Minutes of the 67th Meeting of the
Advisory Committee on Childhood Vaccines

October 30, 2007

Members Present

Jeffrey Sconyers, J.D., Chair
Jaime G. Deville, M.D., Vice Chair
Tawny Buck
Magdalena Castro-Lewis
Margaret Fisher, M.D.
Charlene Gallagher, J.D.
William Paul Glass, J.D.
Tamara Tempfer

Ex Officio Member Present

Marion Gruber, Ph.D.
Barbara Mulach, Ph.D.
Dan Salmon, Ph.D.

Executive Secertary

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

Staff Liaison

Michelle Herzog

Welcome and Report of the Chair

Mr. Sconyers called the meeting to order, welcomed those present and introduced new Commission members:

Ms. Magdalena Castro-Lewis, National Alliance for Hispanic Health, representing the general public.

Dr. Margaret Fisher, a pediatric and infectious disease physician and Medical Director at Children's Hospital, Monmouth (NJ) Medical Center.

Ms. Charlene Gallagher, an attorney, Senior Division Counsel, Vaccine Business Unit, Wyeth Laboratories, representing industry on the Commission.

Dr. Daniel Salmon, ex-officio member, a vaccine safety specialist at the National Vaccine Program Office.

Approval of June 2007 Meeting Minutes

Mr. Sconyers invited approval of the minutes of the June 7, 2007 ACCV meeting, which was held by teleconference.

(On motion duly made by Mr. Glass and seconded by Ms. Castro-Lewis, the minutes were unanimously approved.)

Mr. Sconyers invited the report of the Director, DVIC.

Report from the Division of Vaccine Injury Compensation
Geoffrey Evans, M.D., Director

Dr. Evans reviewed the agenda for the meeting and described the informational material provided to ACCV members including an autism update from the Office of Special Masters, and a report on *Thimerosal and Autism Spectrum Disorders* by the Senate Committee on Health, Education, Labor and Pensions.

Noting that the average number of non-autism claims received annually has been between 140 and 150, the claims for 2007 spiked to 235 mainly because the two-year filing deadline for influenza vaccine injury claims (dating eight years prior to the announcement of eligibility) was July 1, 2007. The 184 claims related to that deadline were lower than expected. There has also been a slight decline in the number of autism-involving-thimerosol claims during past three years, although the rate may increase as the current autism hearings progress.

The annual awards during 2007 were the highest in the history of the program, about $91.4 million, largely because of the increased number of hepatitis B claims filed in the late 90's being adjudicated and reaching judgment. The average annual awards stand at about $564 million for the past five years, with attorney's fees and costs at about $2 million. The Vaccine Injury Compensation Trust Fund, which had recently been receiving about $200 million, took in $300 million in 2007, mainly because influenza vaccines are now covered by the VICP. About a third of the annual Trust income is derived from interest earnings.

Dr. Evans listed a number of significant activities that have occurred since the last meeting:

Dr. India Jevaji represented DVIC in an ex-officio capacity at the Advisory Committee on Immunization Practices in Atlanta on June 27-28. The Committee revised guidelines for the use of hepatitis A vaccine in children 12 months to 4 years of age. On July 25, Dr. Jevaji and Dr. Evans participated in a workgroup concerned with maternal immunization of women during pregnancy and breastfeeding. Dr. Evans stated that he

had participated as an ex-officio member at the meeting of the National Vaccine Advisory Committee in Washington on October 22-23, and had attended the Advisory Committee on Immunization Practice in Atlanta on October 24-25. Finally, Dr. Jevaji participated in a telephonic meeting of the Brighton Collaboration Working Group on July 16 (a CDC project to harmonize definitions related to vaccine safety).

On July 5, DVIC published a *Federal Register* Notice that outlined the new formula for calculating average costs of a health insurance policy. It is a key factor in determining lost earnings when an injured individual reaches 18 years of age and, as part of an award, is entitled to lost earnings compensation. The previous method overestimated average health insurance costs, which are deducted from the lost earnings award amount. The new average cost of health insurance is approaching $400 per month.

Mr. Sconyers expressed appreciation for the report and invited questions. Hearing none, he invited Mr. Rogers to present a report from the Department of Justice.

Report from the Department of Justice
Mark Rogers, J.D., Deputy Director, Torts Branch, Civil Division

Mr. Rogers reported that three attorneys had left his office and the process to replace them had begun. He added that he might again be assigned in a temporary duty status to a military command for an indefinite period of time. If so, Vince Matanoski would assume the duties of Acting Deputy Director. Mr. Rogers provided copies of his remarks to the ACCV prior to the meeting.

Providing a brief update on cases filed since the last Commission meeting, Mr. Rogers noted that 204 cases had been filed, 120 non-autism (86 influenza vaccine cases) and 94 autism cases. Anticipating the deadline mentioned in Dr. Evans' report, Mr. Rogers stated that with millions of influenza vaccinations it was difficult to estimate how many claims might be filed before the July 1, 2007 deadline. There were only 86 influenza claims filed. There were 94 autism claims filed; of those, he anticipated that many would be dismissed as untimely.

In terms of cases resolved, there were 123 claims resolved in total. Of those, 47 claims were compensated. Within that, 28 were settled mainly by mutual agreement to terms. Mr. Rogers emphasized the benefits of amicable settlement. Seven cases were compensated as a result of proffer, which is a similar agreement by the parties that must be approved by the Special Master. There were seven entitlement decisions against the Government. There were five death claims in which the Government conceded compensation based on the evidence.

Mr. Rogers stated that there were 76 dismissals. Of those, 47 were non-autism. Within that group, seven were voluntary dismissals in which the petitioner simply withdrew; and 16 were summary judgments in which a proposal is made by either party and the Special Master rules on the evidence existing in the record. In addition, there were four trials resulting in dismissal of petitioner's case. There were six dismissals for failure to

produce necessary evidence or documentation (usually by the petitioner). Those dismissals typically occur after the Special Master has provided ample time for a petitioner to develop the case but there is insufficient documentation to prosecute the claim. There were eight motions to dismiss usually for jurisdictional reasons (mainly statute of limitations problems), and six dismissals for other reasons. Of the 28 autism cases dismissed, those claims were dismissed either because the original petition was untimely, because there was a lack of documentation, or the petitioner simply asked that the case be dismissed. Finally, there was one voluntary withdrawal pursuant to Section 21(b) of the Vaccine Act., which reflects petitioner's statutory right to leave the Program if after a certain amount of time they do not want to continue with the proceedings.

Turning to developments in the autism area, Mr. Rogers explained that one key case had been tried. The case, Cedillo v. HHS, was based on the theory that the combination of MMR and vaccines containing thimerosal create a synergism to cause autism spectrum disorder. One Special Master served as the lead while two additional Special Masters also heard evidence simultaneously. The decision has not been rendered in that case yet.

There are two follow-up trials under that same theory. The case, Hazelhurst v. HHS, was completed in Charlotte, North Carolina, and the case Snyder v. HHS, is still on target for trial, November 5, 2007 in Orlando, Florida.

A series of three cases based on a second theory, that vaccines containing thimerosal alone cause autism, will be heard in Washington, DC from May 12-30, 2008. The specific petitioners have not yet been identified, however, the Government has received three expert reports from petitioners. The parties are operating under scheduling deadlines to file expert reports with the Government's expert reports due February 23, 2008.

Finally, there is a third theory of causation that MMR alone causes autism. That theory will be tested in the summer of 2008, and the Special Masters expect that all of the proceedings in all of the theories will be completed by September 2008.

In the area of appeals, Mr. Rogers noted that two cases were presented to the Supreme Court for review by petitioners. In Markovich v. HHS, the Government maintained that the 36-month statute of limitations to file a claim begins with a symptom that is determined by an objective medical standard. The petitioner claimed that the standard was subjective and could not be relied on to identify the first symptom that would start the statute of limitations clock. The Supreme Court denied the petitioner's writ of certiorari. The second case, Pafford v. HHS, involved a ruling by the Federal Circuit that it was the petitioner's burden (and not the respondent, as the petitioner claimed) to show a medically acceptable time frame linking the onset of the illness to the vaccination. The Supreme Court denied petitioner's writ of certiorari.

The Federal Circuit affirmed the Special Master's dismissal in the Marks v. HHS case. In Marks, the Special Master dismissed petitioner's claims because they were not supported by medical records or expert medical opinion. In a second case, Walther v.

HHS, the Federal Circuit agreed with the petitioner that the Special Master applied an incorrect legal standard by requiring the petitioner to eliminate other possible causes of injury. That was remanded for further hearing and is in litigation.

In the Court of Federal Claims there were five new cases, four of which were decided. In Anderson v. HHS, the Court affirmed the Special Master's dismissal of petitioner's claim because petitioner failed to provide objective evidence that petitioner's alleged vaccine - related injuries lasted more than six months, which is a requirement for compensation under the Act. In a similar case, Ruiz v. HHS, the Court affirmed the Special Master's decision to dismiss petitioner's case based on petitioner's failure to establish that the alleged vaccine-related injuries lasted for more than six months. In Ianuzzi v. HHS, the Court reversed the Special Master's award of attorneys' fees to petitioners' counsel. The Government argued, in this affirmative appeal, that some of the attorneys' fees had been incurred prior to the filing of petitioner's claim, before petitioner had retained counsel, and after judgment was issued in the case. Finally, in Hocraffer v. HHS, the Court agreed with the petitioner on appeal that the Special Master had improperly excluded certain evidence submitted by the petitioner's attorney in the damages phase of the trial and failed to properly calculate pain and suffering. That case was remanded to the Special Master for further review.

Mr. Rogers turned to the issue of the time it takes to complete a case. Mr. Rogers explained that his office reviewed every case filed during calendar year 2002 to determine whether or not each had been resolved and, if not, why. Referring to a Power Point presentation, Mr. Rogers explained that there were 772 cases filed in 2002 that were still open on October 1, 2007. Of those, 746 were autism cases that have mainly been delayed because of the process related to the current series of test cases being processed. Of the 26 non-autism cases still pending, seven were waiting for petitioner to provide an expert opinion report, 10 were in the damages phase (settling on attorney's fees, pending settlement negotiations, or rulings on entitlement), six were related to scheduling, and three were pending decisions on motions made by petitioner (to transfer case to the Omnibus Autism Proceedings) or respondent (motion to dismiss). In terms of unresolved cases, the following (broken down into areas of responsibility) represent the percent attributed to the entity that has the power to affect the delay. The Court controls 6% of the instances that require resolution to move the case forward; the respondent controls 7%, and the petitioner controls 87%.

In the 7% that falls under the purview of the respondent, about 27% is spent in developing and processing expert witness reports; about 40% is spent fulfilling the statutory requirements after receiving a petition (which must be completed within 90 days unless an extension of time is granted by the Court); and 33% is Aother,@ working on briefings assigned by the Special Masters, on settlement negotiations, or on other administrative matters.

In the 6% that falls under the purview of the Court, about 65% of the time is attributed to scheduling; and 35% of the time is attributable to the Court issuing a decision.

For the 87% that falls under the purview of the petitioner, about 44% is spent obtaining medical records (which constitutes a significant portion of petitioner's time inasmuch as the Special Masters issue orders requiring petitioner to document the case before proceeding) and 22% in obtaining expert medical/technical reports. The balance is allocated to stayed proceedings, which are ordered by the Special Master who typically issues a stay at the petitioner's request.

In summary, Mr. Rogers explained that his office and the Court had a very small opportunity to affect the speed with which cases move through the system. Primarily, the petitioner holds the key to reducing the length of time a case requires for completion.

Review of Vaccine Information Statements
Charles Skip Wolfe, National Center for Information and Respiratory Diseases (NCIRD), CDC

Mr. Wolfe expressed appreciation for the Commission's valuable counsel in reviewing the Vaccine Information Statements (VIS) as they are revised from time to time. He explained that the VIS program appears to be an important informational tool as evidenced in part by the 13 million hits on the VIS/childhood vaccination schedule on the NCIRD web site. He invited comments on the five Vaccine Information Statements submitted to the ACCV for review. He noted that all of the VISs were in circulation and that they would be updated based on NCIRD requirements and comments of the ACCV.

Mr. Wolfe explained that the varicella VIS revision was required because the ACIP had recommended a two-dose schedule for children. Dr. Fisher suggested that the word "catch up" used to describe the change might not be clear to parents, and suggested that describing it as a "new recommendation" would be appropriate. Noting that the VIS might be in existence for some time, and the term "new recommendation" might become confusing, there was also a suggestion that it include a revision date and perhaps a brief explanation for the change, including a comment that the two-dose schedule would also be appropriate for adults.

The next VIS to be reviewed was for meningococcal vaccines. This will be the first review of this particular VIS since it was just added to the injury table. There has been a change recommending use in children 2 to 11 years old. Dr. Fisher questioned why the wording has not been changed. Mr. Wolfe indicated the wording would be changed based upon the recommendation published by the ACIP.

The meeting was interrupted by an emergency egress exercise and upon resuming the meeting, Mr. Wolfe stated that, during that interruption, members of the ACCV had suggested that, under the section describing who should not be inoculated, individuals who have previously had the disease should be included. In addition, there was a recommendation that the National Vaccine Injury Compensation Program be described in some way on the VIS. Mr. Wolfe stated that the description is usually included, but can be absent when the VIS is published before the vaccine is included in the program. The next revision would include that information.

Concerning the hepatitis B VIS, Mr. Wolfe commented that the revision was similar to the varicella VIS in that the ACIP had published a recommendation that there should be a birth dose administered. In addition, there were a number of vaccination schedules in previous VISs that had been deleted, which subsequently resulted in a number of inquiries as to the reason for the deletion. Mr. Wolfe commented that the three-dose schedule would be described, but there would be an additional comment that there were other schedules that could be discussed with health care providers. He stated that the deletion of a specific reference to Baker's yeast was also deleted and that a more generic "yeast allergy" had been inserted in the contraindications section.

Mr. Wolfe stated that the human papillomavirus (HPV) vaccine VIS was the first of its kind since the vaccine had only recently been added to the injury table. He added that, because of federal legislation, even though it is not specifically relevant, a statement about the use of condoms in the prevention of sexually transmitted disease would have to be included.

Finally, Mr. Wolfe noted that rotavirus vaccine is a newly licensed vaccine, immediately covered by the program because as earlier version had been covered. He urged ACCV members who might have subsequent thoughts and recommendations concerning the VISs reviewed, to submit them at any time.

Ms. Castro-Lewis recommended that it would be appropriate to include an announcement on the standard VIS that a translation was available for Spanish-speaking individuals, and that announcement should be in Spanish. Mr. Wolfe agreed that a statement could be included at the bottom of each of the vaccine information statements.

Update on the National Institute of Allergy and Infectious Diseases (NIAID), Naitonal Institutes of Health (NIH) Vaccine Activities
Barbara Mulach, NIAID, NIH

Dr. Mulach announced that NIAID recently awarded a $50 million contract for modeling immune response, mainly in the mouse model. The research will look at the whole immune system instead of individual immune responses. The NIAID immunology group is also studying immune response in various groups of individuals (e.g., the elderly, pregnant women) to determine whether there are differences in how immune systems respond to threat and whether there are methods for improving that response in these specific groups.

Dr. Mulach announced that the *Jordan Report* had been publicly released and made available to members of the ACCV. In addition to information on specific vaccines, it includes updates on other areas of research -- influenza vaccine research, tuberculosis, malaria, vaccine supplies, adolescent vaccine schedule strategies, et cetera.

Although not specific to vaccines, the Department of Health and Human Services has released a new biodefense strategic plan that, in addition to dealing with potential

biological attack threats, includes discussion of emerging infectious diseases, strategies for therapeutic vaccines, vaccine delivery strategies (e.g., patch versus intradermal), and the potential enhancing effects of adjuvants.

Discussion of Petitioners' Satisfaction Survey
Tamara Overby, Chief, Policy Analysis Branch, DVIC

Ms. Overby explained that the Program will conduct a retrospective survey evaluation of the claims process from the perspective of the petitioner. The study is being developed in response to ACCV recommendations and the results of an OMB evaluation in 2005 that found that the Program had never conducted an evaluation, a process that should be undertaken on a regular basis. Ms. Overby stated that the evaluation questionnaire was developed and previously distributed to ACCV members as a draft. Comments received from ACCV members have been incorporated in the revised draft distributed at this meeting.

The survey will be sent to a target group of about a thousand individuals who filed claims during the past five years that were either dismissed or were compensated. The purpose is to determine what the petitioners thought of the overall process. She conceded that the survey was long (about 40 questions) and would take some time to complete, and that there was no way to estimate a response rate.

The Program does not have personal information about the petitioners, so the survey will be sent to the petitioner's attorney to be forwarded for completion. After speaking to several petitioners' attorneys there is reason to believe that the attorneys will cooperate in requesting their clients to complete the survey.

A private contractor has been hired to conduct the survey and tabulate results. A small pilot survey will precede submission of the survey to OMB for approval, a legal requirement for all surveys originated by federal agencies. She added that the survey will be available in Spanish on request.

Mr. Sconyers acknowledged the leadership of ACCV members Dr. Deville and Ms. Buck in supporting the process of moving the survey forward. During discussion, Ms. Overby affirmed that the survey would be available on the DVIC web site. It will be mailed to petitioners and a prepaid return envelope will be included in the survey package.

Report from ACCV Futures II Workgroup
Jaime Deville, M.D.

Dr. Deville discussed the full-day meeting of the ACCV's Futures II Workgroup, which first considered the safety provisions of the National Childhood Vaccine Injury Act of 1986, for which sustained funding has not been provided. Dr. Salmon was present and provided a thorough review of NVPO activities, a description of the Investigational New Drug process from early clinical studies through the Phase I, II and III clinical trials, to licensing. He covered the FDA's inspection and control process, and the various

surveillance networks that exist to track adverse events related to drugs. He discussed the interrelated activities of various federal agencies interested in drug safety, and the new effort to develop a vaccine safety plan that would be reviewed by the Institute of Medicine.

Dr. Deville stated that the Workgroup looked at the Petitioners' Satisfaction Survey, deciding that it was too long, a characteristic that might adversely affect response rate. There was discussion on how make the survey more user-friendly.

A discussion of structured settlements was postponed until a later meeting because the invited expert on the subject was unable to attend. Finally, the Workgroup discussed the administrative requirements of VICP, reaching an agreement that the flat funding for the program over the past years (of about $3 million since 1994) along with the increased financial requirements due primarily to expert witness program costs, staffing needs and the autism caseload is not sufficient. This has resulted in a detriment to some activities, such as outreach and the conduct of meetings and conferences. The issue will be on a future agenda.

Dr. Deville listed several agenda items for future meetings -- the petitioner's structured settlement issue, a review of the vaccine injury table, using the Trust Fund to fund HHS vaccine safety activities, the VICP administrative budget and program needs, and a review of the final results of the Petitioners' Satisfaction Survey.

Report on Autism Hearing from Petitioner's Attorney
Tom Powers, J.D., Williams, Love, O'Leary, Crain & Powers PC

Mr. Powers provided an update on the process by which the Office of the Special Masters will sort out how to handle over 4,800 claims alleging vaccine-related autism. Three Special Masters (Hastings, Campbell-Smith and Vowell) have been selected to hear three test cases in each of three categories based on theories of damage. It is anticipated that once the nine test cases have been heard, and decisions handed down, those decisions will provide a reasonable framework for expediting the handling of the 4,800 pending cases and any others that may be filed. Each of the Special Masters will preside over one of the three cases for each theory and write the opinion on that case; although all three Special Masters will sit en banc during each of the hearings.

The first causation theory maintains that exposure to thimerosal-containing vaccines in combination with MMR is a cause of autism (called the combined thimerosal/MMR theory of causation). The first test case, Cedillo v. HHS, was completed in June and took 12 hearing days, producing hundreds of scientific papers and thousands of pages of transcript. The second test case, Hazelhurst v. HHS, was heard in North Carolina in early October and took only four hearing days, in part because some of the product of the Cedillo v. HHS case could be applied to the case. The third case, Snyder v. HHS, will be heard in Florida in early November.

The second causation theory is that mercury-containing vaccines, whether or not accompanied by MMR vaccination, caused autism (called the thimerosal-only theory). Three test cases will be selected in November and various petitioners are beginning to develop and submit the necessary documentation to proceed. The cases will be heard in May of 2008.

The third causation theory states that the MMR vaccine, notwithstanding whether there is thimerosal present or not in the vaccine, can cause autism (MMR-only theory). Three cases will be heard by the end of September 2008.

During discussion, Mr. Powers stated that it will take at least two or three months before the briefs are available to close the Cedillo v. HHS case. Asked about whether the first three cases will affect the outcome of the other two causation theory cases, Mr. Powers suggested that there is more overlap in the MMR-only cases than in the thimerosol-only cases, and the thimerosal-only case will probably not help in the MMR-only case.

Mr. Powers noted that the Office of Special Masters has been working to develop a process to handle the thousands of claims filed once the test cases have been decided and the framework for processing cases has been defined. It appears that the Office will create groups of 50 or so cases and allow petitioners' attorneys to submit enough supporting documentation to make decisions on eligibility, mainly on the basis of timeliness of filing the original claim. The management process will be challenging, sorting out those clearly eligible, those clearly ineligible, and those in the middle which will require some effort to resolve.

Update from the National Vaccine Program Office (NVPO)
Dan Salmon, Ph.D., NVPO

Dr. Salmon briefly discussed activities at NVPO. The National Vaccine Advisory Committee (NVAC) met the week before the ACCV meeting and discussed the National Vaccine Plan, an overall strategic plan for federal vaccine activities, which includes vaccine safety and the injury compensation program. The plan development process includes public comment and review by the Institute of Medicine.

The NVAC also approved the adolescent criteria for state-mandated school vaccination schedules and intends to develop the criteria in an article for journal publication. It is one of several other recently published articles that look at the issue of compulsory vaccination.

The NVAC Safety Subcommittee has merged with the NVAC Communications Subcommittee and expanded its membership to include consultants in immunology, toxicology, neurology, epidemiology, biostatistics and pharmacology. The Immunization Safety Office of CDC is developing a research agenda that will deal with very specific hypothesis-driven research issues. The agenda will be reviewed by the Subcommittee. Another task that NVPO will ask the Subcommittee to take on is a broad review of the

current federal system for vaccine safety. NVPO is developing a comprehensive report of the federal system that will serve as a basis for the review.

Dr. Salmon commented that the ACCV might be interested in an NVPO assessment of maternal immunization -- whether or not pregnant women should be routinely vaccinated with vaccines normally made available to the public, and whether or not pregnant women should be specifically vaccinated against certain high-risk diseases that should be prevented in pregnant women.

Update on the Center for Biologics and Evaluation Research (CBER), Food and Drug Administration (FDA) Vaccine Activities
Marion Gruber, Ph.D., CBER, FDA

Dr. Gruber commented on a series of FDA drug approvals:

A Sanofi Pasteur vaccine for H5N1 avian flu was approved for persons 18 to 63 years of age, but the company will not make the vaccine available to the commercial market. The Federal Government will purchase the drug for its Strategic National Stockpile for distribution by public health officers in the event of a pandemic flu outbreak.

On August 31st, FDA approved smallpox (vaccinia) vaccine only for persons at high risk of smallpox infection. Clinical trials revealed that the vaccine is effective but there is a relatively high rate of serious adverse events, such as myocarditis, and the sponsor was required to develop a "RiskMAP" program to fully inform recipients of its potential risks.

On September 19th, FDA approved FluMist, an intranasal live attenuated vaccine for influenza for children beginning at 2 years of age. It had previously been approved for individuals 5 to 49 years of age. Since the vaccine is known to induce wheezing in some recipients, the manufacturer was required to develop a RiskMAP. It was contraindicated for children with asthma or active airway disease. Further the manufacturer, MedImmune, was required to launch a large post-marketing trial to evaluate safety signals and safety outcomes such as asthma and wheezing.

On September 28 the FDA licensed an inactivated influenza vaccine, made by an Australian company, for individuals 18 years and older. The vaccine was shown to increase immune response against the influenza subtypes present in the vaccine.

Dr. Gruber noted that there are now six manufacturers of influenza vaccines licensed in the U.S.

Finally, Menactra, which has been approved for individuals 11 to 55 years of age, was recently approved for children 2 to 10 years of age. Menactra protects against invasive meningococcal disease. Dr. Evans commented that ACIP had recommended limited use in high-risk children in the younger age group of 2 to 10 years. Routine use is not recommended.

On October 4th, FDA published a *Federal Register* Notice about development of effectiveness and safety assessments related to vaccines developed for use in pandemic situations. The question is how to conduct a safety assessment for a vaccine that is reserved for a unique disaster situation? The *Federal Register* Notice seeks interested parties who are able to develop programs that can monitor adverse events and assess efficacy following the administration of the pandemic influenza vaccine.

During discussion Ms. Tempfer asked about differences in the six influenza vaccines available and how a consumer would decide which to rely on. Dr. Gruber stated that, except for FluMist which is a live attenuated vaccine, there was little difference in the six in terms of influenza virus subtypes in the vaccine. All six have slightly different manufacturing processes and formulations. All contain thimerosal but some are available in thimerosal-free formulations, and the vaccines are approved for different age ranges.

Dr. Gruber discussed the recently passed FDA Amendments Acts of 2007 (HR 3580), which was signed into law on September 27th. It is a major law that reauthorizes the Prescription Drug User Fee Act, the Medical Device User Fee Act, the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act. Although FDA has not yet fully analyzed the law requirements and time lines, Dr. Gruber offered a number of observations.

Title IX authorizes FDA to require post-marketing epidemiological and clinical trials of already-approved drugs and to require safety-related label changes. Manufacturers may also be required to develop formal Risk Evaluation and Mitigation Strategies (REMS) for specified drugs. The FDA must have a scientific rationale to make these requirements and the studies must have a specific primary outcome -- to assess a known risk or signal of risk of drug use. And the studies may only be required if existing surveillance systems (like VAERS) are not able to assess a known serious risk or signals of serious risk. When the requirement is made, the sponsor must submit a time table for the study and describe any obstacles that may exist in conducting the study.

The FDA may determine that a REMS is required to assess whether the benefits of a drug outweigh the risks before or after the drug has been licensed. The REMS would consider the size of the drug use population, the seriousness of the disease being treated, the benefits of the drug, and what mitigation strategies would be appropriate (e.g., package inserts, letters to health care providers). The mitigation must not be a burden to the patient or inhibit reasonable access to the drug.

Dr. Gruber noted that Section 905 of the Act requires that FDA set up a surveillance system to monitor adverse events, the establishment of a "risk identification and analysis system" that would eventually involve monitoring up to 100 million individuals by 2012 from multiple sources. It will involve significant collaborating with public and private entities to provide analysis of drug safety data.

Finally, the law requires establishment of an expert committee to look at data privacy and security and to develop recommendations for the ethical use of post-marketing data.

There was a brief discussion about whether the funding provided in the law would be sufficient for the mandates.

Update on Vaccine Safety Datalink (VSD), Vaccine Adverse Event Reporting System (VAERS), and the Immunization Safety Office (ISO), CDC
Karen Broder, M.D., ISO, CDC

Dr. Broder reported on several issues discussed at the recent Advisory Committee on Immunization Practices (ACIP) meeting in Atlanta. ACIP provides guidance on immunization issues to the HHS Secretary and Assistant Secretary for Health and to the Director of CDC, particularly focusing on how to best use licensed vaccines to prevent communicable disease. It establishes a list of vaccines for distribution through the Vaccines for Children Program.

Dr. Broder briefly described the Vaccine Adverse Event Reporting System (VAERS), operated jointly by CDC and FDA, the largest passive surveillance system that derives its data from voluntary reports by physicians and private individuals, and mandatory reports from manufacturers.

The Vaccine Safety Datalink Project is a collaboration between CDC and eight large managed care organization that provide medical and immunization histories on about 5.5 million people annually. VSP also conducts research on hypotheses that are proposed internally and by outside sources.

Dr. Broder briefly discussed three areas of interest presented at the ACIP meeting -- use of FluMist in children ages 24 to 59 months; early thimerosal exposure and neuropsychological outcomes in children 7 to 10 years; and episodes of syncope reported after vaccination.

In September the FDA approved the use of FluMist in younger children 2 to 5 years of age, who were shown in pre-licensure tests to be vulnerable to an increased risk for development of wheezing after vaccination. Even with the approval, it is not recommended for children who have recurrent wheezing. The ACIP discussion pointed out that physicians might have difficulty defining recurrent wheezing in a busy clinic. ACIP voted to recommend use of FluMist in the approved age group, but to encourage providers to make an effort to determine whether a younger child had recurrent wheezing by asking the parents a proactive question about previous diagnosis or comment by a healthcare provider that the child had had that condition. In that case, the child would receive an inactivated influenza vaccine injection.

Dr. Broder referred to a September paper in the New England Journal of Medicine that described a study of children 7 to 10 years of age exposed to thimerosal at an early age to determine if there were negative effects on neuropsychological functioning -- specifically

speech and language, attention span, fine motor functioning, perception, motor and phonic tics, academic performance, and ADHD. Among 42 outcomes there were minimal significant associations with thimerosal exposure parentally or within seven months of birth. The study showed that the few negative effects were mainly in males and were mainly manifested in behavior and tics. The evidence did not support a causal relationship between thimerosol exposure and psychological functioning at 7 to 10 years of age.

The third study looked at syncope (fainting) after vaccination because it could lead to injury. Although uncommon, one form, vasovagal syncope, can be caused by the pain and/or anxiety that sometimes accompany a vaccination experience. The ACIP approved a recommendation that providers should observe those vaccinated for 15 minutes and if evidence of syncope appears, continue observation until the symptoms abate. Dr. Broder presented a graph (2004 to 2007) of syncopal events after vaccination in individuals 5 years of age and over. The graph clearly demonstrated an increase in syncopal events (mainly in females) within one day of vaccination after the approval and introduction of HPV vaccine (which is a three-dose series) in June 2006.

Dr. Broder commented that the Institute of Medicine, in a 2005 report, recommended that NVAC provide advice on the Vaccine Safety Datalink's research plan. A three-phase process was established. Currently, in the first phase the ISO is developing a draft research agenda with input from outside multidisciplinary consultants, including representatives of pharmaceutical companies, the Interagency Vaccine Group, and others. There have also been brainstorming sessions related to life stages (infants, children, adolescents, elderly, pregnant women) and a number of specific areas have been considered -- non-antigen vaccine components including adjuvants, new vaccine technology, public perception, host factors, vaccination practices, clinical outcomes including adverse events, and other areas. After the draft ISO Scientific Agenda is complete, the National Vaccine Advisory Committee will undertake a scientific review of this Agenda and advise CDC on the content and priorities. CDC will respond to the NVAC feedback and finalize the Agenda.

Public Comment

Mr. Sconyers noted that there were no requests from individuals wishing to make a public comment during the meeting.

Future Agenda Items

Dr. Evans suggested that an occasional agenda item might be entitled "noteworthy quotes by ACCV members." He proposed that the first one be a quote by Dr. Margaret Fisher:

"School children are among the group most responsible for transmission of contagious respiratory viruses, including influenza. Children are inherently more at risk because they congregate in groups. They like to share their secretions. They won't share their toys, but are happy to share their germs."

Ms. Gallagher suggested that a review of the VICP 2008 budget be included in a future agenda, especially with regard to whether there is any ACCV action that would be appropriate.

Concluding Remarks and Adjournment

Mr. Sconyers pointed out the copy of the letter in the meeting book materials that was sent to HHS Secretary Leavitt by the ACCV chair pursuant to actions taken during the March meeting. There being no further business, the meeting was concluded.

(Whereupon at 3:00 p.m., the meeting was adjourned.)