Advisory Commission on Childhood Vaccines
Meeting

March 6, 2008

Minutes

Members Present

Jeffrey M. Sconyers, J.D, Chair
Jaime Deville, M.D., Vice-Chair
Tawny Buck. (via phone)
William P. Glass, Jr., J.D.
Tamara Tempfer, RN-C, MSN, PNP
Margaret Fisher, MD, FAAP
Charlene Gallagher, J.D.
Magdalena Castro Lewis

Ex Officio Member Present

Marion Gruber, Ph.D
John Iskander, M.D., M.P.H.
Barbara Mulach, Ph.D.
Dan Salmon, Ph.D.

Executive Secretary

Geoffrey S. Evans, M.D., Director, DVIC

Staff Liaison

Michelle Herzog, DVIC, HSB, HRSA

Office of General Counsel

Elizabeth Saindon, J.D.

Introduction

Mr. Sconyers convened the 68th quarterly meeting of the Advisory Commission of Childhood Vaccines (ACCV) at 1:05 p.m. and welcomed all participants. On motion duly made and seconded, the minutes of the October 2007 meeting were unanimously approved.

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

Dr. Evans welcomed members and guests in attendance and reviewed the agenda for the two-day meeting.

Financial Report

Dr. Evans reviewed the 2007 filings for non-autism claims (239) and autism claims (167), a total of 406 claims. It was slightly higher than 2006, partly because of the Omnibus hearings in June 2007. During the first four months of fiscal year 2008, there have been 81 claims, 44 non-autism, 37 autism, which is slightly lower than the average number of filings for the same period in past years. The 2007 awards, however, were the highest in the history of the program -- $91 million versus an average of about $59 million for the past six years. Attorneys' fees were similar to past years, about $4 million.

The Trust Fund stands at $2.7 billion, having increased significantly because of the addition of flu vaccine which is distributed to a very large population, about 120 million doses annually. It is anticipated that the fund will increase by about $340 million in 2008, a little over a third of which will come from interest.

DVIC Activities

Dr. Evans updated the Commission on significant DVIC activities since the last meeting. Dr. Rosemary Johann-Liang attended the "Understanding the Genomic Basis of Vaccine Safety Workshop" in Atlanta (January 30-31). The workshop was intended to begin addressing whether there is a genetic factor in individuals that is involved in adverse reactions to vaccination.

From February 5-6, Dr. Evans represented HRSA as an ex officio member of the National Vaccine Advisory Committee. Tammy Tempfer also attended the meeting in her new role as ACCV liaison to NVAC.

On February 21, Dr. Indira Jevaji attended the FDA Vaccines and Related Biological Products Advisory Committee meeting, which considered the GlaxoSmithKline's license application for a new oral rotavirus vaccine, trade name, Rotarix. Finally, both Drs. Johann-Liang and Evans attended the February 27-28 Advisory Committee on Immunization Practices meeting in Atlanta. As reported in the media, the ACIP recommended extending the routine use recommendation for influenza vaccine from 59 months up to age 18 years, effective no later than the 2009-2010 flu season.

Autism

Dr. Evans commented that, despite reports and commentary in the media to the contrary, DVIC has reviewed data concerning the allegation that vaccines cause autism and has

discovered no credible evidence for support. He added that the 6-year anniversary of the Omnibus Autism Proceeding is in July and that the substantial amount of scientific data accumulated during this time has not shown any association between autism and vaccines.

Report from the Department of Justice to ACCV Commission
Vince Matanoski, J.D
Acting Deputy Director, Torts Branch
Civil Division, Department of Justice

Mr. Matanoski reported that he is serving as Acting Deputy Director for the Torts Branch, vaccine section while Mr. Rogers was deployed to Iraq.

Personnel

Since the last ACCV meeting, the Department of Justice (DOJ) has hired three new attorneys, but lost two. The office was in the process of hiring replacement attorneys and staff.

Statistics

Regarding cases filed, Mr. Matanoski noted that the DOJ's numbers were consistent with Dr. Evans's numbers, however, according to the DOJ statistics, there were 90 cases filed since October, 2007, the beginning of the fiscal year. Of those, 52 were non-autism and 38 were autism proceedings. Of the autism claims filed, most were "short form" filings and cases filed without the records. Eventually, more information will be needed in all of these cases before they can proceed. Since October, 2007, there were 122 cases resolved. Mr. Matanoski noted that there were about 1,000 non-autism and about 4,800 autism cases pending in the Program. Of the 122 cases resolved, 43 were compensated and of those, 38 were settled. The settlements highlight the cooperation between the Government's counsel and petitioners' attorneys. There were 79 cases dismissed (49 non-autism, 30 autism). Most dismissals were non-autism and initiated by the petitioners while a few were time-barred.

Autism

In the area of litigation, Mr. Matanoski reported that three trials involving the first theory of causation presented by the Petitioners' Steering Committee (PSC) were completed. The theory in each trial was whether the MMR vaccine causes autism and was tried in the cases of Cedillo v. HHS, Hazelhurst v. HHS and Snyder v. HHS. All of those cases are in various stages of post-trial briefing. The Cedillo case is the closest to completion, while Hazelhurst and Snyder are undergoing further briefing. In the Snyder trial, the PSC sought to obtain information from MMR trials in the United Kingdom on the presumption that the information might assist the special master in determining whether the US labs involved in testing produced valid results. The Government presented evidence from experts that appeared at the UK proceedings regarding the validity of the

lab tests. The status of the PSC's efforts to obtain the information is unclear. If they are successful in obtaining that information, a decision in Snyder may take a little longer while the special master considers that evidence. Overall, Mr. Matanoski did not anticipate any of the decisions in the first round of test cases to be issued before the second theory of causation begins. The second theory, which is whether Thimerosal in vaccines causes autism, is scheduled to start on May 12, 2008 in Washington, DC. That trial is expected to last three weeks. Both sides have filed their expert reports. Currently, the parties are in the rebuttal stages meaning that they have an opportunity to file rebuttal expert reports. Petitioners have the opportunity to file first, and then the Government will determine whether or not rebuttal evidence is warranted. Mr. Matanoski anticipates that the May 12, 2008 trial will start on time.

Regarding whether or not vaccines cause autism, there has been no change in the litigation position of the Secretary. Mr. Matanoski addressed what appears to be confusion surrounding a document that was recently put out in the media. First, DOJ policy is not to comment on cases that are pending in litigation. Because the document involves an active case, Mr. Matanoski could not discuss the contents of that document. Instead, Mr. Matanoski spoke generally about the type of document that was circulated in the media. The document is called a Rule 4(c) report, and is prepared by DOJ in litigation. In regular civil actions, a complaint is filed by a plaintiff and the defendant files an answer, which is a legal document. The Rule 4(c) Report is not a statement of scientific position or research. It is specific to the facts of a particular case filed under the Vaccine Act. The Rule 4(c) Report is used in every case that is filed in the Program. It is not specific to any class of cases. It represents communication from one party to another about a legal position taken on a case and conveys the Government's legal position on compensation in a particular case under the Vaccine Act. These documents are used by the presiding special master to understand the Government's legal position on compensation. The special master typically asks questions about the document and investigates further during the course of the proceedings, particularly when the Government takes the position that compensation is not appropriate. Mr. Matanoski emphasized that the position taken in the Rule 4(c) Report is investigated by a special master as the case progresses. In the autism cases, the Government filed a Rule 4(c) Report in every filed case even when there were no records to review. In those instances, the Government's Rule 4(c) Report noted that DOJ cannot take a position on compensation because there are not filed documents.

Regarding the course of the autism litigation, the PSC may allege new claims for compensation. The legal theories will continue to unfold during the autism proceedings. Mr. Matanoski reiterated Dr. Evans's view that there is no scientific evidence that would change the Government's position on whether or not vaccines cause autism. In fact, there is voluminous scientific evidence directly addressing that question and the scientific evidence has overwhelmingly shown that there is no connection between vaccines and autism.

Recognizing that the Chief Special Master will also address the ACCV members about the volume of cases pending in the Program, Mr. Matanoski noted that there are about

4,800 autism cases pending. Most of those cases lack documentation and/or were filed without supporting records. Within the next two years, however, those cases will be activated. That means that records will be ordered to be filed in each case so that an initial evaluation can be made on jurisdiction, as well as whether they are properly considered part of the omnibus proceeding. With the autism litigation, which is a large part of the volume, there will be about 6,000 total cases to be evaluated. So far, 200 of the autism cases have been activated. DOJ has taken steps to ensure the availability of sufficient resources to evaluate the claims, including hiring contract individuals. The case review will pose significant staffing issues for DOJ, but Mr. Matanoski believed that it will be within the present budget. Considering the increased caseload from 1,000 cases to 6,000 cases, DOJ will be reviewing future budget requests. Overall, the review process will present a huge change in DOJ's operations given the six-fold workload increase.

Appeals

In the appellate area, Mr. Matanoski discussed two decisions from the U.S. Court of Appeals for the Federal Circuit (Federal Circuit). The case, Avera v. HHS, involved attorneys' fees. Petitioners' attorney, who was located in Cheyenne, Wyoming, sought compensation of his hourly rates consistent with hourly rates paid to attorneys who prevail against the Government in certain fee-shifting statutes litigated in Washington, D.C. The rates that petitioners sought for their Cheyenne based attorney are known as Laffey Matrix rates. Mr. Matanoski explained that the Laffey Matrix is used by the U.S. Attorneys' Office in Washington, DC in certain fee-shifting statutory cases when a plaintiff prevails against the Government, and is based on Washington, DC hourly rates. The Laffey Matrix hourly rates are significantly higher than the hourly rates that petitioners' Cheyenne-based attorney would receive in Cheyenne, Wyoming. Petitioners' attorney is located in Cheyenne and performed all of his work there. In seeking Washington, DC rates, petitioners' attorney sought to apply a forum rule analysis. Counsel asserted that because all of the vaccine cases are filed in the Court of Federal Claims, which is physically located in Washington, DC, and a decision issues from the Office Special Masters, also located in Washington, DC, petitioners' counsel should be entitled to the Laffey Matrix rates. The Laffey Matrix rates represented a three-fold increase from petitioners' counsel's Cheyenne, Wyoming. A panel of three judges from the Federal Circuit heard oral argument and decided that under the facts of this case, petitioners' attorney was not entitled to the hourly rates of the forum, which it deemed to be Washington, DC. Petitioners' attorney was entitled to hourly rates consistent with Cheyenne, Wyoming, where he performed all of the work in that case. The Court did not opine upon whether or not the Laffey Matrix constituted the appropriate forum rate.

Mr. Matanoski explained that while the Court in Avera, adopted a forum rule, it applied an exception to the forum rule. Under the exception, if the "bulk of the work" is not performed in the forum (Washington, DC) and the forum rates are substantially higher than the locality where petitioner's counsel is located, then the forum rates (Washington, DC) do not apply. In the Vaccine Program, Mr. Matanoski noted that nearly every case will fall under the exception to the forum rule as most of the cases that go to hearing are

not tried in Washington, DC. Most vaccine cases are tried over the phone or in locations convenient to the petitioners rather than holding any court proceedings in Washington, DC. Most of the petitioners and their lawyers live and work outside Washington, DC. For example, a petitioners' counsel's bill might reflect that for the vast majority of time, eighty hours was spent working at the petitioners' attorney's office in Cheyenne, Wyoming, with six hours of time spent in Washington, DC for a hearing. So, under a strict or common sense interpretation of the Avera "bulk of the work" exception to the forum rule, one would say that most fees will be paid consistent with the market rates for where the petitioner's attorney's office is located and where the bulk of the work was performed. Nevertheless, Mr. Matanoski predicted that there will be a great deal of litigation to test the contours of the Avera decision and its exception to forum rule in the context of the Vaccine Act. Mr. Matanoski expects that a forum rule analysis and its exceptions will be done on a case-by-case basis and be fact specific. Notably, even if the forum of Washington, DC applied, Avera does not discuss an appropriate rate. He predicted further litigation in this area.

Also in the Avera case, petitioners' attorney also requested payment of interim fees, that is, payment of fees before the case was completed pending appeal. The Federal Circuit panel further ruled that an award of interim fees and costs was available under the Vaccine Act, however, petitioners did not demonstrate that interim fees were necessary in their case. The Court in Avera found that the Vaccine Act does not prevent an award of interim fees, however, it offered little guidance on when fees would be appropriate. Thus, Mr. Matanoski expects further litigation as petitioners and the Government attempt to determine the contours of the Court's decision. DOJ has already contacted some of petitioners' counsel, who also expressed an interest in discussing some possible parameters for seeking payment of interim fees. There was a meeting with some petitioner's attorneys to try and reach an understanding of when it would make sense for petitioners to seek interim fees without having a huge impact on the proceedings and where the Government would have an opportunity to review the request. In Avera, petitioners' counsel sought interim fees after a decision on entitlement issued and the case was on appeal. A few scenarios were discussed, including limits on the number of applications for interim fees. The goal is to keep the cases moving. Mr. Matanoski emphasized the impact on the Program, however, if there are multiple applications for payment of interim fees and costs during the course of a proceeding. From DOJ's view, instead of moving the case forward to entitlement, the parties would be involved in trying to resolve the interim fee requests. Mr. Matanoski acknowledged that he understands the views of petitioners' counsel that payment of interim fees could be very helpful to them. Mr. Matanoski emphasized that seeking interim fees on a biweekly or monthly basis could result in longer processing time for decisions. Mr. Matanoski expressed that DOJ and some petitioners attorneys were expected to continue discussions on the parameters of interim fees to try and cooperatively find common ground, however, he predicted that continued litigation would be inevitable.

Another case decided by the Federal Circuit that will impact the Program is Zatuchni/Snyder v. HHS. Originally, it was filed as Snyder but Mrs. Snyder unfortunately died during the pendency of the proceedings, and the case is currently

Zatuchni, which reflects the name of the estate. In the underlying case, petitioner was awarded compensation for her death. The Government contended that petitioner should be awarded $250,000.00, which is the cap available if petitioner's death was found to be related to her vaccine-injury. Petitioner contended that because Mrs. Snyder was alive while her claim was pending under the Vaccine Act, she should also receive compensation for her pain and suffering, as well as lost wages and past unreimbursed expenses. The special master found against petitioner and awarded $250,000.00 but issued findings on how much those damages would be if the Court of Federal Claims reversed. On appeal to the Court of Federal Claims, the judge reversed the special master, and awarded the additional damages.

After hearing oral argument, the Federal Circuit in Zatuchni/Snyder also disagreed with the special master and found that petitioner's estate would be entitled to the additional damages above the $250,000.00 available for vaccine injuries resulting in death. The Government had maintained throughout the appellate proceedings that its waiver of sovereign immunity to be sued limited the amount of damages available to $250,000.00. The Federal Circuit did not address that argument other than to note, in a footnote, that they found the terms of the Vaccine Act to be clear in awarding additional damages. The holding by the Federal Circuit in Zatuchni/Snyder is fairly limited to the facts inasmuch as it would apply where a person filed a claim for vaccine-related injuries, received a favorable ruling that the injuries were vaccine-related, and then died before receiving compensation for those injuries. That fact pattern is rare in the Program. Also, the opinion was a split decision meaning two judges in the majority and one who concurred with the result but not the reasoning. The concurring judge agreed that petitioner was entitled to the additional injury-related damages but for different reasons and disagreed with the entire majority opinion. Mr. Matanoski remarked that essentially there are two diametrically opposed decisions within one opinion that reach the same result. It is unclear whether or not DOJ will seek further review by the Federal Circuit en banc or rehearing; the Solicitor General of the United States makes that determination. A rehearing en banc means that all of the judges sitting on the panel would hear the case along with the original panel.

Mr. Matanoski also discussed another case decided by the U.S. Supreme Court that impacts vaccine cases, J.R. Sand & Gravel v. U.S., involving a question of jurisdiction. The Supreme Court reaffirmed the established rule on jurisdiction. Under the Vaccine Act, a case that is untimely filed lacks jurisdiction at the inception of the filing and should not have been filed. Pending before the Federal Circuit but not yet decided is Mojica v. HHS, which was brought by petitioner. In Mojica, the petition was filed one day late because of an error entirely attributed to Federal Express delivery. There, the judge, Court of Federal Claims, held that the special master correctly dismissed petitioner's case for lack of jurisdiction. Even under those circumstances, the Court of Federal Claims found that equitable tolling did not apply afford jurisdiction.

Another jurisdictional issue was decided by the Court of Federal Claims, in Kay v. HHS. There, the judge, Court of Federal Claims, found that the special master correctly denied petitioners' request for fees and costs after dismissing their claim for lack of jurisdiction

because the petition was time-barred. Petitioners have not yet filed an appeal to the Federal Circuit. Mr. Matanoski generally noted that there were several other fact specific appeals pending and decided by the Court of Federal Claims.

Questions

In response to a question from Ms. Tempfer regarding a newspaper article, Mr. Matanoski clarified that no autism rulings have been issued. Ms. Buck observed that the ACCV had unanimously recommended the payments of interim attorneys' fees and appreciated the Government's efforts to work with petitioners' attorneys on implementing that process. She further observed that the ACCV recommended paying both death benefits and lost wage damages should a petitioner die before the case is decided. Mr. Matanoski predicted that the result of Zatuchni/Snyder will be more litigation and offered a few different scenarios of what areas will be litigated in terms of compensation for death benefits and lost wages.

Omnibus Autism Proceedings Update & Implications of the Causation Standard in the Program
Chief Special Master Gary Golkiewicz

Chief Special Master Golkiewicz presented information on the following topics:

- Causation Standard
  - Policy-based versus traditional tort-based
  - Recent Federal Circuit opinion – leans heavily towards setting a standard whereby more cases are compensated
  - HHS policy – recommendations to change table a balancing act between basing changes on science versus public policy
  - Federal Circuit – "Althen" three-part test for establishing causation.
- Workload
  - Two goals of Act – reduce liability of those manufacturing and administering vaccines; and to provide compensation to those individuals who were injured as a result of a vaccine.
  - Major issues with current process is the time it takes to complete a claim
    - Building of cases including obtaining medical records
    - Scheduling – coordination of activities among all key players
    - Damages phase – disagreements can result in additional litigation and negotitation
  - Possible solutions
    - Alternative Dispute Resolution
    - Program to identify similar cases
- Autism
  - 4,800 cases pending
  - Petitioners advised to hold off filing medical records
  - Timeliness review – 200 month

- Unknown – what Federal Circuit will do with the recommendations from the test cases.

Please see the meeting transcript for Chief Special Master Golkiewicz's full presentation.

Discussion of Newly-Added Vaccines to the Vaccine Injury Table
Rosemary Johann-Liang, M.D.

Dr. Johann-Liang reported that four new vaccines had been added to the Vaccine Injury Table: hepatitis A (2004), influenza (2005,), human papillomavirus (2007) and two meningococcal vaccines, conjugate and polysaccharide (2007).

Since licensure of hepatitis A vaccine, there has been a 70 percent decline in disease, with the largest declines among children. The adverse events reported were minor. There was one report of Guillain Barré syndrome (GBS) in 2005. There have been no recent claims filed for this vaccine.

Influenza vaccine reports have been mostly minor adverse reactions -- soreness at the injection site, various systemic events that occur within a few hours that may persist for a few days (fever, malaise, myalgia, etc.). In the very young, less than 5 years of age, the reported rate is about 11%, falling to 4-5% in children 6 to 10, and in adult studies there has not been a significant difference between placebo controls and subjects who received the vaccine.

An Institute of Medicine study released in 2006 concluded that there was no causal relationship between the influenza vaccine and neurological disorders, such as incident and relapsing multiple sclerosis, nor any proven evidence of causation for GBS. Two Canadian studies reported conflicting results for GBS, so a definitive epidemiological answer has been elusive.

The live attenuated influenza vaccine, which contains the same three antigens and other components (except thimerosol) that are in the trivalent inactivated vaccine has seen a few serious adverse events reported, including GBS, anaphylactic shock and some asthmatic exacerbations, particularly in younger children. When the flu vaccine was added to the Vaccine Injury Table there was a sharp increase in claims filed, which continued until the deadline for filing in 2007. It is of note that, of 195 claims filed, only 20 were for children under age 20. The injuries for those claims were mainly neurologic complications and pain.

There was media coverage in 2007 for the human papillomavirus vaccine (HPV) which resulted in a tripling of VAERS reported adverse events, but relatively few serious outcomes were reported. No adverse event related to death could be causally linked to HPV. There have, however, been a significant number of reports of syncope that are temporally related to HPV mainly among adolescent girls, but a causal relationship is still under investigation. Older women, up to 45 years of age, are beginning to receive HPV and the adverse events reports appear to be similar to those among the adolescents.

Finally, the meningococcal conjugate vaccine, Menactra, was approved in June 2005 for those 11 to 55 years of age. In 2007, vaccine use was lowered to 2 years of age, although because of a number of reasons not related to safety, (economic considerations, the fact that new vaccines specifically for infants are close to approval) there was a recommendation to administer the vaccine only to high risk children 2 to 10 years of age. It was observed that meningococcal disease is rarely seen in children age 2 to 5, and really does not appear in any significant way until the middle teens.

During discussion, Dr. Johann-Liang clarified that only the vaccines had been added to the Vaccine Injury Table, and not any specific adverse events. Potential injuries, if any, must await further post-licensure experience.

Vaccine Safety Datalink (VSD)
John Iskander, M.D., M.P.H.
Associate Director for Science, ISO, CDC

Dr. Iskander explained that the Vaccine Safety Datalink (VSD) is the national active national surveillance program for vaccine safety, located at eight HMO's around the US and capable of conducting vaccines studies on both adults and children. A new development is the Rapid Cycle Analysis (RCA) process. Previously retrospective studies were updated every 6 to 12 months; the RCA conducts targeted studies that can be updated weekly. Target adverse events are selected based on VAERS reports, the biologic characteristics of the vaccine, and issues that may have arisen during pre-licensure testing.

For example, pre-licensure testing revealed that a combination of MMR and varicella vaccine (known as MMRV) may cause an increased incidence of fever. A preliminary look at MMRV given alone versus MMR and V given separately did show 2 times the likelihood of causing fever 7 to 10 days after vaccination. Based on this rapid cycle analysis, the ACIP changed its position from preferring administration of the MMRV to a neutral position on either form of administration, in combination or separately. Another recent study published in *Pediatrics* indicated a possible low risk (1 in 40,000) of thrombocytopenia following MMR administration. However, the study revealed no other acute or long-term complications..

Finally, RCA was applied to the incidence of intussusception related to Merck's rotavirus vaccine, RotaTeq, and the result was that intussusception was no more likely to occur after vaccination than by chance alone.

During discussion, Dr. Iskander commented that the live, attenuated MMR vaccine might have similar adverse effects to mumps, which could include loss of hearing. There were some VAERS reports of loss of hearing, but the data was insufficient to conclude that the vaccine as a causal factor. Therefore, it would be appropriate to consider a controlled study to look at the issue.

Vaccine Adverse Event Reporting System (VAERS) Update
Jane Woo, M.D.

Dr. Woo stated that the National Childhood Vaccine Injury Act mandated the establishment of a reporting system, which became the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system to collect data on adverse events after vaccination. . Reports are submitted by health care providers, vaccine recipients, vaccine manufacturers, and other interested parties. Between 15,000 to 20,000 such reports are received each year.

FDA medical officers review the reports, looking for patterns for vaccines in general and specific vaccine products, as well. Strength of VAERS include timeliness of the data, the ability to determine rare adverse events, lot-specific safety assessment, hypothesis generation, and national and international coverage. Weaknesses of VAERS include under-reporting (some doctors, for example, do not submit reports), over-reporting (e.g., by a media blitz), uncertain number of vaccine doses administered, incomplete reports, and the absence of an unvaccinated control group. .

Concerning specific adverse events, Dr. Woo mentioned that 28 cases of Guillain Barré syndrome have been confirmed among adolescents who received Menactra®. The number of reports is consistent with the number that would be anticipated in the general population. A large study sponsored by the manufacturer will include 10 million people and may help to estimate the risk.

Dr. Woo discussed VAERS reports of syncope after adolescent vaccines, including a phenomenon known as convulsive syncope (fainting accompanied by seizure activity (although it is not a specific seizure disorder). The risk appears to be higher after the simultaneous administration of multiple vaccines. The recommendation that patients be observed for about 20 minutes, in case of an allergic reaction, could also prevent falls and injuries due to syncope.

Finally, FluMist® is now licensed for influenza prevention in health people 2-49 years old. A large post-marketing study will be used to evaluate the safety of the vaccine in children 24-59 months old, with particular emphasis on asthma, allergic reactions, and neurological disorders.

During the discussion, Dr. Woo commented that, although individuals in foreign countries may report adverse events to VAERS, they typically do not. The FDA can encourage, but not enforce, reporting in the medical community. It was noted, however, that the Act mandates physician reporting for certain adverse events. Through web alerts, the FDA and CDC can inform the community of specific concerns and ask people to send reports. Dr. Salmon noted that even the legal requirement to distribute Vaccine Information Statements is admittedly ignored by 40% of those who administer vaccines.

The number of reports to VAERS for individual vaccine lots varies, but lots with a large number of reports do not necessarily have an increased risk of adverse events. Lots vary

in size, so variation in the number of reports per lot based on coincidental events occurring after vaccination is to be expected. FDA looks not only at the number of events per lot and the lot size, but also the type of events and any unusual or unexpected patterns in clinical or demographic characteristics. Dr. Woo stated that, since she has been at the FDA, no vaccine lot has been definitely proven to cause specific adverse events. In addition, while manufacturers report the number of vaccines doses that have been distributed, the number of doses that are administered is not always known. Finally, Dr. Woo noted that VAERS does not conduct clinical trials, but works with CDC and the manufacturers to help design studies that will address potential safety concerns.

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

Dr. Salmon explained that the National Vaccine Advisory Committee had changed its structure to rely on working groups rather than subcommittees to develop recommendations. The Safety Working group will be composed of appointed NVAC members who have expertise in the field, plus a number of consultants from different disciplines, including child and maternal health, epidemiology, genomics, toxicology, neurology and others. There are five members who were also involved in the recent IOM Immunization Safety Review Committee. Finally, he noted that ACCV member, Tawny Buck, was on the working group, as one of two representatives of parents of affected children.

The working group has two main objectives. The first, which came out of the IOM report, is to develop the framework of a research agenda for the Immunization Safety Office project. The second is to look at the entire federal vaccine safety system as to how it could optimize vaccine safety, reduce adverse events, and improve the confidence of the American public in the safety of vaccines.

The first objective will require the CDC to conduct an information-gathering process from which the CDC will develop a draft research agenda. Then, that draft will be reviewed by the NVAC working group, which will make recommendations for prioritization. Then the CDC will develop the final agenda.

The second charge, to review the national system, has resulted in a relatively large review report prepared by the NVPO of what the national vaccine system looks like today. That report will be submitted to the NVAC Working Group on Vaccine Safety and Communications, which will develop a plan for what the system ought to be. The entire process should be competed within about 18 months. Dr. Salmon mentioned that the NVPO working group will have an open meeting on April 11 as part of the information-gathering process.

Finally, Dr. Salmon mentioned that the NVPO is beginning to work on maternal immunization with the objective of developing a report on future activities.

Update on the Immunization Safety Office (ISO/CDC)
John Iskander, M.D.

Dr. Iskander explained that the ISO (which includes VSD and affiliation with the Brighton Collaboration) is responsible for scientific surveillance and research related to vaccine safety. He added that the NVPO was more of a policy office, charged with coordinating federal vaccine activities.

He described an example of research, a study of the varicella vaccine involving more than 50 million distributed doses. The study revealed four confirmed cases of neurological illness which occurred more than six months after vaccination, and all the children involved recovered. A second study involved vaccines which contained thimerosol versus vaccines that did not. The study showed no evidence of local infection or hypersensitivity in either vaccine. He added that new data shows that ethyl mercury, a byproduct of thimerosol metabolism, is rapidly excreted after vaccination.

Concerning GBS, he stated that the results of the Harvard Pilgrim study, previously mentioned by Dr. Woo, should be available in 2009. Also, an NVPO-sponsored animal study at the University of Pennsylvania showed that swine flu vaccine does induce antibodies that may be related to GBS, and further studies are planned. Non-federal scientists, looking at VAERS data, have suggested that vaccines other than influenza vaccine could be associated with GBS. The ISO pointed out some weaknesses in the study design in a published letter to the editor. Finally, there were over 2,500 VAERS reports on Gardasil, the quadrivalent HPV, including some that reported serious adverse events of death, GBS and deep vein thrombosis. Analysis of the VAERS data showed no evidence of causation. Nonetheless, the reports generated some media response.

Concerning a Hib vaccine recall, the recall was based on contamination of the vaccine manufacturing equipment; there was no contamination of the vaccines, nor were there any reported infections.

Finally, Dr. Iskander stated that the ISO was beginning to look at stage-of-life factors related to vaccines -- infants, children, adolescents, adults. A number of independent scientists and consultants providing input into a 5 year scientific agenda have suggested a wide range of issue that could be examined.

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

Dr. Mulach briefly referred to the thimerosal-containing vaccine study mentioned by Dr. Iskander, adding that it was conducted in Argentina and that there was evidence that the thimerosal was rapidly excreted in the children's urine and feces. These results were published in the February 2008 issue of Pediatrics (1). In addition, recently NIH-supported researchers at UC-Davis conducted a study to try to replicate the results of a toxicological study of mice exposed to thimerosal. The initial study by Horning et al

indicated that the mice exposed to thimerosal exhibit altered behavior and neurological changes. In contrast, the results of the UC-Davis study do not indicate pervasive developmental neurotoxicity following vaccine-level thimerosal injections in this strain of mice (2).

References:

1. Pichichero ME, Gentile A, Giglio N, Umido V, Clarkson T, Cernichiari E, Zareba G, Gotelli C, Gotelli M, Yan L, Treanor J. Mercury levels in newborns and infants after receipt of thimerosal-containing vaccines. Pediatrics 121(2):e208-214 (2008).

2. Berman RF, Pessah IN, Mouton PR, Mav D, Harry J. Low-level neonatal thimerosal exposure: Further evaluation of altered neurotoxic potential in SJL mice. Toxicol. Sci. (2008) 101:294-309.

Update from the Center for Biologics, Evaluation and Research (CBER/FDA)
Marion Gruber, Ph.D.

Dr Gruber reported that, since the last ACCV meeting in October 2007, there were no new vaccine approvals. Biologics license applications for the following vaccines are currently under review by FDA: human papillomavirus vaccine, a Diphtheria and Tetanus Toxoids Adsorbed combined with Inactivated Poliomyelitis Vaccine (Pentacel) as well as a rotavirus vaccine (Rotarix) manufactured by GlaxoSmithKline Biologicals. The proposed indication for Rotarix is for the prevention of rotavirus gastroenteritis caused by G1 and non-G1 types (including G2, G3, G4, and G9) when administered as a 2-dose series to infants 6 to 24 weeks of age. For this vaccine safety and efficacy data were presented to the FDA Vaccines and Related Biological Products Advisory Committee on February 20, 2008.

On February 21, 2006, the FDA Vaccines and Related Biological Products Advisory Committee met to consider which influenza viruses should be included in vaccines for use in the 2008-2009 influenza season in the US. Based on surveillance data, responses to current vaccines and availability of strains and reagents, the committee recommended that influenza vaccines for 2008-2009 should be trivalent and also recommended three strain changes compared to the influenza vaccine used in the 2007-2008 season:

Influenza A (H1N1)
- Replace current vaccine strain with alternative H1N1 isolate
  - A/Brisbane/59/2007 (H1N1)-like virus

Influenza A (H3N2)
- Replace current vaccine strain with alternative H3N2 isolate
  - A/Brisbane/10/2007 (H3N2)-like virus

Influenza B
- Replace current vaccine strain with alternative

- B/Florida/4/2006-like virus

The influenza vaccine compositions to be used in the 2008-2009 season in the US are identical to those recommended by WHO February 13, 2008. FDA is currently discussing licensure pathways for quadrivalent influenza vaccines. ACCV participants remarked that the influenza vaccine distributed in the 2007-2008 season was less effective. Dr. Gruber noted that during the 2007-2008 influenza season new influenza strains began to emerge that did not fully match the vaccine strains. The challenges in making decisions regarding what strains to include in the annual vaccines were briefly discussed. Decisions makers need as much time as possible to gather relevant data but that time may impinge on the manufacturing timelines and requirements. The final decision on what influenza strains to include in the annual influenza vaccine is often based on an educated guess.

Public Comment

Mr. Sconyers invited public participation in the meeting. There were no requests by members of the public to comment.

Advisory Commission on Childhood Vaccines
Meeting

March 7, 2008

Minutes

Members Present

Jeffrey M. Sconyers, J.D, Chair
Jaime Deville, M.D, Vice-Chair
Tawny Buck. (via phone)
William P. Glass, Jr., J.D.
Tamara Tempfer, RN-C, MSN, PNP
Margaret Fisher, MD, FAAP
Charlene Gallagher, J.D.
Magdalena Castro Lewis

Ex Officio Member Present

Marion Gruber, Ph.D
John Iskander, M.D., M.P.H
Barbara Mulach, Ph.D.
Dan Salmon, Ph.D.

Executive Secretary

Geoffrey S. Evans, M.D., Director, DVIC

Staff Liaison

Michelle Herzog, DVIC HSB, HRSA

Office of General Counsel

Elizabeth Saindon, J.D.

Unfinished Business from Day One

Mr. Sconyers opened the meeting and invited members to bring up issues related to the preceding day's proceedings.

Mr. Glass referred to an article in the reference materials handout (reference 9.3, Schecter) that stated that thimerosol-containing influenza vaccine from multi-dose vials had been recommended for children age 6 to 23 months. Dr. Iskander confirmed that the recommendation from ACIP was that infants 6 to 23 months of age should receive flu vaccine, but the recommendation did not specify the type of vaccine. Dr. Evans noted

that only Sanofi-Pasteur manufactures a thimerosol-free flu vaccine (about 6 million doses a year), but had had difficulty in effectively distributing the vaccine such that a portion of each year's production remain unused.

Dr. Iskander suggested that most pediatricians would order thimerosol-free vaccine (although only about half of the children receive vaccinations from their physicians). The distribution system is complicated -- it involves the need to order right after the flu season and the doctor's distributor may not know who the manufacturer will be months later. Availability can be uneven geographically and even the CDC's FluFinder program may not be able to help move thimerosol-free vaccine efficiently.

There was a brief discussion about the premise that, with the removal of thimerosol from children's vaccines, incidence of autism should decline. But it was noted that the diagnostic parameters are expanding and the sophistication of diagnosis is increasing so that the rate could well continue to increase. Mr. Glass commented that thimerosol in flu vaccine could confound the premise. He added that the diagnosis of autism is an evolutionary phenomenon and that parents have often experienced significant delays in finally receiving a definitive diagnosis. He expressed concern that statements from the government and in the press that claim children's vaccines are thimerosol-free are misleading, and the words "except for influenza vaccine" should be added as a caveat. Ms. Buck agreed, noting that parents should have the option of choosing a thimerosol-free vaccine and that there should be sufficient education to allow an informed decision in that matter. Ms. Buck requested information be provided on the price to practitioners who requested thimerosal-free vaccines and how it differed from regular vaccines.

On another matter, there was a request that a legislative update be provided. Dr. Evans stated that there had been little activity on the Hill since the last ACCV meeting. Two bills have been introduced in Congress -- the Mercury-Free Vaccines Act (H.R. 881) and the Comprehensive Comparative Study of Vaccinated and Unvaccinated Populations Act (H.R. 2832). There has been no further action.

Report from the ACCV Future II Workshop
Jaime Deville, M.D.

Dr. Deville reported that the working group had been interested in four issues. The first is how the VICP is responding to the needs of minority populations in terms of how they access the program benefits. This is being addressed through the administration of the Petitioners' Satisfaction Survey.

The second issue is structured settlements, how monies are paid, and how the Department of Justice appoints brokers to arrange the payments. The working group became aware that a significant proportion of the structured payments are handled by a single broker. It was reported that petitioners are concerned about their rights in deciding who makes arrangements for the settlements. There was an observation that, although the Department of Justice had previously provided a briefing on this issue, it was not possible

to obtain a petitioners' attorney perspective. The individual who had brought this issue to the workgroup's attention declined an invitation to present.

The third issue was the fact that the administrative budget of the VICP had not increased in a number of years. That issue became moot when a sizeable increase in that budget was approved.

Finally, the working group was concerned that sufficient funding was not provided for research related to vaccine safety. Four alternatives were discussed. First, for the ACCV to request that the Secretary devote a portion of the HHS budget to vaccine safety research; second, that a small portion of the Trust Fund be diverted for vaccine safety research; third that interest on the Trust Fund be used for vaccine safety research; and fourth, that a new excise tax on vaccines be established, the income from which would be devoted to vaccine safety research. There was a brief discussion of the various proposals, which made it clear that there was a lack of consensus as to how the issue should be approached. Limitations on direct partnerships between the government and private sector were discussed, although it was conceded that there has been significant public-private partnership under which information has been shared, an approach that could be helpful.

There was a suggestion that the issue should be brought to the full Commission as a future agenda item, and there was some concern expressed that the proposal could be outside the charter of the Commission. Mr. Sconyers suggested that one approach would be to develop a series of alternative proposals for the full Commission to consider, rather than focus on the narrow issue of increased vaccine safety research. He expressed appreciation to Dr. Deville and Ms. Buck and the working group members for their contributions to the process

Petitioners Satisfaction Survey
Rebecca Ledsky
Altarum Institute

Ms. Ledsky briefly described the process by which a petitioner's satisfaction survey was developed. The Office of Management and Budget requires a periodic evaluation of every federal program, and Altarum was hired to facilitate that evaluation for the DVIC. The first step was to develop an evaluation feasibility study that would be followed by a specific evaluation. The product of that effort was to assess whether petitioners who completed the claims process were satisfied with the outcome. Survey questions included how the individual learned about the program, how the claims process worked, the outcomes of the process (award and payment, the role of the life care planners), and how the claimants felt about the various players in the process (the DVIC, the Department of Justice attorneys, and the special masters).

The survey will go to anyone who completed the process, with or without a positive award outcome, in the last five years, a total of about 700 individuals. The survey would be self-administered, either in writing or online, and would be anonymous. Although not

required, space is provided in the questionnaire for individual to expand responses with written comments. A Spanish language version would be available. After four months, the anonymous data would be analyzed and a report would be prepared for the DVIC.

The survey will be distributed in the spring and summer so that the report can be written by October. Its purpose is to provide baseline data to reflect what the DVIC is accomplishing currently.

During discussion, there was a comment that some individuals might prefer to respond in person, perhaps in a telephone conversation and there was a recommendation that the Spanish language version be included in the original transmission of the survey, and not just "made available." In addition, the Spanish language versions should be reviewed by an individual familiar with the issues related to vaccine safety and the DVIC, and not just a professional translator. Mr. Sconyers requested that the report be available for the December Commission meeting.

Election of Chair and Vice Chair

Mr. Sconyers invited nominations for Vice Chair and Chair for the next annual term of office**.**

(On motion duly made by Mr. Glass and seconded by Dr. Fisher, Ms. Tawny Buck was elected Vice Chair by unanimous acclamation.)

(On motion duly made by Ms. Tempfer and seconded by Dr. Fisher, Mr. Sconyers was elected Chair for a second consecutive term by unanimous acclamation.)

Public Comment

Ms. Tempfer suggested that the fall Commission meeting be scheduled to coincide with the November 19th Judicial Conference.

Mr. Sconyers noted that there were no requests for public comment.

Future Agenda Items

Mr. Sconyers stated that several suggestions for future agenda items had been made during the course of the meeting. There was a request that the CDC provide an orientation presentation to familiarize Commission members with the CDC web site. He added that a discussion of the structured settlement issue and the appointment of brokers would be considered for the agenda, and that the minutes of the working group concerning those issues would be provided in advance. Similarly the working group minutes related to future vaccine safety research, as well as a copy of the Commission's charter would be sent to members so that a discussion of that issue could be included on the next agenda. Finally, he noted that a speaker would be invited to discuss the issues

related to thimerosol-free and thimerosol-containing influenza vaccine and its use in the pediatric population.

Ms. Castro-Lewis requested that an agenda item be considered that would update the Commission on the state of vaccine safety research and its future direction.

Mr. Sconyers requested that the Commission establish an agenda committee to work with Dr. Evans' office to develop appropriate agendas for future meetings.

Adjournment

Dr. Evans announced that Tamara Overby would be leaving the DVIC after six years, to serve as Division Director for the Division of Applications and Awards in HRSA's Bureau of Clinician Recruitment and Service. He congratulated Tamara on her promotion.

On motion duly made and seconded, there was unanimous agreement to adjourn. The meeting adjourned at 12.20 p.m.

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Jeffrey Sconyers, J.D. ACCV Chair	Jaime Deville. M.D. ACCV Vice-Chair
_____	_____
Geoffrey Evans, M.D. Executive Secretary, ACCV	Date