

# A COMPREHENSIVE REVIEW OF FEDERAL VACCINE SAFETY PROGRAMS AND PUBLIC HEALTH ACTIVITIES

December 2008



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## **Acknowledgements**

This report is the result of discussions held with the Inter-Agency Vaccine Group, coordinated by the National Vaccine Program Office, as well as individuals from the Departments of Defense and Veterans Affairs. The following individuals are acknowledged for their contributions.

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## Executive Summary

The evaluation of safety for vaccines is conducted through a network of diverse, yet integrated activities that cuts across Federal agency responsibilities and includes the private sector and academic investigators. This document describes the United States vaccine safety system and articulates the roles and responsibilities of various agencies and their activities in evaluating vaccine safety. The development, licensure and widespread use of a vaccine involves activities and programs from a broad range of groups, including State health departments, academia, industry, healthcare providers, professional organizations, third party payers, managed care organizations, philanthropic and service organizations, and agencies within the Department of Health and Human Services (HHS), including the National Institutes of Health (NIH), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and the National Vaccine Injury Compensation Program (VICP) in the Health Resources and Services Administration (HRSA). The Department of Veterans Affairs (VA), the Department of Defense (DoD), and international organizations such as the World Health Organization (WHO) also contribute to knowledge about vaccines and their widespread use. Ensuring vaccines are as safe as possible is the goal of these collective endeavors. Safety assessment is a continuous process. As new information becomes available about vaccine safety and efficacy, changes are made in manufacturing and/or recommendations for use. Additionally, at various points in the process, the benefits and risks of a vaccine may change as a result of new knowledge and changes in disease risk. This document reviews the Federal immunization safety system and provides examples throughout to illustrate the types of vaccine safety activities that are conducted. In addition to Federal vaccine safety activities, contribution to vaccine safety by other groups is briefly discussed.

## Background

The safety expected of vaccines that are routinely administered is different from therapeutic medical products. Vaccines are given to healthy individuals before they contract the disease that the vaccine targets. Many vaccines are administered to large populations such as infants and children, whereas few drugs are recommended to such large sectors of the population. Additionally, many pediatric vaccines are required by State laws for school entrance.

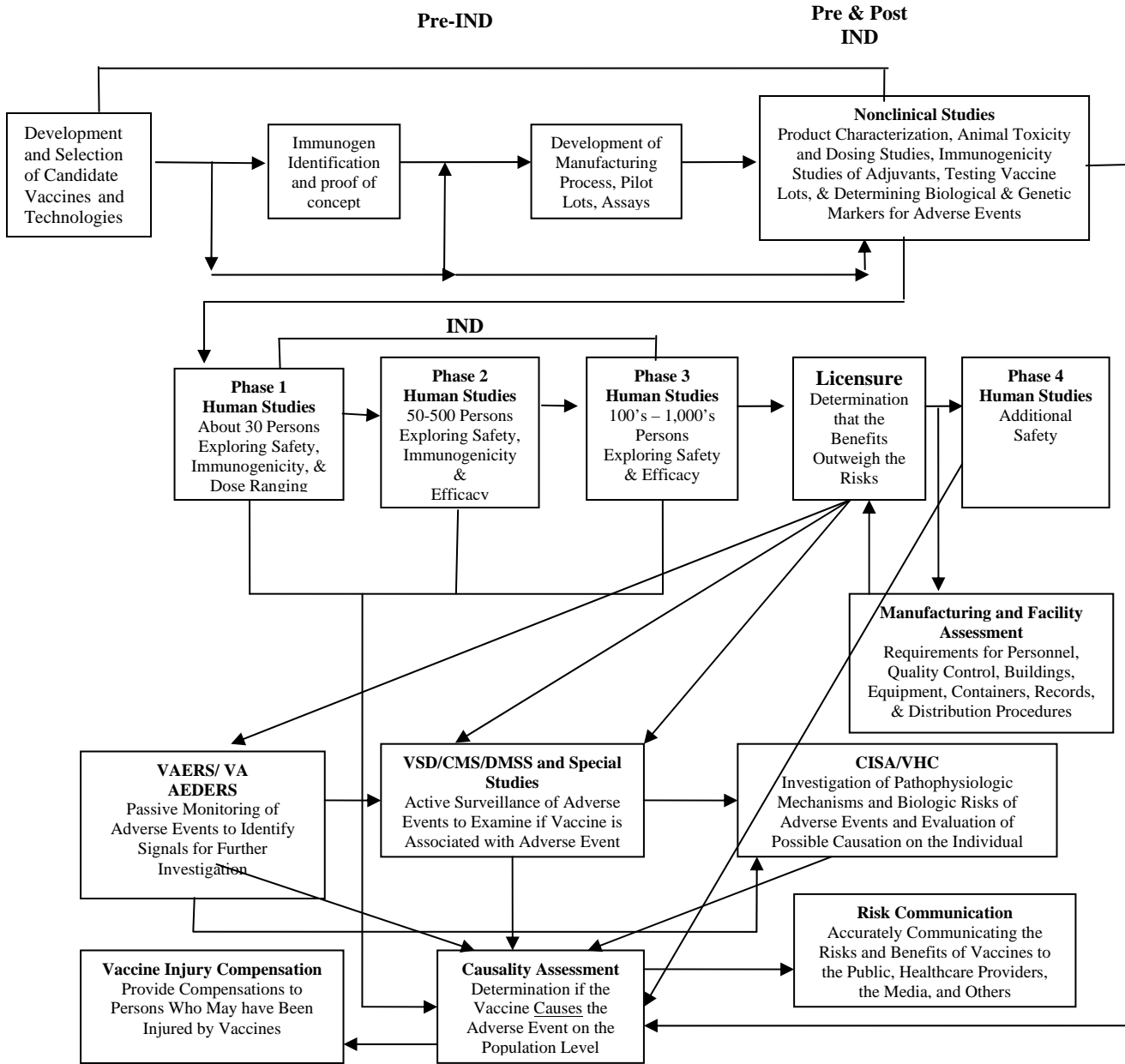
All medical products, including vaccines, have risks. Therefore, for a vaccine to be viewed as safe, its benefits must exceed its risks. The Code of Federal Regulations defines safety as “relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into considerations the character of the product in relation to the condition of the recipient at the time”.<sup>1</sup> The benefits of vaccines are viewed in terms of the vaccine effectiveness in preventing disease and, importantly, the incidence, associated morbidity and mortality, and treatment options of the disease. Adverse events following immunization may be temporally associated with vaccination (i.e., an adverse event occurs after receipt of the vaccine) but may or may not be caused by the vaccine. When an adverse event is caused by the vaccine, it is categorized as a vaccine adverse reaction. Vaccine adverse reactions are defined as minor, such as a sore arm or low grade fever (which may be fairly common), or can be more severe such as anaphylaxis (which is extremely rare, for example estimated to be caused by measles-mumps-rubella (MMR) vaccine at a rate of 1/20,000 to 1/1,000,000 doses distributed)<sup>2</sup>. Vaccine adverse reactions are dichotomized as local (e.g., sore arm, swelling at site of injection) or systemic (e.g., fever, irritability).

The value of a vaccine is also dependent on the disease circumstances in which it is provided.<sup>3</sup> An example of a changing risk/benefit calculation based on time can be seen with use of smallpox vaccines. Smallpox was a very serious disease caused by the variola virus and spread largely by respiratory transmission. As recently as the last century, approximately 300 million people died of smallpox. Smallpox vaccines were considered safe when smallpox was circulating in the United States; however, they caused several serious vaccine adverse reactions including eczema vaccinatum, encephalitis, and progressive debilitating infections in persons with immunodeficiency disorders. When smallpox was prevalent in the United States, the benefits of the vaccine clearly outweighed the risks. Nonetheless, many persons were concerned about the

safety of the smallpox vaccine and the perceived risks of the vaccines became most prominent as the disease was effectively controlled through vaccination. After elimination of smallpox in the United States and before global eradication of smallpox, the risks of the vaccine were deemed to be greater than the benefit (the prevention of a potential reintroduction of smallpox in the United States), and consequently, the United States stopped routine smallpox vaccination in 1972, five years before smallpox was eradicated.

The development, licensure, and use of vaccines require many steps. It starts with the development and selection of candidate vaccines and technologies, followed by development of manufacturing processes and controls and nonclinical trials, and later clinical studies, licensure, commercial production and distribution, recommendations for use by medical practice bodies, informing of the public, and ultimately, some level of vaccine coverage among the target population. Safety is an important consideration throughout all of these steps. As a vaccine is increasingly used in the general population, additional experience and information is gained about a vaccine's safety profile, considering issues of safety, immunogenicity and effectiveness including impact on carriage, transmission and herd immunity. In addition, over time, many vaccines can have an impact on the epidemiology of the diseases that they were designed to control, thus potentially affecting the risks to benefits ratio. This may lead to a change in recommendations for the use of the vaccine. See **Figure 1** for a visual depiction of the national vaccine safety system throughout the stages of vaccine development, licensure, and use.

There have been considerable advances in vaccine technology over of the past several decades that have led to opportunities to improve the safety of vaccines. Advances in vaccine technology and manufacturing process controls, such as the use of cell culture systems and starting materials that are screened and well characterized, coupled with the numerous advances in manufacturing technology (e.g., barrier isolator systems and sterile connecting devices which minimize potential contamination during the manufacturing process) have substantially improved vaccine safety during production.



**IND** – Investigational New Drug; **VAERS** – Vaccine Adverse Event Reporting System; **VA AEDERS** – Veterans Affairs Adverse Event Reporting System; **VSD** – Vaccine Safety Datalink; **CMS** – Centers for Medicare & Medicaid Services; **DMSS** – Defense Medical Surveillance System; **CISA** – Clinical Immunization Safety Assessment Network; **VHC** – Vaccine Health Centers Network

**Note:** There are additional relationships that sometimes occur between activities that are not connected in this figure. Additionally, there are sometimes related activities not discussed. For example, causality assessment can, at times, lead to identifying risk factors to mitigate risk or the development of a new vaccine formulation.

**Figure 1: Federal Vaccine Safety Throughout the Product Lifecycle**



New technologies have fostered the development of new vaccines with improved safety profiles. For example, the whole-cell pertussis vaccine that was prepared from suspensions of inactivated *Bordetella pertussis* bacterial cells was replaced by acellular pertussis vaccines that contain purified antigens of *Bordetella pertussis* and cause fewer vaccine adverse reactions. See **Table 1** for discussion of the development of acellular pertussis vaccines.

As new vaccine technologies became available, hepatitis B virus vaccine derived from the plasma of infected individuals was replaced by recombinant hepatitis B vaccines, which were licensed in 1986 and 1989. Any vaccine ingredient that is of human or animal origin has the potential of introducing adventitious agents (e.g., unwanted or unintended viruses, bacteria, or prions). While the plasma-derived vaccine was not shown to transmit any type of disease, this new recombinant vaccine technology eliminated any theoretical concerns. The recombinant hepatitis B vaccines are produced by inserting the gene for hepatitis B surface antigen into common baker's yeast; these yeast produce hepatitis B surface antigen, which is harvested and purified. Hepatitis B infection cannot result from use of the recombinant vaccine since no infectious viral DNA or complete viral particles are produced in the recombinant system. This revolutionary technology is being used to develop new safe and effective vaccines, such as the quadravalent HPV vaccine.

## Vaccine Development

### Nonclinical Studies

Nonclinical safety assessment plays an important part in the development of preventive vaccines. Nonclinical studies are defined as research that does not use humans, such as laboratory and animal studies. Nonclinical safety assessment consists, in part, of product characterization by adequate physical, chemical and biological methods, demonstration of control over the manufacturing process, and the development and establishment of adequate lot release tests to assess the safety, purity, and potency of the product.<sup>4</sup>

A critical aspect of nonclinical safety assessments of vaccines are toxicity studies in animal models. The objective of these studies, conducted prior to the initiation of clinical trials (which are carefully designed and controlled studies in humans), is to screen for and, if detected, to identify and characterize potential toxicities of the vaccine under the same parameters of the proposed phase 1 clinical trial to support moving forward with the proposed clinical

**Table 1: Development of Acellular Pertussis Vaccines**

- Pertussis was a serious and common childhood respiratory disease prior to introduction of whole-cell pertussis vaccines, combined with diphtheria and tetanus toxoids (DTP) in the 1940's in the United States.
- Pertussis rates and deaths fell steadily following the introduction of whole-cell pertussis vaccines in the United States, the United Kingdom, and other developed countries.
- Whole-cell pertussis vaccines, prepared from suspensions of killed *Bordetella pertussis* organisms, were associated with commonly occurring mild adverse reactions and with rare but serious adverse reactions such as acute encephalopathy.
- Because of concerns about the safety of whole-cell pertussis vaccines in the United Kingdom, Japan, Sweden and other developed countries, immunization rates plummeted and rates of pertussis rose dramatically.
- In the United States, the number of lawsuits against whole-cell pertussis vaccine manufacturers for alleged vaccine injury rose 80-fold, threatening the vaccine supply as some manufacturers withdrew from the market.
- The National Childhood Vaccine Injury Act of 1986 established a process to provide compensation for vaccine-associated injuries following universally administered vaccines and some liability protection for vaccine manufacturers, and the success of this program led to an increase in interest by vaccine manufacturers in childhood vaccines.
- Development of a safe, effective pertussis vaccine was deemed to be a national priority by the United States Public Health Service (PHS), and PHS Agencies moved together to accelerate development and evaluation of acellular pertussis vaccines comprised of purified antigens of *B. pertussis* which would be as effective as whole-cell vaccines but which would cause fewer adverse reactions.
- A high-profile national research and development program produced several candidate acellular pertussis vaccines which were evaluated extensively in head-to-head clinical trials. The National Institutes of Health sponsored the trials in their Vaccine and Treatment Evaluation Units, and the National Vaccine Program Office, the Food and Drug Administration and the Centers for Disease Control and Prevention played active roles in the PHS-wide effort. The National Institutes of Health sponsored trials that evaluated the safety and immunogenicity of 13 different acellular pertussis vaccines (combined with diphtheria and tetanus toxoids, as DTaP).
- Four candidate DTaP vaccines, which differed in formulation, were selected for evaluation in safety and efficacy field trials in Sweden and Italy, two countries that did not include pertussis vaccine in their national childhood immunization programs at that time. The Sweden and Italy trials evaluated the efficacy of the vaccines in preventing culture-proven pertussis disease.
- Two of the candidate DTaP vaccines evaluated in the Swedish and Italian trials, as well as other DTaP vaccines evaluated in other clinical trials, are included in many national childhood immunization programs. Today, acellular pertussis vaccines are considered the gold standard with regard to safety and efficacy of pertussis vaccination in the United States, Canada, Australia, and many European countries. Acellular pertussis vaccines cause far fewer adverse reactions compared to whole-cell pertussis vaccines.

investigation. Parameters to be considered in designing animal toxicology studies include the availability of relevant animal models, the timing, dose, route, and technique of vaccine administration, and the choice of study endpoints. Potential toxic effects of the product are evaluated with regard to target organs, dose, route(s) of exposure, duration and frequency of exposure, and potential reversibility of observed toxic effects. It is important to evaluate very broad measures because most toxicities are not predictable. If nonclinical studies raise concern over the safety of product use in humans, product development is reconsidered.

In addition to conducting such toxicity assessments prior to the initiation of clinical trials, it may be necessary to conduct nonclinical toxicity studies in parallel with clinical product testing. Examples of when additional safety assessments may be necessary include changes in the manufacturing process, product formulation, or route of administration, addition of novel adjuvants, or to further evaluate potential safety concerns that may have arisen from the initial phase 1 and 2 clinical trials. Toxicity assessments for vaccines can be conducted either as dedicated, stand alone toxicity studies or as combination safety/immunogenicity studies with toxicity endpoints incorporated into the design of the study.

If no toxicological data exist for a novel adjuvant, toxicity studies are usually conducted with the adjuvant alone as well as with the antigen/adjuvant formulation to ensure safety of the adjuvant irrespective of the antigen. Adjuvants are immune stimulating ingredients intended to improve the immune response. Use of an adjuvant in a vaccine minimizes the number of doses needed to provide protection. If a vaccine is formulated with an adjuvant, the effect of the adjuvant should be demonstrated in nonclinical studies. The NIH's Vaccine Adjuvant Discovery Program has a goal of discovering compounds that trigger activation of vaccine immune responses via innate immune receptors, providing a pipeline of novel vaccine adjuvant candidates. Understanding the molecular basis of immune activation stimulated by these compounds provides insight into pathways to attenuate or eliminate unneeded inflammatory responses to the adjuvants while retaining requisite immune-stimulatory activity.

Special nonclinical safety studies may be needed to evaluate the safety of a vaccine in specific target populations. For example, if the target population for a preventive vaccine product includes pregnant women or females of reproductive age, toxicity studies to assess potential adverse effects of the product on fetal developmental are performed in animals.<sup>5</sup>

Nonclinical safety assessments in animal models are valuable tools to help determine a safe dose, schedule, and route of administration and to identify potential or unknown toxicities. However, currently available animal models are limited in terms of their ability to detect rare toxicities or specific toxicities that may occur in a human subpopulation. To improve on this situation, the FDA is working with manufacturers to develop better animal models and assays to measure activity and potential drug-induced toxicity at an early stage in product development.<sup>6</sup>

For a new vaccine in which there has not been experience in humans, the dosage that is used in humans for the first time is carefully considered so that study participants are not exposed to any more of the new vaccine than necessary. When viable animal models are available, the starting doses in humans are supported by findings from animal studies. Toxicities identified in nonclinical trials will inform study designs and help guide safety assessments in clinical trials.

### **The Investigational New Drug (IND) Application**

Once a sponsor (the organization or manufacturer or individual developing the vaccine) has collected adequate nonclinical data for a new vaccine to warrant clinical studies in humans (clinical trials), an IND application is submitted to the FDA. An IND is required for clinical studies of a new vaccine as well as a vaccine that is not licensed in the United States, even though the vaccine may already be used in other countries.

The IND application must contain information about the vaccine; the method of manufacturing; quality control testing information; information about the planned study for both investigators (the scientific experts responsible for the study at their respective study locations) and potential study subjects; toxicology data; and clinical protocols (or plans) for each human study.

Furthermore, the investigators must provide a statement of their qualifications and experience. Additional information about the planned study or candidate vaccine can be requested by the FDA as needed.

Upon receipt of a completed IND application, the FDA has 30 days to determine whether the study subjects will be exposed to unreasonable and significant risks, in which case the study is not allowed to be initiated. The FDA also must determine whether the IND contains all the information required by law. FDA review includes evaluation of “stopping rules” in studies, which are triggered if serious adverse events occur at a level previously designated as unacceptable. After this 30-day review period, the clinical trial may proceed; however, the FDA

has the option to stop any study at any time if safety concerns arise. To ensure continued safeguards, the sponsor is required, during the course of the trials, to submit annual reports and to notify the FDA of any serious or unexpected adverse events within 15 days. The FDA carefully monitors these reports to ensure product safety.

## Clinical Trials

Prior to beginning clinical trials, the sponsor must obtain Institutional Review Board (IRB) approval to ensure that all appropriate safeguards for human subject protection are in place. An IRB contains at least five members with varying backgrounds who perform a complete review of research activities conducted by the institution.

The IRB must determine that all of the following requirements are satisfied in order for a study to be approved: (1) risks to subjects are minimized; (2) risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result; (3) selection of subjects is equitable; (4) informed consent (ensuring participants understand the potential risks, benefits, rights, and responsibilities) will be sought from each prospective subject or the subject's legally authorized representative; (5) informed consent will be appropriately documented; (6) when appropriate, the research plan makes adequate provision for monitoring the data collected to protect the safety of subjects; and (7) when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. There are often additional responsibilities for children and vulnerable populations, given that many vaccines are for children and the elderly.

The IRB must conduct continuing review of the studies. The investigator is required to report changes in research activities and any unanticipated problems to the IRB. Every investigator conducting human subjects research is responsible for ensuring the safety and rights of participants in studies.

Clinical trials often have a Data Safety Monitoring Board (DSMB) of external experts to review study data, and they are empowered to stop a study that appears to pose unacceptable risks to participants or if the studies show such a benefit that it would be unethical to not provide the treatment to those in the control group. The primary purpose of a DSMB is to provide independent assessment regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. An

independent DSMB includes members who are completely unaffiliated with the study investigators and have no financial, scientific, or other conflicts of interest with the study. Current or past collaborators or associates of study investigators are not eligible to serve on these boards. DSMBs typically include experts in the fields of relevant clinical medicine, clinical trial methodology, and biostatistics. The initial responsibility of the DSMB is to approve the clinical trial to begin. After this approval, and at periodic intervals during the course of the trial, the Board's responsibilities, typically, are to (1) review the research protocol, informed consent documents, and plans for data and safety monitoring; (2) periodically evaluate the progress of the trial, including assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that can affect study outcome; (3) consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial; (4) review clinical center performance, make recommendations, and assist in the resolution of problems reported by the study investigator; (5) protect the safety of the study participants; (6) report on the safety and progress of the trial; (7) make recommendations to the funding agency (if applicable), the study investigator, and at times, to the FDA concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study; (8) if appropriate, conduct interim analysis of efficacy and safety in accordance with stopping rules that are clearly defined in advance of data analysis and have the approval of the DSMB; and (9) ensure the confidentiality of the trial data and the results of monitoring. This external committee review provides another layer to ensure study participant safety.

Clinical trials are categorized as phases 1 through 4 (See **Table 2**). All phases of the testing under INDs are regulated by the FDA. Clinical trials conducted outside of the United States do not require an IND; however, sponsors usually have these studies under an IND if they plan to pursue United States licensure of their product. If the proposed clinical study is the first evaluation of a vaccine candidate in humans, the number of subjects to be studied is limited and each subject is carefully monitored. These studies are usually conducted with healthy adult volunteers.

**Table 2: Four Phases of Vaccine Clinical Trials**

**Phase 1** trials involve small numbers of healthy subjects or patients (e.g., up to 30). These studies are used to determine whether the product causes vaccine adverse reactions with increasing doses and, if possible, to gain early evidence of efficacy, such as immunogenicity.

**Phase 2** trials utilize controls (comparators, such as placebo) to help discern a true vaccine response and larger numbers of subjects (e.g., 50–500). They are designed to further assess product safety and short term vaccine adverse reactions and to obtain preliminary information on dosing and the effect of dose on the immune response.

**Phase 3** trials use large numbers of subjects (hundreds to thousands to tens of thousands) to assess efficacy and safety. These data are critical in the evaluation the overall benefit-risk relationship of the product, gather information to be incorporated into the package insert (called physician labeling), and support licensure. This phase may also be used to collect data concerning lot consistency and the acceptability of manufacturing scale-up operations.

**LICENSURE**

**Phase 4** studies are conducted after a vaccine is licensed. These studies delineate additional information about the vaccine's risks, benefits, and optimal use.

Dosages are often explored in phase 1, with vaccination of small cohorts of subjects at lower dose levels evaluated carefully before increasing the dose. In many phase 1 studies, clinical laboratory assessments (e.g., blood counts, liver and kidney function tests, cardiac muscle isoenzyme) are made after vaccine dosing to evaluate vital organs for vaccine adverse reactions that may not be clinically overt. Phase 1 studies are frequently conducted open label (i.e., with every person having full knowledge of the treatment assigned). While only common vaccine adverse reactions occurring at a rate of approximately 10 percent can be detected in such small studies, enrollment is limited to avoid exposure of larger number of subjects to products about whose safety little is known.

Objectives in phase 2 studies include both evaluation of safety and a vaccine effect, usually measured by immune response. Several studies may be conducted during phase 2 studies. Phase 2 studies are usually randomized and have a comparison group (called “controls,” who receive a placebo or another vaccine). If not determined in the phase 1 study, specific studies are conducted to identify a final dose by using a variety of doses that subjects are randomized to receive. A pilot evaluation of vaccine effect on disease may be conducted, and refinement of immune response assays takes place during phase 2 studies.

In phase 2 studies, entry criteria to participate as a volunteer in a study are not as limited as in phase 1 studies, and the vaccine may be studied in the populations for which it is intended. Safety of concurrent use with other vaccines, as occurs with vaccines used in early childhood,

may also be studied. In general, phase 2 studies include up to several hundred subjects, which is usually sufficient to detect vaccine adverse reactions that occur at a rate of one percent and describe, with precision, rates of common solicited vaccine adverse reactions, such as fever or injection-site pain.

Before phase 3 studies are initiated, vaccine sponsors and the FDA will typically meet to discuss study designs and the data needed to license the new vaccine. Phase 3 studies are designed to provide the data to support the vaccine's efficacy and additional safety data that are needed to qualify for a license from FDA. Studies evaluating vaccine efficacy in preventing uncommon diseases may require many thousands of subjects to reach definitive conclusions about efficacy; these large efficacy studies also provide the bulk of a vaccine's safety database. When effectiveness is inferred from outcomes based on immune responses, additional studies dedicated to safety evaluation may be needed.

The size of the entire safety database provided to support licensure may vary greatly, depending on whether a safety signal has been identified in earlier studies, a new vaccine manufacturing process is being utilized, a new adjuvant is included in the vaccine, or other considerations. If no serious vaccine adverse reaction occurs in a safety database of typical size, a serious vaccine adverse reaction risk of approximately 0.1 percent (1 in 1000) can be ruled out with 95 percent confidence. The safety database of the recently licensed rotavirus vaccine exceeded 70,000 infants (half rotavirus vaccine recipients, half placebo recipients). A study of this size was needed to assess the rare risk of intussusception (an intestinal blockage that was identified in the first generation rotavirus vaccine). Intussusception was seen at a rare but increased rate after administration of the rotavirus vaccine that was licensed in 1998 and therefore removed from the market.

Even large clinical trials may not detect rare vaccine adverse reactions. The size of the clinical trial needed to detect vaccine adverse reactions depends upon the background rate of the adverse event and the incidence of the vaccine adverse reaction of interest. **Table 3** describes the range of sample sizes of clinical trials needed to detect adverse events depending on their frequency. Because of nearly universal use of some vaccines, even a modestly small increase in the risk of a vaccine adverse reaction can affect a large number of people. For example, if an adverse event occurs at a rate of



1 per 1,000 and the vaccine causes a true doubling in that rate, a clinical trial with 50,000 persons (which is larger than most clinical trials) would be needed to detect that increase. Such an increase could result in an additional 4,000 children experiencing the vaccine adverse reaction annually if the entire birth cohort of approximately 4 million children received the vaccine each year. Postlicensure surveillance (see below) is in place to detect vaccine adverse reactions that occur too rarely to be identified during clinical trials.

<b>Table 3: Sample Sizes Needed During Clinical Trials to Detect Increases in Rates of Rare Vaccine Adverse Reactions</b>		
<b>Rates of event (%)</b>	<b>Sample Size*</b>	<b>No. Potentially Affected Annually<sup>1</sup></b>
0.1 vs. 0.2	50,000	4,000
0.1 vs. 0.3	17,500	8,000
0.05 vs. 0.1	100,000	2,000
0.01 vs. 0.02	500,000	400
0.01 vs. 0.03	175,000	800
* Two-arm, power=80%, alpha (2 sided)=5%		
<sup>1</sup> If the entire birth cohort of approximately 4 million children received the vaccine each year.		
Adapted from Ellenberg SS, Safety considerations for new vaccine development. <i>Pharmacoepidemiol Drug Saf.</i> 2001 Aug-Sep;10(5):411-5.		

## Vaccine Licensure

A sponsor (manufacturer) must submit a biologics license application (BLA) to the FDA for licensure of a vaccine. A BLA includes sections on chemistry, manufacturing and controls, and a description of the manufacturing facility. It contains the results of clinical trials that demonstrate the product to be safe and effective, results of required testing that demonstrate manufacturing consistency, product specifications, and proposed product labeling, including the package insert. The BLA also contains information about the facility used to make the vaccine and data demonstrating that the facility meets standards to assure that the product continues to be safe, pure and potent (effective). These regulations cover the facility’s personnel, quality control, buildings, equipment, containers, records, and distribution procedures to ensure a consistent and safe product.

Prior to granting a license, the FDA performs inspections of the manufacturing sites where vaccines are produced to evaluate compliance with current Good Manufacturing Practice (cGMP) and other applicable standards. The FDA also performs a review of the manufacturer’s processes and procedures for testing the product. Product name and labeling is reviewed for promotional aspects. Toxicologists provide their assessment of the animal testing that was done, and medical epidemiologists and postmarketing safety evaluators review the sponsor’s proposal

for postmarketing surveillance and the need and focus for phase 4 safety studies. Unusual vaccine adverse reactions and imbalances in adverse events identified in the license application review, whether statistically significant or not, are noted as these may deserve special focus in postlicensure phase 4 studies. The FDA will approve an application for licensure only after concluding that the product is safe, pure and potent when used as described in labeling, which must appropriately describe the potential risks of using the product.

FDA evaluation of a vaccine for an infectious disease must consider the frequency and severity of the disease to be prevented and knowledge of vaccine efficacy coupled with its total safety profile. Decisions about whether or not to approve a license for a vaccine take into account both vaccine safety and efficacy. In making these benefit-risk determinations, the FDA may seek advice from external experts, such as from the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC), prior to approval. The VRBPAC includes a broad range of expertise in areas important for assessing the safety of vaccines. See **Table 4** for a description of VRBPAC. More information on VRBPAC can be found here:

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

<b>Table 4: Vaccines and Related Biological Products Advisory Committee</b>
<b>PURPOSE</b> – Advises the FDA Commissioner in discharging responsibilities as they relate to helping to ensure safe and effective biological products and any other product for which the FDA has regulatory responsibility.
<b>FUNCTION</b> – Reviews and evaluates data concerning the safety, effectiveness, and appropriate use of vaccines and related biological products that are intended for use in the prevention, treatment, or diagnosis of human diseases, and any other product for which the FDA has regulatory responsibility. The committee also considers the quality and relevance of FDA’s research program, which provides scientific support for the regulation of these products and makes appropriate recommendations to the Commissioner of FDA.
<b>STRUCTURE</b> – The committee consists of a core of 12 voting members including the Chair. Members and the Chair are selected by the Commissioner or designee in accordance with the law from among authorities knowledgeable in the fields of immunology, molecular biology, rDNA, virology, bacteriology, epidemiology or biostatistics, allergy, preventive medicine, infectious diseases, pediatrics, microbiology, and biochemistry. The core of voting members may include one technically qualified member who is identified with consumer interests. In addition to the voting members, the committee may also include one nonvoting member who is identified with industry interests.
<b>MEETINGS</b> – Meetings are held approximately three to five times a year at the call of the Chair with the advance approval of a Government official, who approves the agenda. A Government official is present at all meetings.  Meetings are open to the public except as determined otherwise by the Commissioner or designee. Notice of all meetings is given to the public. Meetings are conducted and records of the proceedings kept as required by applicable laws and Departmental regulations.

Vaccine manufacturers must meet cGMP standards, which assure the quality of the product. The “c” in cGMP stands for “current” and reflects the fact that manufacturing practices change over time with improvements in processes, techniques and vaccine production technology.

Compliance with current standards may require periodic modernization of facilities and manufacturing practices to assure that manufacturing standards remain current for products licensed earlier. cGMP includes manufacturing processes and standard operating procedures; manufacturing consistency; product quality control (monitoring specifications, sterility, and stability); process validation; safety and environmental aspects; data quality control and oversight; state-of-the-art technology; and inspection and certification by regulatory agencies.

## Vaccine Manufacturing

Once a vaccine is licensed, the facilities used to manufacture the vaccine are inspected by the FDA at least every 2 years. During these inspections, experienced investigators from the FDA carefully examine and evaluate the operation for compliance with FDA regulations. Because of the complex manufacturing processes for vaccines, each product lot undergoes thorough testing by the manufacturer for purity, potency, identity, and sterility. The FDA requires vaccine manufacturers to submit protocols (i.e., processes, procedures, and standards) showing the results of applicable tests, along with samples, to the FDA for lot release. The manufacturer may not distribute a lot of a licensed vaccine until the FDA releases it and the manufacturer’s own testing is in compliance with licensed specifications.

The FDA can require changes to be made to the labeling of vaccines, including the change of indications, contraindications, warnings, and adverse reactions sections of the labeling. The FDA can require a medication guide. The FDA can also approve a vaccine with a risk evaluation and mitigation strategy to reassess whether the benefits of the vaccine outweigh its risks and includes restrictions in distribution and use. The FDA may revoke a manufacturer’s biologics license if the vaccine is not safe and effective for all of its intended uses, among other conditions. The FDA may also suspend a license whenever it has reasonable grounds to believe revocation may be in order and there is a danger to health. In addition, the FDA can request a recall of a vaccine from various levels of the supply chain, including pharmacies, distributors, and packers. The FDA may also seek court-ordered injunctions against violating manufacturers and seizures of adulterated or misbranded products. In some instances, FDA may recommend criminal

prosecution and civil monetary penalties. The FDA may use one or all of these strategies to ensure maximum safety of the product.

## Monitoring the Impacts of Vaccines after Licensure

After a product has been licensed, certain labeling changes and all manufacturing changes (presenting at least a moderate risk of adverse effect on product safety, purity, or potency) must be submitted to FDA prior to distribution of any product made pursuant to that change. Upon receipt of such a submission, the FDA conducts a thorough evaluation for each change and may require additional testing or validation in order to satisfy all safety or other concerns.

The FDA may obtain agreements from the manufacturers to conduct phase 4 postlicensure studies. Phase 4 studies are designed to obtain additional information on the product's risks, benefits, and optimal use (including its use with other products) or to further assess a potential

**Table 5: Examples of Manufacturer-Sponsored Phase 4 Studies of Vaccine Safety**

- An epidemiologic, comparative study to rule out an increased relative risk of respiratory adverse events.
- Evaluation of educational activities to ascertain vaccination errors in subjects who have conditions that are labeled as contraindicated or are at increased risk of vaccine adverse event.
- Establishment of a pregnancy registry or a registry for specific adverse events of interest in order to increase understanding of the vaccine's risks and evaluate possible risk factors associated with development of the adverse event.

side effect. Phase 4 studies are usually epidemiological studies involving tens of thousands of individuals, and reports and findings of phase 4 studies are submitted to the FDA. Under the Food and Drug Administration Amendment Act of 2007, the FDA may require phase 4 studies or phase 4 clinical trials if surveillance systems are not sufficient to assess known risks

or signals of serious risk. In addition to postlicensure studies, vaccine labeling regarding safety may be required by the FDA within specified timelines. Finally, risk evaluation and mitigation strategies may be required by the FDA. See **Table 5** for examples of phase 4 vaccine safety studies.

## Vaccine Recommendations

The CDC's Advisory Committee on Immunization Practices (ACIP) makes recommendations to the Director of CDC regarding the optimal usage of a vaccine once it is licensed. In making vaccine recommendations, the ACIP weighs the risks of disease against the benefits and risks of vaccination. The Committee also considers financing, delivery, implementation and public health

practice in making its recommendations. The ACIP develops guidance on the appropriate route, dose, frequency, contraindications, and precautions for use and provides information on recognized vaccine adverse reactions. More information on the Committee, including the full set of current ACIP recommendations, is available at

<http://www.cdc.gov/vaccines/recs/acip/default.htm>. See **Table 6** for a description of the ACIP.

<b>Table 6: Advisory Committee on Immunization Practice (ACIP)</b>
<p><b>GOAL</b> – To provide advice that will lead to a reduction in the incidence of vaccine-preventable diseases in the United States, and an increase in the safe use of vaccines and related biologic products.</p>
<p><b>FUNCTION</b> – To provide advice and guidance to the Secretary, HHS, the Assistant Secretary for Health, and the Director, CDC, regarding the most appropriate selection of antigens and related agents for effective control of vaccine-preventable diseases in the civilian population. The committee provides advice for the control of diseases for which a vaccine is licensed in the United States. The guidance covers the appropriate use of the vaccine and may include recommendations for administration of immune globulin(s) and/or antimicrobial therapy shown to be effective in controlling the same disease. Guidance for the use of unlicensed vaccines may be developed if circumstances warrant.</p>
<p><b>STRUCTURE</b> – The committee consists of 15 members, including the Chair. Members and the Chair are selected by the Secretary, HHS, from authorities who are knowledgeable in the fields of immunization practices and public health, have expertise in the use of vaccines and other immunobiologic agents in clinical practice or preventive medicine, have expertise with clinical or laboratory vaccine research, or have expertise in assessment of vaccine efficacy and safety. The committee includes a person or persons knowledgeable about consumer perspectives and/or social and community aspects of immunization programs. The committee also includes eight nonvoting ex officio members representing Federal government agencies involved in vaccines.</p>
<p><b>MEETINGS</b> – Meetings are held approximately three times annually at the call of the Chair with the advance approval of a government official, who approves the agenda. A government official is present at all meetings.</p> <p>Meetings are open to the public except as determined otherwise by the Secretary, HHS, or other official to whom the authority has been delegated; notice of all meetings is given to the public.</p> <p>Meetings are conducted, and records of the proceedings kept, as required by applicable laws and Departmental regulations.</p>

Vaccine recommendations usually precede widespread use of a new vaccine in the population, but other factors (e.g., provider and public acceptance, vaccine financing) influence the pace at which uptake of a new vaccine occurs. Additional information may become known about a vaccine’s safety profile once it is more widely used and post-licensure studies are completed. Post-licensure monitoring of vaccine safety is conducted through passive and active surveillance and clinical studies.

## Vaccine Safety Surveillance

**Vaccine Adverse Events Reporting System (VAERS):** The FDA and CDC coadminister VAERS, which is a national surveillance system that accepts reports from physicians, other healthcare providers, and the public. Although this is a passive system, VAERS can provide an early warning of vaccine safety problems that may require further investigation. Under the National Childhood Vaccine Injury Act of 1986, as amended, providers of childhood vaccines are required to report to VAERS certain health outcomes related to vaccines.

Because the adverse events reported are observations from a variety of sources, a report does not necessarily mean that the vaccine caused the adverse event in question. Sorting out which adverse events are caused by a vaccine from those that occur coincidentally following a recent vaccination is critically important. The safety signals that do appear in VAERS often generate a hypothesis about the association of a vaccine and an adverse event that requires further investigation. In this way, VAERS data serve as an important stimulus for additional in-depth safety studies. The FDA and CDC have published more than 60 papers based on analyses of VAERS data, including surveillance summaries of new vaccines and focused reviews of specific health outcomes.

While the strength of VAERS is its ability to detect signals of rare events and to monitor adverse events on a lot-specific basis, there are a number of caveats that are also considered in the analysis of the data. Many of these fall under the category of reporting biases, such as under-reporting (not all events that occur are reported) or over-reporting (events not related to a vaccine or more than the true number of events are reported). In addition, the system only collects events that have occurred but is not able to consider them in the context of the number of doses given (denominator). Consequently, the data do not allow incidence or prevalence data to be generated, thus not allowing a comparison of the risk of adverse events among persons vaccinated and those who were not vaccinated. Reports submitted to VAERS may be incomplete (containing incomplete data and insufficient information to validate diagnosis). More information about VAERS can be found through this link <http://vaers.hhs.gov/default.htm>.

**Vaccine Safety Datalink (VSD):** Active surveillance of vaccine-related adverse events is accomplished through the VSD. The VSD is a large-linked database of managed care organizations (MCOs) administered by the CDC. The VSD includes eight MCOs that together

cover about 1.8 percent of the United States population under 18 years of age and 1.5 percent of the United States population 18 years of age or older. MCO records available through the VSD include vaccination or exposure data (including date of vaccination and type and lot number of vaccine), outpatient, emergency department, hospital, and laboratory data (outcome data), and demographic information that are potential confounding factors. In addition to data available in the system (e.g., the number of children who receive a particular vaccine), studies conducted through the VSD often include a review of each person's medical record in order to improve diagnostic accuracy or obtain more information that may be relevant to understanding the relationship between a vaccination and an adverse event that develops subsequently.

The VSD is an extremely powerful tool to test hypotheses regarding the associations of vaccines and health outcomes. Unlike the VAERS system, studies through the VSD are able to calculate rates of adverse events among persons who did and did not receive a particular vaccine. This allows for determination of whether an adverse event is more common among persons who received the vaccine. Active surveillance such as the VSD provides the infrastructure needed to conduct rigorously designed and focused vaccine studies including cohort, case-control, and case-series studies. The VSD can be used to detect vaccine adverse reactions that are less common than can be detected through clinical trials.

The infrastructure of the VSD allows studies to be conducted more quickly than free-standing studies. As of 2007, the VSD has been used for 85 articles in peer-reviewed journals and has over 75 ongoing studies. A bibliography of VSD studies can be found here:

[http://www.cdc.gov/vaccinesafety/vsd/vsd\\_publications.htm](http://www.cdc.gov/vaccinesafety/vsd/vsd_publications.htm). See **Table 7** for some recent studies in the VSD. Here is a link for more information about the VSD:

<http://www.cdc.gov/vaccinesafety/vsd/>.

The establishment of the VSD serves an important role in the nation's vaccine safety system by providing the infrastructure for carefully designed epidemiological studies. Yet it is important to recognize that there are limitations to what it can currently accomplish. Like any surveillance system, the VSD is a sample of the full picture of vaccination in the United States population, but it is not necessarily representative of the entire United States population as it is comprised exclusively of persons who are enrolled in MCOs. And while the population in these MCO's is very large, studying certain adverse events, especially rare adverse events that occur in only a

**Table 7: Vaccine Safety Datalink (VSD) – Recent studies**

- A cohort study found that rhesus rotavirus tetravalent vaccine was associated with an increased risk of intussusception 3 to 7 days after vaccination.<sup>7</sup>
- A case-control study of risk of type 1 diabetes following vaccination found no increased risk associated with any of the routinely recommended infant and childhood vaccines, and the timing of vaccination was not found to be associated with risk of type 1 diabetes.<sup>8</sup>
- A large case-control study of vaccination and the risk of multiple sclerosis and optic neuritis in adults found no increased risk with hepatitis B vaccine or any of the other vaccines studied.<sup>9,10</sup>
- A cohort study to quantify the risk of anaphylaxis after vaccination of infants and children found the overall risk to be about 1 case per million doses of any vaccine.<sup>11</sup>
- Monitoring the safety of influenza vaccine in children 5 to 8 years of age receiving influenza vaccine for the first time found that there were very few medically attended events, none of which were serious, significantly associated with the vaccine.<sup>12</sup>
- A series of studies of the relationship between certain vaccines and wheezing lower respiratory disease or asthma found that these vaccines were not associated with wheezing among full-term infants or with the risk of developing asthma. Inactivated influenza vaccines, specifically, were not found to cause exacerbations in children with preexisting asthma.<sup>13,14,15,16</sup>
- Studies to evaluate the safety of pneumococcal conjugate 7-valent vaccine (PCV7) in infants showed, except for erythema, no pattern of increasing local reactogenicity with subsequent doses. Studies are underway to determine the protective antibody levels in children with sickle cell disease and in children who have received the primary pneumococcal series followed by the 23-valent pneumococcal polysaccharide vaccine (PPV23).<sup>17</sup>
- A retrospective cohort study of adult PPV23 recipients, looking at medically attended injection site reactions compared the frequency of those reactions in people getting first, second, or third doses of PPV23. The study found no difference in the rate of vaccine adverse reactions with the number of doses.

segment of that population (e.g., infants or adolescents) may require several years in order to accrue an adequate sample size. Because only a few such adverse events may be expected to occur every year in this population or in any population of this size, it may be difficult to say with certainty that a particular adverse event occurs more frequently or at the same rate among those who have been vaccinated compared to those who have not.

A good example of the strengths and limitations of VSD can be seen in a study that examined a potential association between meningococcal conjugate vaccine and Guillain-Barré Syndrome (GBS). Meningococcal infection -- a form of bacterial meningitis -- is a very serious infection of the covering of the brain (meninges) that can cause severe disability and can be fatal within a day or two following the onset of symptoms. Developing a vaccine to prevent this form of meningitis



has been a priority. A first generation vaccine was developed and licensed by the FDA, but a next generation meningococcal vaccine with an enhanced immune response, a meningococcal conjugate vaccine (Menactra®) was licensed in January 2005 for use in the prevention of this disease among persons aged 11 to 55 years. By September 2005, five cases of GBS occurred following Menactra vaccination in recipients 11 to 19 years of age. At the time, 2.5 million doses of Menactra vaccine had been distributed across the United States. Based on this information, the number of cases of GBS reported postvaccination was similar to what might have been expected to occur without vaccination. However, at closer look, it was the proximity in the timing of these two events -- vaccination and the onset of GBS -- that raised concern.

Among the more than 5 million people enrolled in the 8 MCOs in the VSD, the cohort of 11- to 19-year-olds is between 870,000 and 1,000,000 individuals at any given time. This number represents the average monthly size of the 11- to 19-year-old cohort that can be studied in the VSD to examine a relationship between a vaccine and an identified adverse event in that age group. The power of the VSD is well exemplified by Menactra/GBS because although GBS has a relatively low background rate (1.3 to 1.4 per 100,000 person-years, e.g., per person per year) that makes it difficult to achieve adequate power quickly, Menactra is given to 9 cohorts of persons (11- to 19-year-olds), allowing many more persons to be included in the VSD study than would be available for a vaccine given to persons at a single age (single cohort).

However, the full cohort may not always be available to study. Despite recommendations on the use of a vaccine, the uptake of new vaccines may not be immediate. Therefore, for a newly licensed vaccine like Menactra®, it is likely that only 30 percent of those 11-19 years of age would have received the vaccine. Based upon this level of vaccine coverage in this population, it would require about 20 years to detect an incidence rate ratio of 2.0 (doubling the risk of GBS within 30 days following vaccination) and 5 years to detect an incidence rate ratio of 4.0 (quadrupling the risk of GBS within 30 days following vaccination; one-tailed hypothesis testing,  $\alpha = 0.05$ ; power = 0.80). However, doubling the risk of GBS among 11- to 19-year-olds with 30 percent vaccine coverage would result in about 38 excess cases of GBS during the 20 years it would take for the VSD to determine this level of risk and quadrupling the risk of GBS would result in about 73 excess cases of GBS during the 5 years it would take for the VSD to determine this level of risk. The manufacturer is working with FDA and CDC to study this issue in a consortium of MCOs that are not part of the VSD network to more quickly assess a

possible risk of GBS and Menactra. This study includes approximately 10 million 11- to 19-year-olds.

Recognizing the limitations of the VSD, additional studies are conducted with other data sources when the VSD is unable to address specific research questions. Typically these other studies are in areas where the vaccine has not been widely used in the VSD population, outcomes of interest are not measured in the VSD (i.e., not a part of the medical record), or the outcome is too rare to be studied in the VSD. See **Table 8** for examples of other controlled vaccine safety studies.

<b>Table 8: Other Postlicensure Controlled Safety Studies</b>
<ul style="list-style-type: none"><li>• A capture-recapture analysis of intussusception after rotavirus vaccine found that VAERS reporting completeness was 47 percent.<sup>18</sup></li><li>• Investigation of an association between influenza vaccine and GBS found an increased risk of GBS at about 1 case per million persons vaccinated.<sup>19</sup></li><li>• A case-control study found that a self-reported history of food allergy and antigelatin immunoglobulin E (IgE) were more frequent in persons who reported anaphylaxis after receipt of measles/mumps/rubella (MMR) vaccine compared with controls.<sup>20</sup></li><li>• A case-control and case-series analysis looking at the rotavirus vaccine and intussusception showed the vaccine to be associated with a 22- to 29-fold increased risk 3 to 14 days following a first dose of the vaccine. There was also an increase in the risk of intussusception after the second dose of the vaccine, but it was smaller than the risk after the first dose.<sup>21</sup></li></ul>

For example, the FDA and the Centers for Medicare & Medicaid Services (CMS) have explored the feasibility of using the CMS National Claims History File and Enrollment Database for retrospective and prospective studies. This CMS data set has the potential to be used for vaccine safety studies of the elderly (over 65 years old) who are often underrepresented in other active surveillance systems such as the VSD. Medicare insures about 35 million elderly persons.

An initial proof-of-concept study explored influenza and pneumococcal vaccines, using retrospective data, found that the Medicare data set can be an important adjunct to help to evaluate vaccine adverse events.<sup>22</sup> A follow-up study implemented a process to use Medicare data in a relatively real-time framework and to pilot test a prospective vaccine safety monitoring system for influenza vaccine as a part of pandemic preparedness. This study used Medicare raw weekly data, including claims data identifying influenza vaccination and hospital claims data and diagnostic codes, during the 2006–07 influenza season to identify serious adverse events following vaccination, with an emphasis on GBS. Comparisons were made to data from the previous two influenza seasons. This study was able to generate reports by early November and

weekly updates subsequently, confirming the value of the CMS data for relatively “real time” vaccine safety monitoring, and found that there was no elevation of GBS rates in 2006–07 relative to the previous 2 years. Ongoing studies will explore additional clinical conditions, further assess timeliness of data, and develop analytic methods for optimal comparison groups and sequential monitoring methods.

The introduction and subsequent withdrawal of recommendations for the use of RotaShield® rotavirus vaccine highlights how the United States vaccine safety system works successfully. It also illustrates the difficulties in detecting rare adverse events, the importance for communication between Federal agencies, and the need for post-licensure surveillance. See **Table 9** for the RotaShield® story.

<b>Table 9: Postlicensure Adverse Event Investigation</b>
<b>Rotavirus Vaccine (RotaShield)</b>
<ul style="list-style-type: none"> <li>• Rotavirus infects nearly every child in the United States by 5 years of age and is responsible for 5 to 10 percent of gastroenteritis episodes and 30 to 50 percent of all hospitalizations for gastroenteritis among children under 5 years of age.<sup>23,24,25,26</sup> In 1998, a Rhesus-based tetravalent rotavirus vaccine (RotaShield) was licensed and recommended for routine use. Between September 1998 and July 1999, 15 cases of intussusception (a bowel obstruction in which one segment of the bowel becomes enfolded within another segment) among infants who had received RotaShield were reported to VAERS.</li> <li>• In prelicensure studies, 5 cases of intussusception occurred among 10,054 vaccine recipients and one among 4,633 controls, a difference that was not statistically significant. Intussusception was included as a potential adverse event on the package insert and the company agreed to postlicensure safety studies to better determine the risk of intussusception following vaccination.</li> <li>• VAERS data were analyzed early in the postlicensure period. The number of reported intussusception cases receiving the RotaShield vaccine was in the expected range. Because there is underreporting to VAERS, the actual number of cases could have been higher than reported.</li> <li>• A nationwide effort was made to conduct postlicensure studies that included a case-control study, case series, and a retrospective cohort study to determine whether an association existed between the administration of RotaShield and intussusception in infants.<sup>7,27</sup> Preliminary data in July 1999 suggested an increased risk for intussusception following receipt of RotaShield. However, these data did not have adequate power to establish a statistically significant difference in incidence of intussusception among vaccinated and unvaccinated children. The consistency of findings from the several data sources nonetheless raised strong concerns. Therefore on July 16, 1999, the CDC recommended suspending administration of RotaShield.</li> <li>• By October of 1999, the ACIP had reviewed data from several sources and concluded that intussusception occurs with a significantly increased frequency for the first 1 to 2 weeks after vaccination with RotaShield (an excess risk of about 1 in 10,000). The CDC withdrew its recommendation for vaccination with RotaShield, and the manufacturer withdrew the vaccine from the market and ended production.</li> </ul>

## Case Definitions

A major challenge to vaccine safety studies involves the creation of standard case definitions for outcomes of interest so that all are consistent when comparing potential adverse outcomes following a vaccination. Often, scientific studies will define outcomes of interest differently, and as a result, it is difficult, if not impossible, to combine or compare the results of multiple studies. To address this important gap, the FDA conducted efforts to develop case definitions to aid understanding of the relationship between two reported adverse events: Hypotonic-hyproresponsive episodes after pertussis immunization<sup>28</sup> and acute encephalopathy, encephalitis, and multiple sclerosis reports to VAERS<sup>29</sup>. The approaches pioneered in these studies have been institutionalized through the Brighton Collaboration, an international effort supported by CDC to develop standard case definitions and guidelines. Case definitions are categorized by levels of evidence, including clinical trials versus postlicensure surveillance and whether the case definition applies to a developed or to a developing country.

To date, the Brighton Collaboration has published 23 case definitions. See **Table 10** for examples of case definitions and guidelines developed, or being developed, by the Brighton Collaboration. More information about the Brighton Collaboration can be found at this site: <http://www.brightoncollaboration.org/internet/en/index.html>.

<b>Table 10: Brighton Collaboration</b>
<b>Examples of Case Definitions and Guidelines Developed or Being Developed</b>
<ul style="list-style-type: none"><li>• Generic Guidelines for Surveillance Systems and Clinical Trials</li><li>• Anaphylaxis</li><li>• Encephalitis and acute disseminated encephalomyelitis</li><li>• Skin eruption (rash)</li><li>• Fatiguing illness, including chronic fatigue syndrome</li><li>• Local Reactions, including abscess, cellulitis, induration, and swelling</li><li>• Aseptic meningitis</li><li>• Sudden infant death syndrome (SIDS) including Sudden Unexpected Death</li><li>• Idiopathic Thrombocytopenia</li><li>• Vaccinia virus adverse events following immunization, including eczema vaccinatum, generalized vaccinia, inadvertent inoculation, progressive vaccinia, and robust take</li></ul>

## Clinical and Genetic Assessments of Serious Adverse Events

In 2001, CDC established a network of Clinical Immunization Safety Assessment (CISA) centers with the goal to conduct clinical research on the biological basis of vaccine adverse events and individual variation. CISA has the potential to provide in depth immunological, pathological and genetic information that, by clarifying the mechanisms that underlie a vaccine adverse event, assist clinicians in the evaluation and management of individuals at risk for vaccine adverse reactions, assist individuals in making informed immunization choices, and influence future vaccine design and development. Modeled after similar networks in Italy, Canada, and other countries, CISA is intended to investigate the pathophysiologic mechanisms and biologic risks of vaccine adverse reactions and evaluate possible causation on the individual level. CISA also has the potential to do special studies, such as identifying host risk factors (i.e., genetic risk factors) associated with vaccine adverse reactions.

CISA currently consists of six centers with vaccine safety expertise (Columbia, Johns Hopkins, Vanderbilt, and Stanford Universities, Boston Medical Center, and Northern California Kaiser Permanente). See **Table 11** for major CISA accomplishments since 2001. More information on CISA can be found here: <http://www.cdc.gov/vaccinesafety/cisa/>.

<b>Table 11: Clinical Immunization Safety Assessment (CISA) Network</b>
<b>Key Accomplishments Since 2001 and Ongoing Projects</b>
<ul style="list-style-type: none"><li>• Conducted a clinical risk assessment of new cases of GBS following meningococcal conjugate vaccination, including immune response and DNA studies.</li><li>• Conducted a case-control study of Simian Virus 40 (SV40) and non-Hodgkin lymphoma, finding that SV40 infection is not associated with increased risk of developing non-Hodgkin lymphoma.<sup>30</sup></li><li>• Conducted a clinical risk assessment of myopericarditis following smallpox vaccination, including immune responses and DNA studies.</li><li>• Evaluated new cases of viscerotropic and neurotropic illness following yellow fever vaccine.</li><li>• Developed an evidenced-based algorithm for managing individuals with vaccine hypersensitivity reactions.<sup>31</sup></li><li>• Assessed the safety of live viral vaccine administration in patients with DiGeorge Syndrome.</li><li>• Established an IRB-approved registry and repository that allows for enrollment of persons experiencing an adverse event following immunization and storage of specimens for future studies.</li><li>• Developed and evaluated an algorithm for assessing causality in the evaluation of adverse events following immunization.<sup>32</sup></li><li>• Evaluated adverse events after the fifth dose of DTaP.</li><li>• Conducted telephone surveillance to evaluate adverse events among civilian smallpox vaccine recipients.<sup>33</sup></li></ul>

The NIH has a Population Genetics Analysis Program focused on vaccines. This program focuses on the identification of associations between specific immune response gene polymorphisms and susceptibility to infection or on the quality of response to vaccination. This program studies the correlation of genetic polymorphisms with response phenotypes, such as severity of infection, or with vaccination outcome, through the analysis of expression levels and/or functions of the proteins encoded by the variant immune response genes. See **Table 12** for examples of specific projects in the Population Genetics Analysis Program that directly relate to vaccine safety. The FDA recently completed a study that did not support the hypothesis that certain genes increase the risk of arthritis after Lyme vaccination.<sup>34</sup> This was the first VAERS-based evaluation of a possible genetic risk factor ever conducted.

<b>Table 12: Population Genetics Analysis Program</b>	
<b>Examples of Vaccine Safety Activities</b>	
<ul style="list-style-type: none"> <li>• Genetic Risk for Smallpox Vaccine Related to Myocarditis (in collaboration with DoD and CDC)  <b>Research focus:</b> Identify genetic differences that increase the risk for a major adverse event associated with smallpox vaccination (myocarditis) and determine the mechanism by which these genetic differences confer risk.</li> <li>• Host Genes Conferring Risk for Specific Infections and Vaccination Responses  <b>Research focus:</b> Use the genealogic approach in Iceland to carry out genome-wide linkage scans to map and isolate host genes conferring risk for specific infections and vaccination responses.</li> <li>• Variability in Genes Predicting Antibody Responses and Adverse Reactions to Anthrax Vaccine  <b>Research focus:</b> Investigate variability in host genes predicting variation in antibody responses and adverse reactions to Anthrax Vaccine Adsorbed.</li> </ul>	

Clinical and animal studies are also conducted to improve the understanding of vaccine adverse reactions. For example, the NIH supports the Atopic Dermatitis and Vaccinia Network (ADV N), which is a consortium of academic medical centers that conduct clinical and animal research studies aimed at making smallpox vaccination safer for individuals with atopic dermatitis (AD). People with active AD, or who have outgrown AD, and the people they live with, currently are contraindicated to receiving smallpox vaccinations because of the risk of eczema vaccinatum. Eczema vaccinatum is a severe and potentially fatal skin disease caused by smallpox vaccine. It is estimated that more than 30 million individuals in the United States have AD, many of whom would be at risk for eczema vaccinatum if vaccinated or in contact with a recent vaccinee. The ADV N conducts clinical studies focused on understanding how immune responses in the skin differ among people with and without AD. ADV N animal studies have developed several mouse models of AD that are used to study the immune response to viruses. These mouse models of AD

are also used to assess the contributions of individual genes to the disease and to the risk of eczema vaccinatum. Together, these studies may lead to a greater understanding of the immune systems of AD patients and to the identification of a subset of AD patients who are predisposed to severe viral infections.

## Causality Assessment: What Causes What?

### Independent Vaccine Safety Reviews by the Institute of Medicine

Assessment of causality between vaccines and adverse events has been periodically conducted by the Institute of Medicine (IOM) of the National Academies, funded by various agencies in HHS. The IOM conducted its first report on vaccine safety in 1977 and published causality reviews in 1988, 1991, 1994, 2001, 2002, and 2004. These reviews of causality assessment included topics such as encephalopathy, infantile spasms, Guillain-Barré Syndrome, arthritis, anaphylaxis, optic neuritis, transverse myelitis, thrombocytopenia, sudden infant death syndrome (SIDS), immune system dysfunction, and autism. IOM causality assessment reviews have been conducted by a distinguished panel of experts in pertinent fields, including most recently pediatrics, neurology, immunology, internal medicine, infectious diseases, genetics, epidemiology, biostatistics, risk perception and communication, decision analysis, public health, nursing, and ethics.

IOM vaccine causality reviews consider potential biologic mechanisms connecting the vaccine or vaccine component to adverse events (including theories, experimental evidence, and clinical reports); epidemiological and clinical data; and significance assessment that includes the burden of the adverse event, burden of the vaccine-preventable disease, and salience to the public. This causality assessment, including scientific and significance assessment, ultimately led to recommendations for action in terms of policy, research, and communication. See Appendix 1 for recent issues and findings on causality assessment from the IOM. More information on the IOM Immunization Safety Review can be found here: <http://www.iom.edu/?ID=4705>.

## Laboratory and Animal Studies Postlicensure

Laboratory research plays an important role in postlicensure vaccine safety. Beyond the important role of laboratory research in nonclinical studies, laboratory research is important in vaccine safety areas such as the testing of vaccine lots and ascertainment of vaccine adverse

events that have biologic markers (i.e., vaccine-associated paralytic polio). Additionally, laboratory research has the potential to be an important part of emerging vaccine safety research, such as that determining a possible genetic involvement in vaccine adverse reactions. For example, CISA investigators collect biologic specimens of individuals who may have experienced a vaccine-associated adverse event to be used for future genetic studies.

## Risk Communication and Education

Communicating the risks and benefits of vaccines is inherently challenging. The success of vaccines in controlling, eliminating, and in one case, eradicating serious infectious diseases has resulted in public attention shifting from the risks of disease to the risks of vaccines. Thus, the value of vaccines is often overlooked, and at the same time, society has become increasingly risk averse in areas such as air and highway travel, food products, and toys.<sup>32</sup> Individual risk factors for vaccine adverse reactions, such as genetic predispositions, have not yet been elucidated in many cases. Additionally, quantifying the risks of very rare vaccine adverse reactions is difficult, and many adverse events are temporally associated with vaccines (i.e., many vaccines are administered to young children around the time that other problems become apparent). For example, the measles/mumps/rubella vaccine (MMR) is usually given to children around 12 to 15 months of age, which is around the time that signs of autistic spectrum disorder (ASD) often first appear to parents. Thus, given when the vaccine is administered and when ASD is first recognized, the two events will often be temporally related by chance alone. A temporal relationship between administration of a vaccine and recognition of an adverse event does not necessarily mean a causal relationship, a concept that may be difficult to communicate. In the case of MMR vaccine and ASD, reviews by the IOM and the American Academy of Pediatrics (AAP) have concluded that the two events (MMR and ASD) are not causally related.<sup>35,36</sup>

One tool for risk communication is the vaccine label (package insert), which includes the vaccine indication (who should get the vaccine), conditions of use (under what circumstances the vaccine should be administered), contraindications, warnings and precautions, and descriptions of the safety experience observed in the prelicensure studies.

The CDC carries out studies understand parents' knowledge of, and attitudes toward, vaccines and vaccination. Topics recently studied or currently under study include parental concerns about vaccination; the relationship between vaccine safety concerns and vaccination status; parental



knowledge and attitudes about adolescent vaccination and several recently licensed adolescent vaccines; development and evaluation of risk communication messages and immunization materials; vaccine refusal; vaccination attitudes, beliefs, and behaviors among parents of homeschooled children; comparison of vaccination attitudes, beliefs, and behaviors between adolescents and their parents; and the evaluation of a toolkit to help healthcare providers address parental concerns about vaccination when encountered in their practices. In addition, vaccine safety questions have been included in several recent studies about influenza vaccination conducted among members of the public as well as among healthcare providers. The results of these studies serve to inform the development of effective written materials for parents, including the “Parents’ Guide to Childhood Immunizations” (see below), and questions and answers on specific vaccines and vaccine safety topics that are available on the CDC’s Web site (see below), as well as educational and training materials for healthcare providers.

To routinely monitoring vaccine safety issues and concerns, the CDC carries out daily monitoring of newspaper and wire service stories related to vaccine safety. Daily blog searches are also undertaken to identify emerging issues and concerns. Monitoring of parental concerns about vaccination is also an important strategy, and the CDC has previously piloted the addition of questions about vaccine safety concerns to the National Immunization Survey, an ongoing national telephone survey of the parents of United State preschool children that measures vaccine coverage in this age group.

During 2008, the CDC will again field a module on parental questions, issues, and concerns as part of the National Immunization Survey. The module was developed with input from the Vaccine Risk Communication Subcommittee of the National Vaccine Advisory Committee (NVAC) through recommendations to the Assistant Secretary for Health and external experts from the United States and United Kingdom. Questions include parental perceptions on the value and safety of vaccinations, satisfaction with their interactions with vaccine providers, influences on parental vaccine decision-making, and identification of any vaccines the parent delayed or refused for a child along with the reasons for doing so. Repeating this module periodically will allow the CDC to monitor changes in parental attitudes about vaccination over time. Since the CDC is in the process of expanding the NIS to include the parents of adolescents, there is also an opportunity to assess vaccine questions, issues, and concerns among the parents of older children.

The CDC educates the vaccine's target population (or their parents when the target population is children), healthcare providers, and the public regarding the risks, benefits, and recommended use of a vaccine once ACIP provides practice recommendations that are accepted by the CDC. The CDC writes vaccine information statements (VIS) that are one-page (double-sided) statements briefly describing the risks and benefits of each vaccine (or combined vaccine). VIS are available in several languages and also provide information on where and how to report vaccine adverse events. More information about VIS is available online at <http://www.cdc.gov/vaccines/pubs/vis/vis-facts.htm>.

The CDC has also written, and periodically updates, a book called the "Parents' Guide to Immunizations," which provides parents with easy-to-understand information about the risks and benefits of vaccination. This color booklet introduces parents to 14 childhood diseases and the vaccines that can protect children from them. It discusses how immunity works, how vaccines help, how serious the diseases are, what will happen if the child is not vaccinated, and other related topics. Appendices include information on the immunization schedule, vaccine safety, and who to contact if your child has a vaccine adverse reaction. This publication is available online at <http://www.cdc.gov/vaccines/pubs/parents-guide/default.htm>.

Other web-based resources include a vaccine safety and adverse events web page (<http://www.cdc.gov/vaccines/vac-gen/safety/default.htm>); an overview of information resources about the vaccine preservative thimerosal ([http://www.cdc.gov/vaccinesafety/concerns/thimerosal\\_faqs\\_thimerosal.htm](http://www.cdc.gov/vaccinesafety/concerns/thimerosal_faqs_thimerosal.htm)); a summary of ongoing mechanisms for monitoring adverse events following vaccination ([http://www.cdc.gov/vaccinesafety/about\\_iso.htm](http://www.cdc.gov/vaccinesafety/about_iso.htm)); vaccine-specific and vaccine safety questions and answers for the public and providers (<http://www.cdc.gov/vaccinesafety/concerns/>); and the Immunization Practice Toolkit, a toolkit for immunization providers that includes resources on various immunization-related topics, including vaccine safety (<http://www2a.cdc.gov/nip/isd/immtoolkit/default.htm>).

Another way in which the CDC supports and promotes vaccine safety is by educating providers about proper techniques for vaccine administration and the storage and handling of vaccines, which is important for making sure that vaccines have the intended safety and effectiveness.

An example of CDC educational products, activities, and services is the textbook “Epidemiology and Prevention of Vaccine-Preventable Diseases,” known as the Pink Book, which provides physicians, nurses, nurse practitioners, physician assistants, pharmacists, and others with the most comprehensive information on vaccine-preventable diseases. The Pink Book is updated annually and available to download at <http://www.cdc.gov/vaccines/pubs/pinkbook/default.htm>. It contains chapters on vaccine safety and general vaccine recommendations, including information about how to administer vaccines; vaccine storage and handling; and screening patients for precautions and contraindications to vaccines.

A number of other CD and Web-based materials contain information on vaccine administration and vaccine storage and handling: “Immunization Works” (CD ROM); “Vaccine Storage and Handling Toolkit” (CD ROM); “Immunization Practice Toolkit” (Web-based); “Immunization: You call the Shots” (interactive Web-based self-study program); “The Immunization Encounter: Critical Issues” (archived broadcast/webcast).

In addition, the CDC has an immunization training team that conducts in-person presentations, broadcasts, and webcasts on various immunization topics, many of which include information about vaccine safety, vaccine administration, and vaccine storage and handling. Finally, CDC staff provide an e-mail-based response system (NIPINFO) to answer questions raised by providers and the general public. This response system frequently provides answers to questions regarding vaccine safety, vaccine administration, and vaccine storage and handling.

The CDC has a hotline, established in 1997, that allows healthcare providers and members of the public to call and have vaccine-specific questions answered. In the first 2 years, from 1998 to 2000, the hotline answered 246,859 calls.<sup>37</sup> Approximately one third of the calls were from healthcare providers. The most frequent questions asked included those related to new vaccines, new vaccination schedules, and vaccine safety. While the major goal of the hotline is to provide accurate and reliable information, data from the hotline can also be used to monitor changes over time in calls concerning various topics, including vaccine safety. The phone number for the hotline is (800) 232-4636 (English and Spanish).

The CDC provides information to healthcare providers about the current risks and benefits of vaccination. These communication efforts include ACIP statements, publications in the CDC’s Morbidity and Mortality Weekly Report, and articles on vaccine safety and effectiveness

published in numerous peer-reviewed journals. The CDC sponsors an annual immunization conference (the National Immunization Conference) for health professionals that is open to the public. CDC staff regularly present at scientific and clinical meetings on the emerging science of vaccines and immunizations. The CDC sponsors satellite courses for Federal, State and local public health workers on immunization topics such as vaccine safety and risk communication. These and the CDC's many other vaccine communication materials are available to all at <http://www.cdc.gov/vaccines/pubs/default.htm#vis>.

## Vaccine Injury Compensation

### National Vaccine Injury Compensation Program (VICP)

Persons who may have been injured by vaccines are provided compensation by the VICP, operated by HRSA in conjunction with the United States Department of Justice and the United States Court of Federal Claims. The VICP was established in 1988 and designed to provide financial assistance to individuals and parents who have been found to be injured by covered vaccines. The VICP is based on the premise that no medical product, including vaccines, can be entirely safe and that people inadvertently harmed by properly produced and administered vaccines should receive compensation for the medical expenses incurred. Because vaccine use is frequently mandated through State laws or school entry requirements and there is well documented societal benefit from immunization programs, the program was established in recognition of the need to compensate those who are injured by vaccines that are routinely recommended for all children.

The VICP is a Federal "no fault" system under which awards can be made to vaccine-injured people more quickly and easily than through the tort (civil) system. People who feel that they have been injured through the receipt of a covered vaccine are required to file claims with the VICP before they are allowed to bring a civil suit. This requirement provides some liability protection for vaccine manufacturers, an important component given that the VICP was developed partially in response to a large number of lawsuits in the 1980s against the relatively few vaccine manufacturers in the United States as an effort to prevent these companies from ceasing the production of vaccines.

A claim may be filed on behalf of any otherwise eligible person who has been injured or who has died after receiving a "covered" vaccine regardless of the age of the recipient. Vaccines are

“covered” if the vaccine is recommended by the CDC for routine administration in children once an excise tax has been passed by Congress.

Rules of evidence, discovery, and other legal procedures are relaxed, accelerating the compensation process. Because the program is no-fault, a petitioner need not show any negligence on the part of the manufacturer or administering health care provider. Compensation is awarded if the injury is listed on a vaccine injury table, which was developed and is revised based upon the best available science, within the specified time period or if the claimant can prove that an injury was caused by the vaccine. (See appendix 2 for the Vaccine Injury Compensation Table.) Attorney fees may be paid by the program regardless of the outcome of the claim, thus ensuring that those claiming a vaccine injury have adequate access to attorneys.

The Secretary of HHS is advised on the VICP by the Advisory Commission on Childhood Vaccines (ACCV), a Federal advisory committee that includes health professionals, attorneys, and the general public, including parents of vaccine-injured children, concerning the operation of the VICP. See **Table 13** for a summary of the ACCV. More information about VICP can be found here: <http://www.hrsa.gov/vaccinecompensation/>.

<b>Table 13: Advisory Commission on Childhood Vaccines (ACCV)</b>
<b>PURPOSE</b> – Advises and makes recommendations to the Secretary of Health and Human Services (HHS) on issues relating to the operation of the National Vaccine Injury Compensation Program (VICP).
<b>FUNCTION</b> – The nine voting members of the ACCV provide oversight of the VICP. The ACCV members recommend ways to improve the VICP, including changing the Vaccine Injury Table, proposing legislation covering new and safer childhood vaccines, gathering information about vaccine-related injuries from Federal, State, and local immunization programs, and revising Vaccine Information Statements.
<b>STRUCTURE</b> – The committee consists of nine voting members, including the Chair and four ex officio (nonvoting) members. Members are selected by the Secretary or designee. The voting members include three health professionals who have expertise in the healthcare of children, of which two are pediatricians, three members from the general public, of whom two are legal representatives of children who have suffered a vaccine-related injury or death, and three attorneys of the following composition: One specializing in vaccine cases, one representing a vaccine manufacturer, and one general attorney. The ex officio members are: The Director of the National Institutes of Health, the Assistant Secretary for Health, the Director of the Centers for Disease Control and Prevention, and the Commissioner of the Food and Drug Administration (or the designees of such officials).
<b>MEETINGS</b> – Meetings are held approximately four times a year. A Government official is present at all meetings. Meetings are open to the public except as determined otherwise by the Secretary or other official to whom the authority has been delegated. Notice of all meetings is given to the public. Meetings are conducted and records of the proceedings kept as required by applicable laws and departmental regulations.

## Smallpox Vaccine Injury Compensation Program (SVICP)

The Smallpox Emergency Personnel Protection Act of 2003 (Public Law 108-20, 117 Stat. 638) authorized the Secretary of HHS to establish the SVICP. The program provides medical, lost income, and death benefits. Eligible individuals include certain smallpox vaccine recipients participating in recognized smallpox emergency response plans, unvaccinated individuals injured after coming into contact with a vaccinated individual or with a second person with whom the vaccinated person had contact (“vaccinia contacts”), estates, and survivors.

Smallpox vaccine recipients, survivors and estates must submit their request forms within 1 year of having received the smallpox vaccination. Vaccinia contacts must submit their request forms within 2 years of the onset of their symptoms resulting from vaccinia exposure. For more information, call 1-888-496-0338 or go to <http://www.hrsa.gov/smallpoxinjury>.

## Preparedness Countermeasures Injury Compensation (PCIC) Request for Benefits

On December 30, 2005, the Public Readiness Emergency and Preparedness Act created the Preparedness Countermeasures Injury Compensation (PCIC) Request for Benefits.

Compensation may be provided to an eligible individual for a serious physical injury directly caused by the administration or use of a covered countermeasure, as declared by the Secretary of the HHS. The first designated declaration is for pandemic influenza A (H5N1) vaccine. As a result of this declaration, individuals have 1 year from the date they receive the vaccine to apply for compensation. The PCIC is administered by HHS’s HRSA, Healthcare Systems Bureau. More information about the PCIC or SVICP can be obtained by calling call (888) 496-0338 or going to <http://hrsa.gov/countermeasurescomp>.

## Coordination of HHS Vaccine Safety Activities

In summary, there is a broad range of vaccine safety activities conducted by the NIH, FDA, CDC, and VICP in HHS. These activities cover the spectrum from nonclinical research through clinical studies, postlicensure studies, vaccine injury compensation, and risk communication. HHS vaccine safety activities are coordinated by the National Vaccine Program Office (NVPO).

The NVPO serves as the Secretariat for the National Vaccine Advisory Committee (NVAC), a Federal advisory committee formed in 1987 with the mission of advising the Director of the National Vaccine Program on how to achieve the optimal prevention of infectious diseases

through immunization and the optimal prevention against vaccine adverse reactions. NVAC has a Working Group devoted to vaccine safety. As is the case with other Federal vaccine advisory committees, NVAC includes ex officio members from HHS agencies and other Departments (VA and DoD) to ensure fluid communication among HHS agencies and across the federal government involved in vaccine safety. In addition, the committee has representation from individuals who are engaged in vaccine research or the manufacture of vaccines, from physicians, from members of parent organizations concerned with immunization, and from representatives of State or local health agencies or public health organizations. Thus, vaccine safety policy issues that arise among Federal agencies involved in vaccine safety and their advisory committees can be explored by NVAC. See **Table 14** for more information on NVAC or go to <http://www.hhs.gov/nvpo/nvac/nvaccharter.pdf>.

<b>Table 14: National Vaccine Advisory Committee (NVAC)</b>
<b>PURPOSE</b> – Advises and makes recommendations to the Assistant Secretary for Health (as the Director of the National Vaccine Program) to achieve the optimal prevention of human infectious diseases through immunization and to achieve the optimal prevention against adverse reactions to vaccines.
<b>FUNCTION</b> – To study and recommend ways to encourage the availability of an adequate supply of safe and effective vaccination products in the United States. To recommend research priorities and other measures to enhance the safety and efficacy of vaccines. To advise the Assistant Secretary for Health, as the Director of the National Vaccine Program, in the implementation of Sections 2102 and 2103 of the Public Health Service Act. To identify, annually, for the Director of the National Vaccine Program, the most important areas of governmental and nongovernmental cooperation that should be considered in implementing Sections 2101 and 2103 of the Public Health Service Act.
<b>STRUCTURE</b> – The committee consists of a core of 17 voting members; 15 public members, including the Chair, are selected from individuals who are engaged in vaccine research or the manufacture of vaccines or who are physicians, members of parent organizations concerned with immunizations, or representatives of State or local health agencies or public health organizations. Two members are representatives of the vaccine manufacturing industry who are engaged in vaccine research or the manufacture of vaccines. Committee members are appointed by the Director, National Vaccine Program, in consultation with the Institute of Medicine (National Academy of Sciences); affected entities of the vaccine industry are consulted, as well, for selection of the two representative members. NVAC also includes ten nonvoting ex officio members representing Federal agencies that have an interest or involvement in the development, testing, licensing, production, procurement, distribution, or production of vaccines or in vaccine research.
<b>MEETINGS</b> – Meetings are held approximately three times per year and are called by the Director of the National Vaccine Program Office, the designated Federal officer responsible for developing the meeting agenda. Meetings are open to the public except as determined otherwise by the Secretary, or other official to whom the authority has been delegated. Notice of all meetings is given to the public. Meetings are conducted and records of the proceeding kept as required by applicable laws and departmental regulations.

## Department of Defense Vaccine Safety Activities

The DoD conducts multiple activities to optimize the safety of vaccinations administered to service members, military retirees, and their family members who are healthcare beneficiaries of the DoD. These activities are coordinated through the Military Vaccine (MILVAX) Agency, which is the executive agent for the DoD in this regard. The DoD also collaborates with other federal agencies in the collection and interpretation of safety surveillance data, such as its close collaboration via VAERS.

MILVAX's vision is to protect and enhance the health of service members and military beneficiaries by promoting excellence in immunization policy and practice. This includes enhancing military medical readiness and protecting human health by synchronizing information, delivering education and training, enhancing scientific understanding, promoting quality, and coordinating military immunization programs worldwide. The MILVAX Agency supports all five Armed Services (i.e., Army, Marine Corps, Navy, Air Force, and Coast Guard) and is coordinated through the Army Surgeon General's Office.

Information sharing and consultation for immunizations within the DoD take advantage of various electronic media as well as live interactions. The major outreach services of the MILVAX Agency include a toll-free information line (877-GET-VACC), an e-mail question-and-answer service ([vaccines@amedd.army.mil](mailto:vaccines@amedd.army.mil)), a monthly listserv, and three gateway websites:

- <http://www.vaccines.mil>
- <http://www.smallpox.mil>
- <http://www.anthrax.mil>

The MILVAX Agency synchronizes immunization education and training program information among the Military Services and for DoD staff through an effort known as Immunization University, developed in coordination with the Vaccine Healthcare Centers Network (described below). Immunization University is a collection of guidelines and training resources to help staff deliver the best services possible. Designed to enhance the skills of healthcare workers from a variety of professional and paraprofessional backgrounds, Immunization University offers training on vaccine products and immunization services through distance learning and on-site classes sponsored by MILVAX. MILVAX is committed to making this the most fruitful single resource for access to a wide range of training products relating to immunization services.



The MILVAX promotes quality in immunization and vaccination understanding and delivery with coordination and assessment of United States military immunization programs worldwide. It also assists senior DoD leaders with policy development, especially on policy related to biodefense and pandemic issues. The MILVAX works with clinics, manufacturers, and the Services to promote optimal shipping and handling of temperature-sensitive medical products, including closely monitored shipments of anthrax and smallpox vaccines. The DoD conducts research to enhance the scientific understanding of the benefits and risks of vaccines.

The DoD fosters mutually beneficial relationships between DoD, other government agencies, and professional associations related to immunizations. Examples include provider training on VAERS and the Vaccine Analytic Unit (VAU). The VAU is a collaborative project among the DoD, FDA, and CDC with the primary objective of assessing adverse events associated with the anthrax vaccine and other biodefense vaccines. The VAU uses the Defense Medical Surveillance System, which is an active surveillance system of United States military personnel (about 1.4 million person-years each year from 1998 to the present), and relational databases that contain information on demographics, inpatient and outpatient visits, vaccination, and deployment. Other information systems used by the DoD for vaccine safety studies include the Medical Protection System (MEDPROS – Army), the SNAP Automated Medical System (SAMS – Navy), the Medical Readiness Reporting System (MMRS – Navy Reserve and Marine Corps), the Air Force Complete Immunization Tracking Application (AFCITA), and the Medical Readiness System (MRS, Coast Guard). The DoD has launched a global electronic healthcare record system, the Armed Forces Health Longitudinal Technology Application, which is expected to be completed by 2011.

The VAU developed a research agenda, in collaboration with the National Vaccine Advisory Committee (NVAC), which identified over 100 potential adverse events and recommended 11 topics for further study.<sup>38</sup> The VAU research agenda includes both hypothesis-generating and hypothesis-testing studies. The VAU provides a unique infrastructure for conducting immunization safety postlicensure surveillance studies, offers increased understanding of the safety profiles of anthrax and other vaccines given in the military, and complements VAERS and VSD in its ability to inform policy makers about important vaccine safety questions.

## The Vaccine Healthcare Centers (VHC) Network

The VHC Network serves military beneficiaries and healthcare workers as well as government agency personnel requesting clinical consultations or immunization healthcare-related expert support. As of October 2007, the VHC Network became a division of the MILVAX Agency, conjointly sustaining services and programs that enhance vaccine efficacy, safety, and acceptability. The Network consists of four regional sites: Walter Reed Army Medical Center (WRAMC) in Maryland; Womack Army Medical Center at Fort Bragg in North Carolina; Wilford Hall Medical Center at Lackland Air Force Base in Texas; and the Naval Medical Center Portsmouth in Virginia. The National VHC Network headquarters is located at the WRAMC, under the Army's North Atlantic Regional Medical Command. While the MILVAX main office coordinates DoD vaccine program policy and implementation worldwide, the VHC Network represents a clinically focused platform supporting expert care and consultation, education, advocacy, and research dedicated to quality assurance and continuous performance improvement in immunization healthcare.

The VHC Network provides clinical support and immunology/adverse reaction expert consultations to service members and their families as well as to healthcare workers supporting Military Health System (MHS) beneficiaries within and outside MHS facilities. The clinical support includes the provision of clinical care for persons experiencing adverse events following vaccination and evaluation for medical exemptions, its personnel serving either as primary care providers or as case managers working with the individuals' provider. Patient care activities includes diagnostic assessments such as physical examinations, coordination of specialized testing, evaluation of laboratory test results, consultation with current and/or past healthcare providers, obtaining of medical histories, causality research in accordance with WHO guidelines,<sup>39</sup> development of treatment and multidisciplinary care plans, referrals to other health care providers for subspecialty care, and long-term follow up of patient outcomes.

The VHC Network also responds to questions relating to the safe administration of vaccines to prevent adverse events, the identification of potential adverse events, and the enhancement of safe practices before, during, and after immunization. The VHC Network provides clinical input to administrative decisions in areas such as assistance to service members in obtaining medical exemptions from further immunization and support to patients who are no longer on active duty.

VHC educational accomplishments include Project Immune Readiness (over 30 modules for training on the minimum standards for immunization healthcare in nontraditional sites, specific vaccine information, and guidelines for the management of anaphylaxis and other vaccine adverse reactions–related issues).

The VHC Network conducts research to improve vaccine safety, including the identification, treatment, and prevention of vaccine adverse reactions. Data for vaccine safety studies is obtained from literature reviews, from the clinical activities previously described, and from the military immunization databases. Improving the safety of vaccine administration is accomplished by screening service members’ health histories prior to immunization to identify any potential vaccine-related risks. This screening can result in alteration of the vaccine dose or in medical exemption to immunization, when warranted. The VHC Network identifies previously unrecognized adverse events through an iterative case review process and develops clinical guidelines to assist in the diagnosis of adverse events and care for those affected. See **Table 15** for examples of vaccine safety research conducted by the DoD and the VHC Network.

**Table 15: DoD and VHC Network Vaccine Safety Studies**

- A case series of persons with myopericarditis and acute coronary syndrome following smallpox vaccination<sup>40,41</sup>
- Increased risk of myopericarditis following smallpox vaccination (7.5-fold higher risk). Cases were predominantly male and white. No increased risk found for revaccination.<sup>42</sup> Normalization of echocardiography, electrocardiography, and treadmill testing expected through follow-up of inflammatory cardiac complications after smallpox vaccination.<sup>43</sup>
- A case series of self-reported, short-term safety of anthrax vaccine adsorbed during more than 25 years of use. A minority of vaccine recipients reported systemic and injection site reactions. Females reported higher incidence of injection-site and systemic adverse events than males.<sup>44</sup> A similar review of VAERS reports following anthrax vaccine found no evidence for an unusual rate of serious or medically important adverse events.<sup>45</sup>
- Evaluation of adverse events following anthrax vaccine adsorbed. A standardized health risk appraisal and review of outpatient visits showed no differences between those vaccinated and those not vaccinated.<sup>46</sup>
- A historical cohort study of United States Army personnel found that those vaccinated with anthrax vaccine were not at increased risk of disability.<sup>47</sup>
- A cohort study found that anthrax vaccination had no effect on pregnancy, birth rates, or adverse birth outcomes.<sup>48</sup>
- The health of former workers in a United States military research program who received multiple vaccines and matched community controls found that multiply immunized subjects characterized themselves as slightly less healthy and more frequently reported fatigue than controls. No differences between multiply immunized subjects and controls were seen for numerous self-reported medical conditions.<sup>49</sup>

The VHC Network provides presentations, printed materials, and Web resources to educate servicemen, providers, and others about adverse events and VHC resources. The VHC Network actively involves the CDC and FDA in the surveillance of adverse events associated with biodefense vaccines and reports events to VAERS. Details of the DoD's VHC Network can be found on their website, <http://www.vhcinfo.org/>, and a review from a recent Government Accountability Office (GAO) report at <http://www.gao.gov/new.items/d07787r.pdf>.

## Department of Veterans Affairs Vaccine Safety Activities

The VA Center for Medication Safety and Pharmacy Benefits Management Strategic Healthcare Group (PBM) recently added vaccines to the list of agents followed as part of the national pharmacovigilance program. The updated national VA Adverse Drug Event Reporting System (VA ADERS) is a passive surveillance web-based program available in every VA facility to report serious adverse drug events using the standard FDA MedWatch 3500 form. The VA ADERS web-based program allows for all spontaneous reported adverse drug events, including mild and moderate events, to be reported and evaluated. The MedWatch forms are submitted to the FDA while all reports (serious, moderate, and mild adverse drug events) are housed in a central VA database at the PBM for assessment and surveillance. Spontaneous reported adverse events associated with vaccines are now captured through this program and are assessed and tracked similarly to medications.

In addition to spontaneous reports, the VA will pilot a vaccine active surveillance project, starting in 2008, in collaboration with the FDA. The project focuses on influenza and pneumococcal vaccines. Data from the national databases have been merged, and a statistical model will be applied to conduct a rapid cycle analysis to detect potential vaccine safety signals. If the pilot is successful, it will be transitioned into a standard mechanism for tracking adverse events following vaccines in the VA system.

## Non-Federal Vaccine Safety Partners

In addition to Federal vaccine safety activities, a broad range of other groups contribute to vaccine safety, including State and local health departments, academia, industry, healthcare providers, professional organizations, insurance companies, managed care organizations, and philanthropic organizations. As vaccine providers, public health departments are responsible for reporting adverse events following vaccination to VAERS. They also communicate the risks and

benefits of vaccines to the public, to healthcare providers, and to the media. Academic researchers conduct studies at nearly every stage of the vaccine safety continuum, often funded by HHS agencies and by industry.

Vaccine manufacturers play a critically important role throughout the vaccine safety continuum in optimizing the safety of vaccines. The purpose of this document is to provide an in depth look at the nation's vaccine safety system with a focus on the Federal component of that system. A review of the many vaccine safety activities conducted by vaccine manufacturers and others is not included here.

Healthcare providers communicate the risks and benefits of vaccines, make reports to the VAERS system, and may be involved in the clinical development of promising new vaccines. Professional organizations such as the American Academy of Pediatrics and the American Academy of Family Physicians, in their role of making recommendations for vaccine use, consider both the benefits and risks of vaccines as part of their assessment. MCOs communicate the risks and benefits of vaccinations, and some MCOs participate in the CDC's VSD. Philanthropic organizations fund specific vaccine safety studies, typically in the developing world.

The WHO Global Advisory Committee on Vaccine Safety coordinates vaccine safety activities internationally ([http://www.who.int/immunization\\_safety/en/](http://www.who.int/immunization_safety/en/)). For example, the CDC is participating in an ongoing investigation of yellow fever vaccine-related deaths in Peru, coordinated by WHO.

The United States vaccine safety system has been a successful public/private partnership with a shared objective of optimizing the safety of vaccines. Vaccine safety is an iterative process as new science and new approaches to optimizing vaccine safety are continually interwoven into the vaccine safety system.

## Appendix 1: Institute of Medicine Safety Reviews

Institute of Medicine Immunization Safety Reviews, 2001–2004			
IOM Immunization Safety Review	Outcome	Vaccine	Conclusion
Thimerosal-Containing Vaccines and Neurodevelopmental Disorders (2001)	Neurodevelopmental disorders (e.g. autism, ADHD, and speech language delay).	Childhood vaccines with Thimerosal	Evidence is inadequate to accept or reject a causal relationship (also see 2004 review)
Measles-Mumps-Rubella Vaccine and Autism (2001)	Autistic Spectrum Disorder (ASD)	MMR Vaccine	Evidence favors rejection of a causal relationship
Hepatitis B Vaccine and Demyelinating Neurological Disorders (2002)	Multiple sclerosis – incident	Hepatitis B Vaccine	Evidence favors rejection of a causal relationship
	Multiple sclerosis – relapse		Evidence favors rejection of a causal relationship
	Central Nervous System Demyelinating Disorder – first episode		Evidence is inadequate to accept or reject a causal relationship
	Acute disseminated encephalomyelitis (ADEM)		Evidence is inadequate to accept or reject a causal relationship
	Optic neuritis		Evidence is inadequate to accept or reject a causal relationship
	Transverse myelitis		Evidence is inadequate to accept or reject a causal relationship
	Guillain-Barré Syndrome (GBS)		Evidence is inadequate to accept or reject a causal relationship
	Brachial neuritis		Evidence is inadequate to accept or reject a causal relationship
Multiple Immunizations and Immune Dysfunction (2002)	Heterologous infections	Multiple Vaccinations	Evidence favors rejection of a causal relationship
	Type 1 diabetes		Evidence favors rejection of a causal relationship
	Increased risk of allergic disease, particularly asthma		Evidence is inadequate to accept or reject a causal relationship

**Institute of Medicine Immunization Safety Reviews, 2001–2004**

<b>IOM Immunization Safety Review</b>	<b>Outcome</b>	<b>Vaccine</b>	<b>Conclusion</b>
SV40 Contamination of Polio Vaccine and Cancer <sup>10</sup> (2002)	Cancer	Polio Vaccine	Evidence is inadequate to accept or reject a causal relationship
Vaccinations and Sudden Unexpected Death in Infancy (2003)	Sudden infant death syndrome (SIDS)	DTwP	Evidence favors rejection of a causal relationship
		DTaP Vaccine	Evidence is inadequate to accept or reject a causal relationship
		Haemophilus Influenza (Hib), Hepatitis B (HepB), Oral Polio Vaccine (OPV), Inactivated Polio Vaccine (IPV)	Evidence is inadequate to accept or reject causal relationships
		Multiple simultaneous vaccinations	Evidence favors rejection of a causal relationship
	Sudden unexpected death in infancy, other than SIDS	Multiple simultaneous vaccinations	Evidence is inadequate to accept or reject a causal relationship
	Anaphylaxis in infants	Diphtheria toxoid- and whole cell pertussis	Evidence favors acceptance of a causal relationship
	Neonatal death	HepB	Evidence is inadequate to accept or reject a causal relationship
Influenza Vaccines and Neurological Complications (2004)	GBS	1976 Swine Influenza Vaccine	Evidence favors acceptance of a causal relationship b
		Influenza vaccine administered after 1976	Evidence is inadequate to accept or reject a causal relationship
	Multiple sclerosis – relapse	Influenza vaccine administered after 1976	Evidence favors rejection of a causal relationship
	Multiple sclerosis – incident		Evidence is inadequate to accept or reject a causal relationship
	Optic neuritis		Evidence is inadequate to accept or reject a causal relationship
	Other Demyelinating Neurological Conditions		Evidence is inadequate to accept or reject a causal relationship

Institute of Medicine Immunization Safety Reviews, 2001–2004			
IOM Immunization Safety Review	Outcome	Vaccine	Conclusion
	Demyelinating neurological disorders in children aged 6-23 months		No evidence bearing on a causal relationship
Vaccines and Autism (2004)	Autism	Thimerosal-containing vaccines	Evidence favors rejection of a causal relationship
		MMR vaccine	Evidence favors rejection of a causal relationship



## Appendix 2: National Childhood Vaccine Injury Act

National Childhood Vaccine Injury Act Vaccine Injury Table <sup>a</sup>		
Vaccine	Adverse Event	Time Interval
<b>I.</b> Tetanus toxoid-containing vaccines (e.g., DTaP, Tdap, DTP-Hib, DT, Td, TT)	A. Anaphylaxis or anaphylactic shock B. Brachial neuritis C. Any acute complication or sequela (including death) of above events	0-4 hours 2-28 days Not applicable
<b>II.</b> Pertussis antigen-containing vaccines (e.g., DTaP, Tdap, DTP, P, DTP-Hib)	A. Anaphylaxis or anaphylactic shock B. Encephalopathy (or encephalitis) C. Any acute complication or sequela (including death) of above events	0-4 hours 0-72 hours Not applicable
<b>III.</b> Measles, mumps, and rubella virus-containing vaccines in any combination (e.g., MMR, MR, M, R)	A. Anaphylaxis or anaphylactic shock B. Encephalopathy (or encephalitis) C. Any acute complication or sequela (including death) of above events	0-4 hours 5-15 days Not applicable
<b>IV.</b> Rubella virus-containing vaccines (e.g., MMR, MR, R)	A. Chronic arthritis B. Any acute complication or sequela (including death) of above event	7-42 days Not applicable
<b>V.</b> Measles virus-containing vaccines (e.g., MMR, MR, M)	A. Thrombocytopenic purpura B. Vaccine-strain measles viral infection in an immunodeficient recipient C. Any acute complication or sequela (including death) of above events	7-30 days 0-6 months Not applicable
<b>VI.</b> Polio live virus-containing vaccines (OPV)	A. Paralytic polio --- in a non-immunodeficient recipient --- in an immunodeficient recipient --- in a vaccine assoc. community case B. Vaccine-strain polio viral infection --- in a non-immunodeficient recipient --- in an immunodeficient recipient --- in a vaccine assoc. community case C. Any acute complication or sequela (including death) of above events	0-30 days 0-6 months Not applicable 0-30 days 0-6 months Not applicable Not applicable
<b>VII.</b> Polio inactivated-virus containing vaccines (e.g., IPV)	A. Anaphylaxis or anaphylactic shock B. Any acute complication or sequela (including death) of above event	0-4 hours Not applicable
<b>VIII.</b> Hepatitis B antigen-containing vaccines	A. Anaphylaxis or anaphylactic shock B. Any acute complication or sequela (including death) of above event	0-4 hours Not applicable
<b>IX.</b> Haemophilus influenzae type b polysaccharide conjugate vaccines)	A. No condition specified for compensation	Not applicable
<b>X.</b> Varicella vaccine	A. No condition specified for compensation	Not applicable
<b>XI.</b> Rotavirus vaccine	A. No condition specified for compensation	Not applicable

<b>National Childhood Vaccine Injury Act Vaccine Injury Table <sup>a</sup></b>		
<b>Vaccine</b>	<b>Adverse Event</b>	<b>Time Interval</b>
<b>XII.</b> Vaccines containing live, oral, rhesus-based rotavirus	A. Intussusception B. Any acute complication or sequela (including death) of above event	0-30 days Not applicable
<b>XIII.</b> Pneumococcal conjugate vaccines	A. No condition specified for compensation	Not applicable
<b>XIV.</b> Any new vaccine recommended by the Centers for Disease Control and Prevention for routine administration to children, after publication by Secretary <sup>b,c</sup>	A. No condition specified for compensation	Not applicable

a = Effective date: February 1, 2007

b = As of December 1, 2004, hepatitis A vaccines have been added to the Vaccine Injury Table (Table) under this category. AS of July 1, 2005, trivalent influenza vaccines have been added to the Table under this Category. Trivalent influenza vaccines are given annually during the flu season either by needle or syringe or in a nasal spray. All influenza vaccines routinely administered in the U.S. are trivalent vaccines covered under this category.

b = As of February 1, 2007, meningococcal (conjugate and polysaccharide) and human papillomavirus (HPV) vaccines have been added to the Table under this Category.

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