# Advisory Commission on Childhood Vaccines (ACCV)
# Meeting and Conference Call

## October 24, 2006

### Minutes

**Members Present**

Don L. Wilber, M.D., Chair
Marguerite E. Willner, Vice-Chair, via conference call
Tawny Buck
Jaime Deville, M.D.
William P. Glass, Jr., J.D., via conference call
Jeffrey M. Sconyers, J.D.
Tamara Tempfer, RN-C, MSN, PNP

**Ex-Officio Members Present**

Marion Gruber, Ph.D. for
Norman Baylor, Ph.D., Center for Biologics and Evaluation Research, Food and Drug Administration (FDA)
Robert L. Davis, M.D., M.P.H., Director, Immunization Safety Office, Centers for Disease Control and Prevention (CDC) (via conference call)

**Executive Secretary**

Geoffrey Evans, M.D., Director, Division of Vaccine Injury Compensation (DVIC), Healthcare Systems Bureau (HSB), Health Resources and Services Administration (HRSA)

**Staff Liaison**

Cheryl Lee, DVIC, HSB, HRSA

**Introduction**

Dr. Don Wilber convened the 64th quarterly meeting of the Advisory Commission of Childhood Vaccines (ACCV) and welcomed all participants. The minutes of the March 9 meeting were approved.

**Report from the Division of Vaccine Injury Compensation (DVIC): Geoffrey Evans, M.D., Acting Director**

Dr. Evans welcomed the members to the meeting, and mentioned that the National Vaccine Injury Compensation Program (VICP) was operating in its 19th year.

Dr. Evans welcomed and introduced the three new ACCV members. Ms. Tamara "Tammy" Tempfer was appointed as the health professional representative. Ms. Tempfer is a nurse practitioner at Children's Hospital Ambulatory Pediatrics Clinic in Buffalo, NY. In this position, she provides primary and adolescents care on an outpatient basis to children by managing treatment and follow-up. She also provides primary care and case management to special needs children. She is involved in the pediatric residents teaching program as a clinic resource person and coordinator.

Mr. Jeffrey Sconyers was appointed as the general attorney representative. He is the Vice President and General Counsel of Children's Health Care System in Seattle, Washington. He serves as a board member of the American Health Lawyers Association, and is involved in many professional activities. He is a member of the Washington State Hospital Association Public Policy Committee, instructor in health law at the University of Washington's School of Law, and editor-in-chief of the *Washington Health Law Manual*.

Ms. Buck was appointed as a member from the general public. She is the parent of a child who has suffered a vaccine-related injury from a DTP shot. Ms. Buck is an executive board member of LINKS, a parent resource center that provides advocacy services to families of children with special needs.

Dr. Evans provided updates of the VICP's Post-1988 Statistical Report, as of October 2. In Fiscal Year (FY) 2006, the number of autism claims filed has decreased to 166 and the number of non-autism claims filed has stayed steady at 150.

The average yearly awards paid for FY 2000-2006 was $59.6 million for petitioners' award, and $4.0 million for attorneys' fees and costs. As of August 31, the balance in the Vaccine Injury Trust Fund (Trust Fund) was over $2.3 billion. Currently in FY 2006, the Trust Fund has received approximately $225,598,888.00 in revenue, of which $148,308,750.00 was excise tax collection, and $77,290,138.00 was from interest. The Trust Fund balance will continue to increase due to excise taxes on the influenza vaccine, since this vaccine is given annually.

On October 25, the U.S. Court of Federal Claims will conduct its 19th Annual Judicial Conference. The ACCV members will be attending sessions on the Omnibus Autism Proceedings, and causation determinations in the VICP.

A letter from Ms. Debbie Faulkner was sent to the ACCV detailing the experience of her son, Eric, after receiving the smallpox vaccine. The VICP does not cover smallpox vaccine, and HRSA's Smallpox Vaccine Injury Compensation Program was established in the last few years.

The ACCV Chair received a response letter dated May 31 from Michael O. Leavitt, Secretary of Health and Human Services (HHS). The Secretary thanked the Chair for conveying the recommendation by the ACCV that a scientific panel be established to periodically review the Vaccine Injury Table.

On May 2, the VICP awarded a contract to Alliances for Quality Education (AQE) to administer the Medical Expert Panel (MEP), which was formerly called the Expert Witness Program. The AQE will assume the logistical responsibilities of the MEP, and medical experts will be considered consultants to AQE.

Dr. Evans provided an update on legislative activities. On July 26, Representative Dave Weldon (R-FL) introduced the Vaccine Safety and Public Confidence Assurance Act of 2006 (H.R. 5887). This bill would provide responsibilities for the Nation's vaccine safety to an independent agency within the HHS, removing most vaccine safety research from CDC.

Dr. Evans provided a report on meetings attended by DVIC Staff. On April 4, Drs. Evans, Robert Weibel, Indira Jevaji, and Sarah Atanasoff participated in a training session on influenza at the Department of Justice (DOJ). Drs. Atanasoff and Jevaji provided an extensive overview of the influenza disease and vaccine program in the U.S. They provided information on the indications, contraindications, and adverse events associated with both the inactivated and live viral products, and background incidence of disease in adults.

On May 8-12, Dr. Evans attended the annual project meeting of the Clinical Immunization Safety Assessment (CISA) Centers and Vaccine Safety Datalink (VSD) in Berkeley, California. Both of these projects are sponsored by the CDC. CISA performs focused vaccine research on individuals who experience significant adverse events after vaccination, while the VSD utilizes extensive clinical databases among seven health maintenance organizations in order to perform planned vaccine safety studies.

On June 29 – 30, Dr. Evans represented HRSA as an ex-officio member of CDC's Advisory Committee on Immunization Practices (ACIP) meeting in Atlanta. The major topic at the meeting was the use of the newly licensed human papillomavirus vaccine, Gardasil. ACIP unanimously recommended routine use of this vaccine in girls 11-12 years old, with permissive use as early as 9 years old, and catch-up of girls and women 13-26 years of age. Human papillomavirus is the leading cause of cervical cancer in women.

The ACIP also unanimously approved a second dose of varicella to be given at 4-6 years along with measles-mumps-rubella vaccine, which has been recommended at 4-6 years for over a decade. Although varicella rates have declined significantly since licensure of varicella zoster vaccine in 1996, there continues to be outbreaks among school children.

On June 6-7 and September 26-27, Dr. Evans represented HRSA as an ex officio member at the National Vaccine Advisory Committee (NVAC) meeting. The topics at the June

meeting covered influenza vaccine primarily among adolescent immunization programs and updates on the HHS' Influenza Pandemic Plan. At the September meeting, topics were held on influenza programs for vaccination of healthcare workers, and vaccine financing, and research and development.

**Report from the Department of Justice (DOJ): Vincent Matanoski, J.D., Acting Deputy Director for the Torts Branch, Civil Division**

Staffing and Hiring

Mr. Matanoski noted that Mark Rogers, J.D., Deputy Director, Torts Branch, Civil Division, DOJ remains on active duty in the Marine Corps, but he is expected to return and will likely address the ACCV at the March 7-8, 2007 meeting. Mr. Matanoski reported that the Office of Vaccine Litigation, DOJ, has authority to hire three new attorneys, and noted that the office recently lost one attorney. The ability to hire is critical not only to fill that gap, but also to meet the needs of the Program. Referencing his report to the ACCV in March 2006, Mr. Matanoski reiterated that the Office of Special Masters has expanded from six special masters to eight special masters, which has resulted in the increased capacity of that office to move the cases.

Litigation

*Autism*

Mr. Matanoski offered DOJ's views on litigation trends using the end of the Fiscal Year (FY) 2006 as a reference point. In FY 2006, Mr. Matanoski noted that there continues to be a decreased trend in the number of autism cases filed. There were 316 cases filed in the last fiscal year, and roughly 163 of those were autism. Mr. Matanoski attributed the continued decrease in autism filings to the fact that most claims are already in the Program. There are approximately 4,700 pending cases alleging autism as a result of the receipt of vaccines. That number remains nearly the same as was reported to the ACCV in March 2006. The autism proceeding is scheduled for trial in mid-June 2007, and is estimated to span two-three weeks. While the expected trial length is longer than any typical vaccine trial, the length is consistent with the high number of experts expected to testify for both parties. Mr. Matanoski discussed a few issues that still require resolution, such as placing limits on the duration of expert witness testimony, and whether or not the trial should be accessible publicly or closed. In order to ensure that the fact finder has sufficient opportunity and information to make an informed decision, the government opposes any limits placed on the duration of testimony. Regarding access to the proceeding involving 4,700 petitioners, the question centers on whether or not all petitioners have rights to be present, as well as how the Court allows access to the hearing. Many of these issues are expected to be addressed by the Court and discussed by the parties between now and the expected June 2007 trial.

*Hepatitis B vaccine*

This area of litigation has been ongoing for several years; however, in the last six months litigation involving hepatitis B vaccine has become quite active. The new special masters have taken the hepatitis B cases and started to move their respective dockets. There has been one major trial involving neurodemyelinating conditions, and several groups with about eight different conditions are currently moving towards resolution. Mr. Matanoski expects the hepatitis B case groupings to be resolved next year.

*Flu vaccine*

There has been a slight increase in number of flu cases that have been filed. Referencing his prior report in March 2006, however, Mr. Matanoski reiterated that the majority of filings is still expected to occur in June-July 2007, two years after the flu vaccine was added to the Vaccine Injury Table.

*All cases*

As for the overall number of cases that were resolved in Fiscal Year 2006, of the 316 that were filed, 280 of those were resolved, which equates to 36 more pending cases. Mr. Matanoski explained that the overall number of cases reflects autism cases that will not be resolved, either by settlement or voluntary withdrawal, until the end of the Omnibus Autism Proceeding.

Appeals

Appellate litigation has been active. The case of Markovich v. HHS is pending in the Federal Circuit Court of Appeals (Federal Circuit). This case involves an important issue of interpreting the statute of limitations. The case was originally dismissed because it was untimely filed. The issue on appeal may involve resolution of what constitutes the triggering event to start the tolling of the three year (or 36 month) statute of limitations under the Act. In DOJ's view, the statute states that the first symptom or manifestation of onset of symptoms starts the limitation period. However, the Court of Federal Claims decision in Setnes v. HHS offered a different interpretation of the statutory language focusing on the term "manifestation." In DOJ's view, that interpretation alters when the tolling period starts by essentially expanding the time period within which a claim is considered to be timely filed. In DOJ's view, Setnes is inconsistent with the statute; rather, under the statute, the limitation period begins to run based on the first symptom or manifestation – whichever comes first. Under either interpretation, the Markovich case would be time barred; therefore, it is unclear whether the Federal Circuit will even address the Setnes issue in that case.

Since the last report, the Capizzano case was decided by the Federal Circuit. As expected, the decision followed the Althen decision, which Mr. Matanoski discussed in March 2006. The Capizzano decision differed from Althen in that it focused on the

statements of treating physicians. The Federal Circuit closely examined the statements of treating physicians and gave them a lot of evidentiary weight or suggested that such statements should be afforded significant weight.

In DOJ's view, emphasizing such statements can prove troublesome, as many of these statements are often made without explanation when they are transcribed into medical records. For example, in Mrs. Capizzano's medical records, there appeared the words, "arthritis post immunization." Absent any context, the question becomes what is the significance of those words? Mr. Matanoski posed whether the treating doctor is saying simply that the arthritis came after immunization, which no one disputed chronologically, or is the doctor implying that there is a causal connection between the vaccine and arthritis? Focusing on those statements may be difficult in terms of litigating these cases as this has not been the subject of past litigation.

In the past, when faced with similar statements made by treating doctors, the parties have considered the context of statement(s) in terms of the overall case to advance the best interpretation. If more attention and special evidentiary weight should be given to statements made by treating doctors, the respondent may be required to get more facts and perhaps even testimony from the person who made the statement. Such facts/testimony would go to answering what the doctor meant when he or she said, "arthritis post vaccination." Was the doctor simply stating a chronological fact or implying a causal connection? If it is the latter, causal connection, then the question becomes what is the basis for that decision or opinion: was it based on a good understanding of the medical science of the causal issue?

It will be difficult to probe this area because many of the petitioners counsel take the view that the government should not bring treating doctors into the litigation either through affidavits, testimony or even statements. Mr. Matanoski has explored these options with some of petitioners' counsel without much success. Recognizing that most doctors will likely not want to be involved in this litigation, Mr. Matanoski remarked that the decision in Capizzano, to the extent that it is read to require greater focus on statements made by treating doctors, may nonetheless require more involvement by treating doctors in litigation under the Act.

A decision was issued by the Court in Snyder v. HHS. It involved the same petitioners' law firm that was used in Capizzano. The appellate issue in Snyder involved the death benefit available under the Act. Judge Wheeler originally reviewed the case on causation and, contrary to the special master, found for petitioner. Judge Wheeler remanded the case to the special master for certain findings as to whether or not petitioner's death was a sequela of her vaccine related injury, and whether or not the petitioner's estate was entitled to pain and suffering, lost wages, and unreimbursed expenses – damages that in the past were reserved for injury cases.

The special master found that petitioner was only entitled to death benefits under section 15(a)(2), consistent with about 18 years of jurisprudence on this issue. In DOJ's view, there were two aberrational cases that dealt with pre-Act cases where the amount of

compensation for attorneys' fees and costs, and pain and suffering was limited to $30,000. Judge Wheeler found that the estate of the individual was entitled to $250,000 (death benefit) plus approximately $550,000 in other damages. In DOJ's view, Judge Wheeler's decision is problematic and wrong.

Judge Wheeler reasoned that the Act stands in the place of civil litigation for wrongful death. However, in DOJ's view, the Act does not substitute for civil litigation and is different. The amount of damages available in civil litigation for wrongful death and lost earnings is different from what is available under the Act. The standards of proof are different and presumptions of causation under the Act are unavailable in civil litigation. Mr. Matanoski offered that Congress left the option to file a civil action available to petitioners who are dissatisfied with the result in the Program because the litigation is different. DOJ is closely examining the decision in Snyder to determine if taking the next step of appealing the decision to the Federal Circuit is warranted. Mr. Matanoski emphasized that such a step would not be taken without careful deliberation and consideration, but the decision represents a break with nearly 18 years of jurisprudence and demands close scrutiny.

Another appellate decision was issued in Pafford v. HHS, which touched primarily on the issue of alternative causation in a cause-in-fact case. In Pafford, there was evidence of another potential cause of the alleged vaccine injury. The special master could not find that the vaccine was the more likely cause of the child's injury because petitioners had not adequately addressed other potential causes. There was evidence of a positive titer for an infectious agent that was known to be a potential cause of the alleged injury. In upholding the special master's decision, the Court focused upon which party bears the burden of proving in causation cases that the vaccine and not another more likely cause was responsible for causing the condition.

The Federal Circuit agreed that in a cause-in-fact case, petitioners bear the burden of showing that the vaccine was more likely the cause of the injury than the other potential cause; it was not Respondent's burden to show that the other potential cause was responsible. Petitioners moved for review of the Federal Circuit's decision, *en banc*, meaning review by the entire 12 judges on the Federal Circuit. Mr. Matanoski noted that the decision was not unanimous, which may be why petitioners sought review by the entire Federal Circuit panel.

In the DOJ's view, the decision in Pafford is correct. In actual causation cases, unlike Table injury cases where a presumption attaches, there is no burden shifting. In Table injury cases, if a presumption attaches, it is a rebuttable presumption; the burden shifts to the government to prove a factor unrelated. Conversely, in actual causation cases, it is petitioner's burden to show that the vaccine is more likely than not the cause. If petitioners satisfy that burden, the case ends. In order to satisfy that burden, however, petitioners must convince the fact finder that other potential causes are less likely than the vaccine.

Settlements

Mr. Matanoski emphasized the importance of settlements being resolved in a timely manner, which are very important to DOJ and petitioners. The Court has set a 15-week time period for completing the settlement approval process. According to statistics from the last fiscal year, the DOJ met that 15 week target in 98% of the cases. That result is a testament to hard work by DOJ attorneys and DVIC, which is also involved in that process. Mr. Matanoski also acknowledged petitioners who work with the DOJ prior to and during the process.

Questions

Dr. Wilber asked Mr. Matanoski's view on why there was fewer autism cases filed. He wondered whether it was due to the IOM report or similar information.

Mr. Matanoski declined to speculate. He offered that thimerosal was removed as a preservative in vaccines during the year 2000. He acknowledged that there may be a vaccine containing thimerosal that was administered after the 2000 time-frame provided that the vaccine lot had not expired. Overall, Mr. Matanoski felt that the decline in cases may be attributed to the lack of thimerosal being used in vaccines, except for its use in flu vaccine. He further noted that the majority of people who suffered claims *circa* 2000 have already filed their claims to avoid being time-barred, and that the majority of those claims and theories of causation involving MMR and thimerosal, for instance, derive from that era. Mr. Matanoski acknowledged that autism continues to be diagnosed although vaccines are less likely to contain thimerosal, so the explanation of causation is less likely to focus on that theory. The research initially pointing to the MMR vaccine has not held up to scientific scrutiny as some may have expected.

Dr. Wilber asked whether all of the 4,700 autism cases would be tried during the two-three weeks in June 2007.

Mr. Matanoski explained that the issue at trial concerns general causation and whether or not vaccines can cause autism. Deferring to petitioners, Mr. Matanoski offered that the theories are expected to involve thimerosal and MMR. There will not be evidence offered on particular cases, contrary to the DOJ's view that several cases emblematic of the condition should have been tried to provide a factual predicate for the Court to use. Instead, the trial will be more general. There is some concern in DOJ that the trial will prove to be too general and less useful in specific application to the pending cases. The Court is considering various formats. One possible scenario involves creating a hypothetical fact pattern representative of most cases that allege autism as a result of vaccinations. The trial would not result in a case specific decision; however, the results of the trial will then start to be applied to individual cases.

Mr. Matanoski considers the time period for fully resolving these claims to be years away because any decision will have to be applied to individual cases and their facts. If a

decision finds causation, then the damages phase will begin. If there is a decision finding no causation, then an appeal will likely follow given the wide impact of any decision on so many pending cases. There is the possibility that some cases may be compensated while others may not, which also provides the opportunity for the parties to carefully consider appellate options. Overall, the appellate process could likely take some time. Conclusion of the autism proceeding is likely to take several years.

**Update on the Immunization Safety Office (ISO), Centers for Disease Control and Prevention: Robert Davis, M.D., M.P.H**

In 2005, the ISO was moved from the National Immunization Program (NIP) to CDC's Office of the Director, Office of the Chief Science Office (OCSO). This move resulted from concerns about potential conflicts of interest that vaccine safety monitoring and evaluation were being performed in the same program that has immunization recommendations and education responsibilities. This move will allow CDC to meet its commitment to increase vaccine safety activities and to be able to keep pace with the increasing number and combinations of recommended immunizations.

The vision of the ISO is: (1) to perform surveillance and high-quality research for CDC vaccine safety activities; (2) to identify adverse events after vaccination; (3) to assess causality and preventable risk factors; and (4) to identify preventable risk factors for the population at large and to prevent vaccine adverse events from affecting the population.

Over the last 15 years, the CDC has been working on improving their communication strategies to healthcare organizations so that they can incorporate CDC's vaccine safety data into public health policy decisions, and the public can choose vaccination with confidence and the least possible risk.

The ISO consists of the following four programs: (1) the Vaccine Safety Datalink (VSD) project; (2) the Vaccine Adverse Event Reporting System (VAERS); (3) the Clinical Immunization Safety Assessment (CISA) Network; and (4) the Brighton Collaboration.

Dr. Davis described the inter-relationships of these four programs in ISO. For instance, in VAERS a signal will be generated that a particular vaccine is causing an adverse event. There will be many reports of this adverse event associated with a particular vaccine. The VSD will test the link of the adverse event to the vaccine, and generate a hypothesis using large cohort studies or any number of epidemiologic methodologies. The next step involves the CISA Network enrolling patients who have experienced the adverse event and begin collecting blood samples and performing in-depth biologic protocols. The Brighton case definitions will be created from a study of the adverse event and shared with experts around the world.

In the last 15 years, CDC has experienced many successes in indentifying vaccine adverse events. The rotavirus vaccine was found to be associated with intussusception in young children, and as a result the vaccine was withdrawn from the U.S. market. A study was performed, and recognized the increased risk for seizures following the

administration of DPT and MMR vaccines. The benefits of these vaccines strongly outweighed the risk of the public health impact. Physicians were notified of the risks and were able to inform patients about the VICP.

There were many adverse events associated with smallpox vaccine, with the most serious being myocarditis. This resulted in smallpox vaccine being discontinued in the civilian vaccination program. The influenza (intranasal) vaccine was associated with Bell's palsy in Europe, and future vaccine development in the U.S. is currently being studied.

Formerly, the second dose of MMR vaccine was given to older and younger age groups in the U.S. The ISO provided research that revealed the second dose was associated with increased risks for arthralgia, rash, fever and other effects. This prompted CDC to change their policy and recommended that only the younger age group received the second dose of MMR vaccine.

Several studies have proved that vaccination does not increase risk for disease. Hepatitis B vaccine did not increase the risk for multiple sclerosis. Research showed that not using the whole cell pertussis and switching to the acellular pertussis vaccine led to an increased safety profile and decreased the risks for fever and seizures. After the administration of MMR, no increased risk was found for inflammatory bowel disease. There was no increased risk for type 1 diabetes with routinely recommended childhood vaccines, for aseptic meningitis after MMR (Jeryl-Lynn) vaccine, and for asthma after childhood vaccines.

The key partners that interact with ISO are the public, healthcare providers, state governments, local governments and other Federal agencies, including the FDA and NIH. The ISO communicates extensively with vaccine manufacturers and outside scientists, and the ISO has their scientific findings utilized by other offices within CDC.

Vaccine Adverse Event Reporting Systems

VAERS was established by the National Childhood Vaccine Injury Act of 1986 (Act), as amended, and VAERS became effective in November 1990. The VAERS is headed by Scott Campbell, MSPH, of the ISO. VAERS is an early warning passive surveillance system that is used to detect problems related to vaccines.

The mission of VAERS, which is in partnership with FDA, is to provide a comprehensive post-marketing surveillance of all vaccine products licensed in the U.S. in a timely manner in order to protect all persons from unacceptable risks related to immunization.

The goal of VAERS is to identify adverse events following immunization (AEFI). Adverse events are reported from vaccine manufacturers, patients, parents, providers, and from people who have suffered adverse events following immunization. The ISO is currently using paper records to record reports of adverse events, but future plans include ISO using the internet to record reports of adverse events.

Trends of adverse events are being analyzed, including clinical, epidemiologic, and laboratory investigations, regarding causal/non-causal relationships between a vaccine or vaccine combinations and adverse events following immunization. The result of this analysis is to provide information for setting public health policies in vaccine safety.

One of the biggest achievements in VAERS was its role in identifying intussception as an adverse event following administration of the first rotavirus vaccine, RotaShied®. On July 16, 1999, an article published in the Morbidity and Mortality Weekly Report identified intussception from 15 recipients who received the RotaShield® vaccine. The publication of this article resulted in many similar reports to CDC, and this triggered two large investigations by CDC and FDA, in collaboration with state and local health departments throughout the U.S. The ACIP withdrew its recommendation to vaccinate infants with RotaShield® vaccine. In October 1999, the vaccine manufacturer voluntarily withdrew RotaShield® from the market.

The long term plans for VAERS include completing research on the newly-licensed vaccines (i.e., MMRV, MCV4, RTV, varicella zoster, HPV4, and Tdap).

Vaccine Safety Datalink Project

In 1991, the VSD began as a collaborative project between CDC and four HMOs (Group Health Cooperative, Northwest Kaiser Permanente, Northern California Kaiser Permanente, and South California Kaiser Permanente). In 2000, the VSD expanded and included four more HMOs (Harvard Pilgrim Health Care, Health Partners, Kaiser Permanente Colorado, and Marshfield Clinic). These eight HMOs provide comprehensive medical and immunization histories of over 5.5 million people from a population of over 9 million people.

The VSD performs two types of analyses for studying adverse events. A screening analysis is performed and automated data is used to get a preliminary assessment of vaccine-outcome associations. Additional in-depth analysis includes chart reviews and interviews to collect additional information on certain patients to validate outcomes, and to verify vaccination history or clinical information.

The VSD is working on two evaluation studies. The first study involves thimerosal exposure and the risk for neurodevelopmental disorders. A cohort design is used and patients are enrolled based on their known exposure to thimerosal. These patients were invited to participate in a two-day clinical evaluation to obtain their neurocognitive developmental status. Parents of patients were interviewed to get an idea of other thimerosal exposures that they may have had, and an extensive chart review was done for the exposure assessment.

The second study is examining the exposure to thimerosal and the risk for developing autism using a case control design study. A one-day clinical evaluation of autism cases is being conducted and extensive interviews and chart reviews are being performed for thimerosal exposure assessment.

The management of the VSD involves using data from each of the HMOs. Legal requirements and patient confidentiality controls are in place to govern the datasets from the HMOs. A scientific protocol is used to access only the minimum amount of data. At the end of the study, the data is transferred to a dataset that can be used by the public.

Clinical Immunization Safety Assessment

The CISA Network conducts in-depth clinical investigations of individuals with unusual or severe vaccine adverse events, and is headed by Claudia Vellozzi, M.D., M.P.H.

In 2001, CISA was established to investigate the pathophysiologic mechanisms and biologic risks of AEFI and to provide evidence-based vaccine safety assessments. CISA is a network of six academic centers with each having vaccine subject matter experts. The centers are the Boston Medical Center, Columbia University Medical Center, Johns Hopkins University, Northern California Kaiser Permanente, Stanford University Medical Center, and the Vanderbilt University Medical Center.

The mission of CISA is to conduct clinical research of immunization-associated adverse events and individual variation (i.e., what is it about this person that makes them susceptible to a specific vaccine adverse event). CISA also provides evidence-based information that assists clinicians in the evaluation and management of individuals at risk for adverse events, and to help individuals make informed immunization choices.

In the next 1½ years, the priorities in ISO include getting a better understanding of the risk factors for developing Gullian-Barre Syndrome (GBS) following vaccination. Evidence-based guidelines are being developed to help clinicians manage hypersensitivity. Guidelines are also being produced to help physicians figure out how to vaccinate or re-vaccinate specific children, adolescents, or adults who may have varying degrees of immunodeficiency (e.g. LVV in DiGeorge Syndrome).

Brighton Collaboration

The Brighton Collaboration is a collaborative project that includes the volunteer efforts of over 900 investigators from around the world to help ISO develop a set of standardized case definitions for studying vaccine adverse events.

One of the challenges facing the ISO is (e.g. rotavirus, HPV, Tdap, MMR-V, and MCV4) to conduct an in-depth analyses of new vaccines and their safety profiles. Other challenges include producing vaccines for adolescents, and studying challenging diseases such as stroke and myocardial infarction to evaluate whether it is a causal or temporal relationship. The ISO has been requested to address rarer and rarer adverse events that may be due to vaccination, including GBS. The ISO is involved in an ongoing effort to educate the public regarding the safety of vaccines. Future vaccines that are currently being developed will protect against cancer or chronic diseases.

The ISO is creating a strategic plan, which will require public engagement and input from NVAC. The ISO is working to have the plan available towards the middle or end of next year.

The ISO is also pursuing an active surveillance of new vaccines for assessment of vaccine safety. They are working on the Pandemic Influenza Preparedness Plan and to ensure that a pandemic influenza vaccine will be safe.

Lastly, the ISO is involved in merging vaccine safety research into the era of personalized medicine so that vaccine strategies can account for individual variations for certain populations at risk. The ISO will identify these populations and offer alternative vaccine strategies, while meeting the needs of CDC to perform a large scale public health vaccination campaign.

**Petitioners' Attorneys View of the National Vaccine Injury Compensation Program: Kevin Conway, J.D.**

Mr. Kevin Conway, J.D. is a partner with the law firm of Conway, Homer & Chin-Caplan, P.C., and represents petitioners in the VICP who have filed claims for vaccine-related injuries. Mr. Conway stated that he was invited to address remarks made by Dr. Paul Offit in his presentation, "Vaccine Liability 50 years After the Cutter Incident," at the March ACCV meeting. Mr. Conway also provided a petitioner's attorney perspective on the VICP.

In response to Dr. Offit's remarks at the March meeting, Mr. Conway agrees with Dr. Offit that women who are vaccinated and their unborn children should be covered by the VICP, and that all vaccines should be covered by the VICP. Mr. Conway also agrees with Dr. Offit that oral polio vaccine can cause harm, and also agrees that it cannot be scientifically proven that any other vaccine causes permanent injury.
Mr. Conway does not agree with several opinions that Dr. Offit expressed. For instance, Mr. Conway favors having an "opt out" provision in the VICP, and does not believe that vaccine manufacturer should be protected from lawsuits.

Before the VICP was established in 1986, vaccine manufacturers were being sued for injuries from DTP vaccines. At that time, there was a safer acellular vaccine available that was being used in Japan. The vaccine manufacturers did not use the safer vaccine because it would have implied that DPT vaccine caused harm. The vaccine manufacturers ended up paying huge claims for injuries from DPT vaccines, and the manufacturing of vaccines was becoming unprofitable. The vaccine manufacturers had threatened to stop making vaccines. In 1986, Congress enacted the VICP to protect vaccine manufacturers from further lawsuits caused by vaccine injuries.

The law firm of Conway, Homer & Chin-Caplan had several cases filed against vaccine manufacturers before the Act was passed, and subsequently, their cases were transferred to the VICP. The original Vaccine Injury Table (Table) had only three vaccines listed, which was polio, MMR, and DPT, and the injuries listed on the Table were residual

seizure disorder, anaphylactic shock, and encephalopathy. In later years, more vaccines were added to the Table.

In 1995, the Table was amended to remove seizures as an injury, and to revise the definition of encephalopathy. Currently, virtually all of the cases in the VICP are off-Table cases. In the past 18 years, Mr. Conway's firm has reviewed over 5,000 alleged vaccine injury claims, and have filed between 2,500 to 3,000 claims in the VICP. He estimates that half of one percent of these claims has been Table injury claims.

Mr. Conway discussed what the standard of proof should be in the VICP, (e.g. what evidence is sufficient for a petitioner to prove their case). First, there is no scientific certainty that vaccines cause permanent injury. If scientific proof is not available, then, what standard should apply? The Act answers this question. It provides that petitioners must show only by a preponderance of the evidence that the vaccine more likely than not caused the injury. Case reports, the Physician's Desk Reference, manufacturers' package inserts, and VAERS data is helpful and can be used as evidence.

Mr. Conway stated that a vaccine injury case usually starts with a treating physician's diagnosis of a vaccine reaction. This information is helpful, but it does not explain why the vaccine is the likely cause of the injury.

There are recent Federal Circuit decisions that have addressed the standard of proof issue. In the Althen v. HHS decision, Dr. Derek Smith, a neuroimmunologist from Harvard Medical School and the medical expert in the case, stated that a tetanus vaccine was the likely cause of multiple sclerosis (MS). Dr. Smith concluded in his analysis that although it cannot be proven scientifically that tetanus vaccine causes MS; Ms. Althen was healthy before the vaccine; her symptoms happened within an appropriate time after the vaccine for an immunological disease; it is biologically plausible that the vaccine can cause MS; and there was no other likely trigger of her disease.

The autism cases are the new crisis in the VICP. Mr. Conway stated that the Autism Omnibus General Order #1 does not refer only to thimerosal as a potential cause of autism, but it does address whether vaccines can cause symptoms on the autism spectrum. He stated that Dr. Offit informed him that rubella vaccine given to a pregnant woman can trigger autism, and that several environmental exposures can trigger symptoms of autism.

Mr. Conway stated that he is pro-vaccine and that vaccines are good for society. Many new vaccines have been manufactured to combat diseases. He believes the VICP is a successful program, and more people are being compensated for vaccine injuries. In his experience in handling vaccine injury claims, there has been "virtually no one opting out of the VICP in 20 years." If the Program is to remain successful, all new vaccines should be covered by the Table, all family members should be permitted to have claims in the Program, a fair "achievable" standard of proof must be applied to the claims, and the statute of limitations must be a generous one. However, a vaccine injured person must

have the right to sue the manufacturers if the Program fails. Such a civil remedy is critical to motivating pharmaceuticals to continue to produce the safest possible vaccines.

**March ACCV Meeting Follow-up: Extending the Statute of Limitations: Marguerite E. Willner, ACCV Member**

Ms. Willner stated the current VICP statute of limitations (SOL) for injuries is 3 years. Currently, all states have a provision to toll the SOL until the child reaches the age of majority (e.g., a minor would have 3 years to file a claim once they reached 18 years of age). She feels that the current 3-year SOL does not allow sufficient time for an individual to file a claim or to acknowledge the first symptom of a vaccine injury. She stated that in the past, the ACCV voted to extend the SOL to 6 years for injuries.

Ms. Willner asked Vincent Matanoski, J.D. his views on extending the SOL, whereupon he stated that the issue of the three-year SOL is currently in litigation, and that it would therefore be inappropriate to take a position on extending the SOL.

Mr. Matanoski stated that the Act provides that the SOL for an injury starts 3 years after the first "occurrence of the symptom or manifestation of onset" of such injury. He stated that the SOL should be clear so that Act's streamlined claim procedures do not get bogged down in collateral litigation over the SOL issues, as was the situation before the Federal Circuit made it clear that equitable tolling did not apply to cases brought under the Act.

Ms. Willner stated her concern that the current SOL may operate to extinguish a cause of action before a right of action accrues to the petitioner -- that is, before a minor or his guardians ever know that the symptom or manifestation of onset of an injury has anything to do with a vaccine. She recalled Mr. Shoemaker's comments that sometimes even injured people under the care of a pediatrician won't know that there's a possibility that the vaccine caused their injury, and there is no science to prove or disprove what causes such an injury.

Cliff Shoemaker, J.D., petitioners' attorney, stated that the SOL should be tolled until a child reaches the age of majority. He feels that it is important that autism cases filed with the VICP that have missed the SOL not be barred for this reason, so that Federal, civil, and state courts will not endure years of litigation. He also stated that the VICP is designed to protect vaccine manufacturers from litigation, and to compensate children who have been injured by vaccines.

Ms. Willner agreed, adding that there is some case law concerning tolling the SOL for minors in malpractice cases and sexual abuse cases, etc., and some courts have found the SOL unconstitutional that cut off the minor's right to access to the court and on due process grounds as well. Ms. Willner asked if extending the SOL is something the ACCV would like to look into further or if the ACCV would prefer to send a message to the Secretary reiterating its support for extending the SOL and if so, for how many years

-- six years, age of majority, or any other suggestions? She asked if the ACCV wished to pursue this issue in a separate workgroup.

Dr. Wilber suggested that a workgroup be formed to discuss extending the SOL and to address other legislative changes needed to improve the VICP. Ms. Willner agreed that establishing a workgroup to address such issues would be helpful.

**Update from the National Vaccine Program Office (NVPO) and the Interagency Vaccine: Kenneth Bart, M.D., M.P.H., Consultant**

Dr. Bart was not in attendance at the ACCV meeting. He emailed the following summary of NVPO activities.

The NVPO has been involved in the following three issues: (1) pandemic preparedness; (2) influenza risk management; and (3) the report to the Secretary of HHS on "Ensuring the Optimal Safety of Vaccines."

The NVPO is the lead office for several of the 199 tasks that are assigned to HHS in the Implementation Plan for the National Strategy for Pandemic Influenza. The tasks encompass vaccine production capacity, prioritization of vaccines, antivirals and other counter measures, and communication of research activities. The NVPO is also coordinating work with CDC and others on community mitigation strategies during a pandemic, such as social distancing, isolation of cases and quarantine of their contacts, school and business closures, and mask use. The Institute on Medicine held meetings on these topics to advise the HHS on their relative merits and implementation feasibility.

The NVPO is co-chair with the Office of Public Health Emergency Preparedness for the newly established HHS-wide "Influenza Risk Management Group." The group's purpose is to provide a forum for decision makers from stakeholder agencies, to identify and address risk management issues related to the development, acquisition, deployment and utilization of medical and public health countermeasures for pandemic and seasonal influenza.

The NVPO and agencies in HHS developed a report to the Secretary entitled "Ensuring the Optimal Safety of Vaccines" and a strategic plan for vaccine safety entitled "The National Vaccine Safety Plan: Priority Goals and Objectives." These documents are currently under final review.

**Update on the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Activities: Barbara Mulach, Ph.D.**

Ms. Mulach was not at the meeting, but provided the following summary of NIAID vaccine activities.

Smallpox

NIH has supported multiple Phase I clinical trials that demonstrated initial safety and immunogenicity of modified vaccinia virus ankara (MVA) vaccines (highly attenuated next generation smallpox vaccines). So far, MVA has been administered to over 1,000 healthy individuals under NIH-funded clinical trials. NIH is also supporting ongoing Phase I trials in special populations that are contraindicated for Dryvax (e.g., those with HIV or atopic dermatitis). Phase II trials to further evaluate safety and immunogenicity of MVA vaccine in healthy individuals and individuals with HIV and atopic dermatitis have also been initiated.

NIH supports the Atopic Dermatitis and Vaccinia Network (ADVN), a nationwide research group that seeks to reduce the risk of eczema vaccinatum, a severe and potentially deadly complication of smallpox immunization. The ADVN Clinical Studies Consortium conducts research to better understand why people with atopic dermatitis have such severe reactions to smallpox vaccine by evaluating their immune responses after natural exposure to less harmful skin viruses such as herpes simplex. The ADVN Animal Studies Consortium is establishing animal models of atopic dermatitis and will investigate their immune responses to vaccinia—the virus used in smallpox vaccine—and other skin viruses such as varicella, which causes chickenpox and shingles.

NIH is also conducting studies to determine correlates of protection for smallpox vaccination.

Influenza

NIH continues to support the development and testing of candidate avian influenza vaccines. NIAID has initiated a series of clinical trials to evaluate these vaccine candidates, including studies to evaluate various strategies to determine optimal use of vaccines in limited supply. Recent results include the following:

- NIH supported a trial to evaluate the safety and immunogenicity in healthy adults of a Chiron/Novartis H9N2 vaccine combined with an adjuvant known as MF59. A report published in Clinical Infectious Diseases in November 2006 showed that a good antibody response was generated among the lowest dosage of the adjuvant-containing H9N2 vaccine. Studies also showed that a single dose of vaccine with adjuvant was as good as two doses of unadjuvanted H9N2 vaccine.

- NIH supported researchers at the University of Rochester Medical Center evaluated a prime-boost strategy using different subtypes of H5N1 vaccines, comparing the immune response to a single 90-microgram dose of one variant of avian flu vaccine in two groups of adults: those who had received a different variant of H5N1 avian flu virus vaccine some eight years earlier and those without pre-exposure to any H5N1 virus or vaccines. Preliminary results showed that more than twice as many of the individuals who had received the priming dose of clade 3 H5N1 vaccine responded with substantial antibody levels to a single dose of clade 1 H5N1 vaccine than did those with no prior H5N1 exposure. These early but promising data indicate that priming with an antigenic variant

vaccine before a pandemic occurs may be one strategy used to help control a pandemic. (http://www.niaid.nih.gov/news/newsreleases/2006/IDSA.htm)

- NIH supported a Phase I trial to evaluate the response to intradermal (under the skin) administration of the Sanofi Pasteur H5N1 vaccine; the purpose of the study is to determine if a smaller intradermal dose may be as immunogenic as a larger dose administered intramuscularly. All dose regimens of inactivated influenza A/H5N1 vaccine administered intradermally and intramuscularly were safe and well tolerated for all study participants. It was concluded that at the doses tested there was no clear advantage with regard to immunogenicity of intradermal administration when compared with intramuscular administration. Plans are under way to directly compare the immune responses generated by vaccinating either into the skin or into the muscle with an H5N1 vaccine containing higher levels of the same amount of antigen. (http://www.niaid.nih.gov/news/newsreleases/2006/IDSA.htm)

**Update on the Center for Biologics and Evaluation Research, Food and Drug Administration: Marion Gruber, Ph.D.**

On May 25, the FDA approved a license application for ZosterVax, a lyophilized preparation of the Oka/Merck strain of live attenuated, varicella-zoster virus. The vaccine is manufactured by Merck. The vaccine is indicated for prevention of herpes zoster (shingles) in individuals 60 years of age and older. Merck has agreed to conduct several postmarketing studies to further assess the safety of this product including a large-scale (20,000 vaccinated subjects) observational safety study conducted in a U.S. heath maintenance organization (HMO) to gain further knowledge of the safety of the vaccine in the course of ordinary clinical practice.

On June 8, the FDA licensed Gardasil, a non-infectious recombinant, quadrivalent human papillomavirus (types 6, 11, 16 and 18) recombinant vaccine. Gardasil is a vaccine indicated in girls and women 9-26 years of age for the prevention of diseases caused by human papillomavirus, namely cervical cancer, precancerous genital lesions and genital warts. It is given as three injections over a six months period. The vaccine is only effective when given prior to infection. The vaccine was evaluated and approved in six months under FDA's priority review process, a process for products with potential to provide significant health benefits. Merck has agreed to conduct several postmarketing studies including studies assessing: (a) the short-term safety of the vaccine (U.S. Managed Care Organization (MCO), 44,000 vaccinated subjects); and to (b) collaborate with the cancer registries in four countries in the Nordic Region (Sweden, Norway, Iceland, and Denmark) to assess long-term outcomes following administration of GARDASIL®; and (c) studies to assess the interaction between administration of GARDASIL® and pregnancy outcomes. Merck will also establish a pregnancy registry in the U.S. to prospectively collect data on spontaneously-reported exposures to GARDASIL® during pregnancy.

On October 5, the FDA approved a license application for FluLaval, an inactivated trivalent influenza virus vaccine. This vaccine is for immunization of persons 18 years of age and older against influenza disease caused by influenza virus types A and B contained in the vaccine. Thimerosal is added as a preservative. The vaccine is manufactured by ID Biomedical Corporation of Maryland. The vaccine was evaluated and approved in six months under FDA's accelerated approval pathway, which allows the agency to approve products for serious or life threatening disease based on early evidence of a product's effectiveness. In this case, the manufacturer demonstrated that the vaccine induced levels of antibodies in the blood likely to be effective in preventing seasonal influenza. The manufacturer will conduct further studies to verify that the vaccine will decrease seasonal influenza disease after vaccination. With the addition of FluLaval, there are now five FDA-licensed vaccines in the U.S. for the upcoming flu season.

Biologics license applications for the following vaccines are currently under review by FDA: (1) a combination DTaP/IPV/Hib vaccine (Pentacel); and (2) smallpox vaccine for persons who are at risk for smallpox infection.

On March 2, the FDA announced the availability of two draft documents entitled "Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines" and "Guidance for Industry: Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." These draft documents are intended to provide vaccine manufacturers of pandemic and trivalent inactivated influenza vaccines guidance on clinical development approaches to facilitate and expedite the licensure of influenza vaccines for the prevention of disease caused by influenza viruses. Public comments have been received and have been reviewed by the agency. The guidance documents are currently being revised and the comments received are being taken into consideration.

The FDA and CDC have updated a previous alert to consumers and health care providers regarding reports of GBS following administration of Meningococcal Conjugate Vaccine A, C, Y, and W135 (trade name Menactra), manufactured by Sanofi Pasteur. The statement was posted October 20 on FDAs/CBER's website. On October 3, the FDA approved a supplement to the Biologic License Application for Menactra revising the package insert to include a warning statement that GBS has been reported in temporal relationship following administration of Menactra vaccine. At the present time, there are no changes in recommendations for vaccination. CDC's Advisory Committee on Immunization Practices will be reviewing this information at its next meeting on October 25-26.

**Future Agenda Items**

Ms. Willner stated that she would like to address the 3-year statute of limitations in the VICP, and if someone is eligible for the $250,000 death benefit or other awards if they die after a prolonged illness. She also requested a discussion on the documents needed to meet filing requirements, and exit interviews.

Dr. Evans stated that the Program will provide the ACCV with a report of compensable and non-compensable cases, and the timeframes for adjudication of claims. He also stated that the December 5-6 meeting is cancelled due to not having enough issues to warrant a regularly scheduled meeting. The next ACCV meeting is schedule for March 7-8, 2007.

Mr. Sconyers stated that he is glad to hear that DOJ meets the Court's 15-week deadline for the settlement process in 98% of cases. Mr. Sconyers requested that data be reported to the ACCV on the mean and distribution range or standard deviation of various measures to determine the variability in the data.

The meeting adjourned at 4:08 p.m.

/S/

Don Wilber, M.D.
ACCV Chair

/S/

Marguerite Willner
ACCV Vice-Chair

/S/

Geoffrey Evans, M.D.
Executive Secretary, ACCV

03/08/07

Date