Safety Datalink (VSD) Projects. *Pediatrics* 1997;100:767-71.
42. Davis R, Kramarz P, Bohlke K, et al. Measles-mumps-rubella and other measles-containing vaccines do not increase the risk for inflammatory bowel disease. *Archives of Pediatric and Adolescent Medicine* 2001;155(3):354-9.
43. Institute of Medicine. <http://www.iom.edu>; August 1, 2002.
44. Institute of Medicine Immunization Safety Review Committee. <http://www.iom.edu/imsafety>; August 1, 2002.
45. Brink E, Hinman A. The Vaccine Injury Compensation Act: The new law and you. *Contemporary Pediatrics* 1989;6:28-42.
46. Bureau of Health Professionals. Background information on VICP. <http://bhpr.hrsa.gov/vicp/abdvic.htm>; August 1, 2002.