Advisory Commission on Childhood Vaccines

June 9-10, 2011

Day One

Minutes

Members Present

Sherry K. Drew, JD, Acting Chair
Charlene Douglas, Ph.D.
Kristen Feemster, M.D.
Thomas Herr, MD
Sarah Hoiberg
David King
Ann Linguiti Pron, MSN, CRNP, RN
Jason Smith, J.D.
Michelle Williams, JD

Executive Secretary

Geoffrey Evans, M.D., Director, DVIC

Staff Liaison

Andrea Herzog, Principal Staff Liaison

Agenda Item: Welcome, Report of the Chair and Approval of Minutes

Ms. Drew, Acting Chair, called the meeting to order, noting that both days of the meeting would be conducted via teleconference. She welcomed all in attendance to the 79th meeting of the ACCV. She invited approval of the minutes of the March 2011 meeting. In preliminary discussion, Ms. Hoiberg commented that some of her constituents had expressed displeasure over the Commission's deferral of action with regard to deciding on a recommendation to the Secretary to add an injury to the Vaccine Injury Table, noting that it was a misconception that the Commission had disapproved such action. For the benefit of those in the public who may read the minutes, she felt that the record should show that the Commission's decision was a deferral of action until the Institute of Medicine report was received, which would include a discussion of Guillain Barre Syndrome (GBS) that would contribute to the final decision and recommendation.

Mr. King noted that the minutes indicated that a new chair would be elected at the June meeting, but that action was not on the current agenda. Ms. Drew explained that, in discussion with Dr. Evans, since the process involves a written vote, a process not amenable to a teleconference setting, that the election of the new chair would be deferred until the next ACCV meeting.

Finally, there was a minor typographical error identified on page 8, which was corrected. On motion duly made and seconded, the minutes of the March 3-4, 2011 meeting were unanimously approved.

Report from the Division of Vaccine Injury Compensation,

Dr. Geoffrey Evans, Director, DVIC

Dr. Evans welcomed those present on the telephone to the 79th meeting of the Commission, and explained that the teleconference was not a precedent, but that several prior meetings have been conducted in a similar fashion. The most recent teleconference was in July 2010, during which revisions to Vaccine Information Statements were discussed. It was felt that the agenda for this meeting was

conducive to a teleconference format, that it would be less costly than an on-site meeting, and that time would be saved for members since travel would not be required.

Dr. Evans announced that Ms. Patricia Campbell-Smith, the newly appointed Chief Special Master, had contacted him to indicate that she planned to attend the September meeting to meet the commissioners. With regard to DVIC personnel, he noted that Kay Cook had moved on to a position with the Bureau of Primary Health Care in the Office of Administrative Management, and that two new members of DVIC were now in place in the Medical Analysis Branch – Cdr. Karen Williams, a pharmacy officer, and Dr. Marcia Gomez. Dr. Gomez will also be involved in management of the Commission, working with Andrea Herzog.

Turning to the numbers, Dr. Evans commented that, at the current pace, the number of petitions filed in the fiscal year should be over 400, similar to the 447 filed in FY 2010. Similarly, adjudications are on a track to approximately match FY 2010, with non-autism about the same as the year before, and the number of dismissals for autism cases standing at 104, a figure that would not match the numbers to be presented by the Department of Justice. Dr. Evans explained that the two offices look at different timeframes with regard to petitions and adjudications. There was a brief discussion about whether or not the numbers could be brought into harmony, a subject that has been raised a number of times in the past, with agreement between DVIC and the Department of Justice that each method serves a purpose, as long as the differences are clearly understood. However, at the request of members of the Commission, Dr. Evans agreed to look into the possibility of aligning the statistics more closely.

Finally, Dr. Evans pointed out that settlements have become more important in concluding cases, a process by which the two parties involved work out a jointly acceptable conclusion to a case, including agreement on compensation. The Special Master must still approve the settlement, but the process is more efficient and usually faster. However, Dr. Evans pointed out a slight increase in the number of claims that the Department is not conceding and is defending such that the Special Master makes the final determination of the validity of the claim and the entitlement, if any. Settlements, though, do continue to resolve over 70% of cases.

The Program has awarded over $120 million to petitioners, which is about on track with FY 2010. However, attorney's fees at $11.7 million thus far, are above last year's awards, mostly because of the increased number of autism cases that have been dismissed as a result of the rulings in the Omnibus Autism Proceeding. The Trust Fund stands at just under $3.3 billion, and net cash flow continues to be positive, although at a lower rate partly because of the economic conditions that affect interest rates. The large number of influenza doses which are subject to excise tax has helped keep the net cash flow positive.

Dr. Evans mentioned several activities that occurred since the last meeting, including attendance of DVIC staff at the National Association of Pediatric Nurse Practitioners meeting in Baltimore in March; and attendance at the oral argument in *Cloer* v. Secretary of DHHS held in the U.S. Court of Appeals for the Federal District on May 10. Dr. Evans indicated he would attend the National Vaccine Advisory Committee meeting on June 14-15 (Dr. Charlene Douglas will also attend as ACCV liaison to that group); and the Advisory Committee on Immunization Practices (ACIP) on June 22-23.

Finally, Dr. Evans provided contact information for those who were interested in contacting his office.

Report from the Department of Justice

Vincent J. Matanoski, J.D.
Acting Deputy Director, Torts Branch, Civil Division, Department of Justice
Power Point Presentation Summary

Mr. Matanoski referenced the Power Point materials, entitled June 9, 2011 Department of Justice Power Point Presentation (DOJ PP), as part of his presentation.

Statistics

Mr. Matanoski began his presentation discussing statistics. He noted that there may appear to be differences in the statistics reported by HHS and DOJ. These differences could be attributable to the different time periods each organization was examining. Regardless, the differences engendered confusion. Mr. Matanoski offered that, before the next meeting, HHS and DOJ would discuss how they could better present information for future presentations. Mr. Matanoski expressed confidence in DOJ's statistics, and welcomed any questions about his presentation.

Mr. Matanoski stated that in the last reporting period (February 1, 2011 through May 15, 2011), 106 new petitions were filed. (DOJ PP, p. 2). The majority of new cases were adult cases. Mr. Matanoski commented that when the Program was new, most cases involved children, but the addition of the influenza vaccine to the Table changed the demographics of petitioners, resulting in more cases brought by adults because that vaccine is administered to such a broad cohort of individuals. The administration of the influenza vaccine also accounts for the increased number of filings in the Program. Although the influenza vaccine is usually administered in the fall and winter, it does not appear that the filing of petitions track seasonal trends. Holidays, more than anything else, seem to affect when a petition is filed. Mr. Matanoski remarked that fewer cases were being filed just before the statute of limitations expired, and thought that this might be due to a more active petitioners' bar and better awareness of the Program.

Turning to the remaining statistical slides, (DOJ PP, pp. 3-4), Mr. Matanoski addressed a few significant trends. In the last reporting period, 79 cases were not conceded by HHS, and most of those cases (73) were settled by a stipulation. This represents a very viable and active form of alternative resolution of cases. Mr. Matanoski explained that in a settlement, each party decides that it is in their best interests to settle the case. This is based on a number of factors, and not all of them are linked to the strengths or weaknesses of a case. A stipulation represents a compromise wherein both parties find something in the resolution for themselves.

Mr. Matanoski then highlighted the large number of dismissed cases. During this reporting period, 509 cases were not compensated or dismissed. (DOJ PP, p.3). This increase was expected, as most of the cases (464) were part of the Omnibus Autism Proceeding (OAP). The special masters recently began asking petitioners in the OAP how they would like to proceed with their cases, and those answers are reflected in the number of dismissals. Mr. Matanoski estimated that the next ACCV meeting's statistics would show a similar, if not greater, number of dismissed cases. Thereafter, the number of OAP dismissals would probably decrease gradually over time. Another current OAP related issue involves the resolution of attorneys' fees. Mr. Matanoski reported that the Office of Special Masters (OSM), petitioners' counsel, and respondent are all working together to resolve OAP attorneys' fees.

Ms. Hoiberg asked if some OAP cases were opting out of the OAP and proceeding individually with new theories and injuries. Mr. Matanoski replied that in some cases, petitioners announced their intention to go forward with new theories, but he is not clear on the nature of those theories, presently. Mr. Matanoski thought that those petitioners were probably in the phase of gathering evidence.

Dr. Herr asked if it would be possible to see statistics showing the number of OAP cases still pending and how many had opted out, saying it would be helpful to see how the cases were moving. Mr. Matanoski said that DOJ would try to provide that information. He thought that it would be possible to identify the number of cases that were pending, but more difficult to determine how many were going forward.

Ms. Hoiberg expressed appreciation for the glossary of terms, (DOJ PP, pp. 5-6), and asked if the terms "affirmed" and "remanded" could be added. Mr. Matanoski said that the terms could be added, and explained that "affirmed" means that the case has been reviewed on appeal, and the court on appeal agreed with the decision of the lower court. "Remanded" means that the reviewing court had a problem with the decision, and is sending it back to the lower court. Usually a case is remanded with a specific question or issue for the lower court to address. Mr. Matanoski further explained that when a case is "vacated," it means that the reviewing court has essentially done away with the lower court's decision.

Appeals

Mr. Matanoski discussed appellate activity in the Program. Since the last ACCV meeting, four cases were decided at the U.S. Court of Appeals for the Federal Circuit (CAFC). Two of those cases, Hall and Masias, involved the issue of attorney hourly rates, and were affirmed by the CAFC. (DOJ PP, p. 8). Mr. Matanoski provided some background information on the issue in these two cases, explaining that in the CAFC decision, Avera, the CAFC held that attorney hourly rates generally should reflect those in the forum in which the court was located. In Avera, the CAFC reasoned that since the OSM and the U.S. Court of Federal Claims (CFC) are located in Washington, DC, then Washington, DC would constitute the forum and that prevailing market hourly rates for similar type work in that forum would apply. However, as the CAFC stated in Avera, there was an exception to applying the forum hourly rate. The forum hourly rates would not apply when most of the work was done outside of Washington, DC, and there was a significant difference between the local hourly rate where the work was performed and the hourly rate in Washington, DC. The issue in both Hall and Masias was whether it was proper to use the local rate of Cheyenne, Wyoming, which was where the attorneys in those cases performed most of the work in the case, or apply the a forum rate of Washington, DC. The lower courts in both Hall and Masias each determined that because most, if not all, of the attorneys' work was performed outside of Washington, DC, and there was a significant difference between hourly rates in Cheyenne, Wyoming and Washington, DC, the appropriate hourly rates of Cheyenne, Wyoming should apply to petitioners' counsel. The CAFC affirmed that reasoning on appeal. Additionally, these cases presented a collateral issue: whether the rate for Washington, DC was a general rate for attorneys performing similar work in Washington, DC, or if a different rate, known as the Laffey matrix, rate should apply. The Laffey matrix is a rate used in some complex civil litigation cases involving the federal government outside of the Program. In both Hall and Masias, the CAFC found that the Laffey matrix rates were inappropriate.

Mr. Matanoski then turned to the issues in the Davis case, also decided by the CAFC. Petitioner initially alleged that the influenza vaccine caused transverse myelitis. After respondent's expert filed a report stating that the condition was more likely neuromyelitis optica, the petitioner agreed and alleged that the influenza vaccine caused neuromyelitis optica. The special master found that petitioner's theory was unreliable. Shortly after oral argument, the CAFC issued a "per curiam" decision that affirmed the lower court's decision dismissing petitioner's case. With a "per curiam" decision, the court does not write an opinion; rather, it means that the court essentially agreed with the decision below.

The McCollum case was resolved many years ago using a reversionary trust, which is a vehicle for resolving damages. A reversionary trust enables the parties to agree to slightly more money for damages involving future contingencies. If those contingencies ultimately do not arise, then the unused money is returned to the Program trust fund after petitioner dies. In McCollum, a reversionary trust was established with the expectation that the child would go into residential care; it also provided money for taking care of the child at home if necessary. The appeal involved the question of whether one of the parents could be paid to be the caregiver and keep the child at home. The CAFC agreed with the lower courts that the issue of care could not be addressed at this point in the proceedings, noting that the Program does not permit parents to be paid as caregivers although the Program could pay a medical professional to be the caregiver.

Mr. Matanoski updated the Commission on the Cloer case, reminding them that *rehearing en banc* was an unusual situation. The case has been fully briefed and the CAFC heard oral arguments in May, 2011. Mr. Matanoski attended the oral argument at the CAFC, and observed that the judges asked a range of questions. He declined to speculate which direction the CAFC was leaning in its decision.

Mr. Matanoski touched on two appellate cases at the CFC: Caves and Jane Doe 93. (DOJ PP, p. 10). These two cases were heard by the same special master. They are also similar in terms of the issues, vaccines involved, and injuries alleged; however, the two CFC judges that heard these cases on appeal reached opposite conclusions. In both cases, the special master found that transverse myelitis was not caused by flu vaccine, and that the theory petitioners' experts relied on was not reliable. In Jane Doe 93, the CFC judge held that the special master employed too high of a standard in evaluating the reliability

of petitioner's theory, and reversed the decision, remanding it to the special master to rehear the case and redecide it. In Caves, the CFC judge affirmed the special master's decision, finding that the special master employed appropriate standards to evaluate the reliability of petitioner's theory. Mr. Matanoski predicted that Caves would be appealed by petitioner to the CFC.

Settlements

Mr. Matanoski turned to the chart showing the number of stipulations adjudicated from the last reporting period. (DOJ PP, pp. 13-20). Mr. Matanoski observed that, while there was a wide-range in cases in terms of number of months between filing a petition and filing a stipulation, most cases trend toward one end of that spectrum. He saw two outlier cases: one took nine years and eight months and one case took eleven years. Both cases involved the hepatitis B vaccine, and were stayed for a number of years during the hepatitis B Omnibus Proceeding. Reviewing the data, Mr. Matanoski observed that the average amount of time from filing a petition to filing a stipulation during this reporting period was 22 months. Removing the two outlier cases, the average was reduced to 19 months. Mr. Matanoski expressed that he was pleased with the efficient manner in which cases were being resolved by settlement, noting that there is always room for improvement. He reiterated that many factors influence the time it takes to resolve a petition, and highlighted a key factor as the completeness of a petition when it is filed. The more complete the case is when the petition is filed, the faster it moves through the process to resolution. He mentioned that a factor that goes into the parties' settlement decision-making process is whether or not the case has been through a hearing, and whether the parties want to resolve the case before going to hearing.

Questions and Comments

Mr. King thanked Mr. Matanoski for his presentation, and mentioned the disparity between HHS and DOJ statistics. Mr. King asked if the two agencies could address the issue before the next meeting. Mr. Matanoski suggested that since DOJ and HHS are looking at different snapshots of information, they would discuss if there is a clearer way to present the information to the ACCV. Ms. Drew thanked Mr. Matanoski for his insights, and asked that DOJ expand the glossary for the next meeting. She explained that this would be especially helpful to the new commissioners.

Update from the National Vaccine Program Office

Dan Salmon, NVPO

Dr. Salmon presented a brief update on the efforts of the Vaccine Safety Working Group of the National Vaccine Advisory Committee to create a White Paper on enhancements to the vaccine safety system. The Working Group had completed a draft that will be the subject of a stakeholders meeting on Monday, June 13, at which a broad range of stakeholders will testify. The format will be a series of panels which will be composed of specific interest groups – medical associations, public health associations, consumer/advocacy groups and a catch-all "others" panel. The full NVAC will meet the following two days and will discuss the draft report and the comments derived from the stakeholders meeting. Finally, it is anticipated that the final white paper will be reviewed for approval at the September NVAC meeting. Dr. Salmon added that the current draft is available on the NVPO web site.

Review of Vaccine Information Statements (VIS)

Ms. Jennifer Hamborsky and Mr. Skip Wolfe

Ms. Hamborsky began with the review of the human papillomavirus (HPV) VIS, noting that only a minor change was made – the addition of the indication for anal cancer to the description of Gardasil. Ms. Hoiberg commented that the warning for use in pregnant women appeared harsh and potentially frightening to women, and perhaps softer language would achieve the same warning. The current wording: HPV vaccine is not recommended for pregnant women. However, receiving HPV vaccine when pregnant is not a reason to consider termination of pregnancy.

During discussion, asked whether there was data on whether the vaccine may put the newborn at risk, Mr. Wolfe commented that there was not enough data to come to any conclusion. There are probably only a few cases of pregnant women receiving the vaccine. It was noted that there is an HPV pregnancy registry and pregnant women inadvertently vaccinated are urged in the VIS to contact the registry. Concerning a suggestion to craft a statement that "data thus far has not shown any adverse events related to immunization while pregnant," Dr. Gruber commented that there is really no data that has been analyzed and that such a statement would be misleading. However, she agreed that the language about "consideration of termination of pregnancy" was harsh, and that it could be replaced by a recommendation to contact the HPV pregnancy registry for information.

Ms. Williams noted that there was a comment on women who are breastfeeding in the middle of the discussion about pregnancy risk that seemed out of place, since women who are breastfeeding are probably not pregnant. She felt is could be located as a separate bullet after the discussion of pregnancy risks.

There was a discussion about the common warning to contact a doctor if an individual experiences a serious side effect, with recommendations from Commission members that additional contacts be included – nurse, nurse midwife, health care provider, etc. Mr. Wolfe commented that such suggestions have been made for a number of years and at times those additional contacts were included in the VIS. However, there was a series of focus groups that discussed the wording, and the majority of those who participated agreed that only the term "doctor" should be used. Some interpreted the word "provider" to mean an insurance carrier, like Blue Cross. Ms. Hamborsky added that even adding "call 911" was not recommended, partly because a parent would almost certainly call 911 anyway if a child was in extremis as a result of a vaccination side effect (such as difficulty breathing). Dr. Herr suggested using the term "emergency services" and Mr. Wolfe agreed to consider wording that would reflect the gist of the discussion.

There was a brief discussion about whether the presentation on chronic regional pain syndrome, scheduled for the second day of the meeting, would affect the discussion on adverse events, and Ms. Hamborsky commented that it would probably have more impact on contraindications section than the adverse events section. Mr. Wolfe added that any change in the VIS referring to that syndrome should be deferred until after the ACIP had an opportunity to review it.

Moving to consideration of the influenza VIS, Ms. Hamborsky noted that one change was the deletion of any reference to the pandemic H1N1 vaccine, since it is no longer relevant. It has been incorporated into the seasonal trivalent vaccine. Another minor change prompted by advice from the subject matter experts was the deletion of the contraindication for those who may be allergic to eggs. Finally, wording about injection of TIV was deleted, since the current mode of administration is intradermal.

Asked about the four-week delay in administration of two vaccines, Mr. Wolfe explained that two vaccines could be administered simultaneously, but if not, there should be a time separation between the first and second administration. Dr. Herr commented that the contraindication based on a single episode of asthma or wheezing in the past year seemed overly cautious, since many very healthy children may have an isolated wheezing event that should not present a risk. Ms. Hamborsky stated that the warning could only be changed if the ACIP reviewed it and recommended that change. Dr. Gruber mentioned that the label warning for Flumist indicates that children under five with "recurrent wheezing" should not receive the vaccine.

There was a brief discussion about whether the warning about possible flu-like symptoms after being vaccinated should be strengthened, and there was a suggestion that some explanation of the risks should include the fact that the vaccine is manufactured using a weakened virus that might cause symptoms, but it is effective in inducing a stronger immune response when taken. Mr. Wolfe added that the FDA had suggested stating that the immune response should last through the flu season, rather then for a year as currently stated.

Ms. Hoiberg asked if the risk of GBS should be expanded since there had been a few weak signals generated in two or three of the surveillance systems. Ms. Hamborsky commented that the issue of GBS risk would be discussed at the upcoming ACIP meeting, but that the data now would have to come from

reports related to the trivalent seasonal flu vaccine. There was also concern expressed about including information about the risks of thimerosol, which is present in some vaccines. Dr. Gruber commented that there should be explicit information about any vaccine that contains thimerosol, keeping in mind that federal law requires such a preservative in any bulk, multi-dose container of vaccine. Of course, single-dose vials and pre-filled syringes do not contain thimerosol or any other preservative and therefore do not require such notification. Mr. Wolfe added that in some vaccines thimerosol is present in trace amounts as a result of the manufacturing process.

Ms. Hamborsky invited comment on the meningococcal vaccine VIS, noting some minor changes involving licensing and some recommendations submitted by FDA for consideration. Asked about the difference between the MCV4 and the MPSV4 vaccines, Mr. Wolfe explained that the MCV4 is a conjugated vaccine in which a protein carrier is attached to the polysaccharide, which improves the efficiency of the mechanism of action. The vaccine is more effective in children and provides better booster characteristics than the polysaccharide vaccine.

There was a brief discussion about the possible confusion in the VIS about administration of MCV4 and MPSV4 in pregnant women, and Dr. Gruber clarified that both vaccines may be administered if clearly needed, and that there is no contraindication for use in pregnant women. She added that the statement in the VIS that MCV4 is a new vaccine that has not been studied in women "as much as MPSV4 has," might be inaccurate since she said she knew of no MCV4 studies in pregnant women.

Finally, Mr. Wolfe noted that there are two brand names for the MCV4 (Menveo and Menactra), which have different age indications for use. Dr. Gruber noted that the use of the term "for people younger than 55 years of age" is inaccurate, because the vaccines are not licensed for use in children under 9 months of age. Although Mr. Wolfe commented that the VIS usually does not mention the minimum age for use (only the recommended usage), and usually does not specify brand names, Dr. Gruber felt that to do so would improve the precision of the VIS.

Update on the Immunization Safety Office

Dr. Jane Gidudu, ISO

Dr. Gidudu outlined her presentation, noting that she would discuss the ISO's Scientific Agenda, provide a brief update on febrile seizures related to vaccines administered to children, discuss the ISO communication program, and list several new publications related to vaccine safety. She stated that the ISO is involved in four main program/projects, including the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), the the Vaccine Analytic Unit (VAU), and the Clinical Immunization Safety Assessment program (CISA).

With regard to ISO research, Dr. Gidudu noted that the first draft of the ISO Scientific Agenda was reviewed by the NVAC Vaccine Safety Working Group in April 2008. That review included holding several public meetings so that stakeholders could provide input to the draft ISO agenda. The NVAC submitted comments and recommendations to CDC in June 2009, and by November CDC had reviewed all of the recommendations and returned a response to the NVAC. Many of the recommendations were incorporated in the final ISO Scientific Agenda, which was approved by the Assistant Secretary of Health, DHHS, in February 2011, and posted online March 17, 2011.

The implementation of the agenda has begun and will continue to depend on resource availability, new science developments, changes in circumstances, changes in priorities over time, and unexpected events. There has been some implementation activity on most of the 17 general and capacity-building recommendations in the report, and on some of the 15 specific research-related recommendations, including metabolic/mitochondrial studies and a look at research questions that were prioritized by NVAC. The ISO scientific agenda is a living document that will surely evolve over time.

Dr. Gidudu turned to a discussion of the ISO involvement in the 2009 H1N1 pandemic, one of the largest vaccination programs in U.S. history. There was early concern about the possibility of GBS, as was experienced in the 1976 pandemic, and for the protection of pregnant women, and for the consequences of delivering huge amounts of vaccine in a very short time. Real time surveillance began with over 10,000 reports that came into the VAERS (which were evaluated very rapidly), the conduct of rapid cycle

analysis that was possible through the Vaccine Safety Datalink program, and monitoring of other surveillance programs such as CISA, the Emerging Infections Program (EIP), and the Real Time Immunization Monitoring System (RTIMS). Early results of all this effort indicated that the H1N1 vaccine had a similar risk profile to the seasonal flu vaccine. That increased confidence in the vaccine so that distribution was rapid and efficient, and a collateral benefit was the improved collaboration between FDA and other involved federal agencies. The VAERS analyses were published within three months of the beginning of the vaccination program, a significant accomplishment. Several studies were published and Dr. Gidudu provided the citations during her presentation.

Next, Dr. Gidudu provided an update on febrile seizures in children following concomitant administration of the 2010-2011 trivalent inactivated influenza vaccine (TIV) and the 13-valent pneumococcal conjugate vaccine (PCV13). Fever following vaccination in children is common, increases risk for febrile seizures, and usually has a benign outcome, although the experience may be unsettling for parents and caregivers. Last year, in Australia, the TIV manufactured by CSL Biotherapies was associated with a transient increased risk of febrile seizures, and for that reason was not recommended in the U.S. for children less than 9 years of age. Fluzone was recommended for children 6 to 23 months, and in general FDA and CDC implemented enhanced surveillance for seizures based on the Australian experience, even though that vaccine was not used in the U.S. Analysis of VAERS data and VSD's rapid cycle analysis indicated an increase incidence of seizures related to administration of Fluzone (compared to other inactivated vaccines, TIV and concomitant TIV and PCV13). In infants a year to two years old there was an attributable risk of 61 per 100,000 doses compared to a risk of 43 per 100,000 doses with MMRV and rubella and varicella vaccines administered separately. These findings were presented at the February ACIP meeting. The VSD surveillance and analysis will continue, and the ACIP is working on information provided regarding concomitant TIV and PCV13, and an update will be presented at the June 2011 ACIP meeting.

Dr. Gidudu briefly discussed CDC communications related to vaccine safety, noting that there were several resources including: blogs on www.flu.gov, CDC expert commentary on Medscape, and a continuing medical education session, also on Medscape. She mentioned a number of related publications, providing citations for each.

During discussion Ms. Hoiberg expressed concern that an initial febrile seizure post vaccination might "train" the brain such that additional seizures would follow. Dr. Gidudu commented that sequella after such seizures, although not totally benign; usually result in the child returning to normal function. A small proportion may experience repeated seizures, but most do not. She added that there are a few monitoring studies of seizures post vaccination, but that the focus of those studies is on seizures that fall into the serious category

Update on National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH)

Dr. Barbara Mulach, NIAID

Dr. Mulach brought to the attention of the Commission an April 2011 article in the *Journal of Pediatrics* about the development of a questionnaire designed to identify the potential for autism or autism spectrum disorders in children. It is designed to be completed by parents of one-year-old infants regarding the child's responses, including eye gaze, sounds, words, gestures and visual object recognition. It was developed by researchers at the University of California and tested on about 10,000 infants. Researchers are now working to refine the questionnaire.

Dr. Mulach invited the Commissioners to visit the NIAID web site, and specifically the NIAID Showcase, which highlights selected biomedical research advances in which NIAID has played a major role, including the development of new and improved vaccines to prevent pneumococcal infections, Haemophilus *influenzae* type B (Hib), hepatitis A, and pertussis (http://www.niaid.nih.gov/Pages/NIAIDShowcase.aspx). She also recommended visiting the "NIH Research Matters" web site for information on current and past NIH-supported research activities and

highlights or to sign up for e-mail alerts on health topics of interest (http://www.nih.gov/researchmatters/index.htm).

Update on the Center for Biologics, Evaluation and Research

Dr. Marion Gruber, CBER, FDA

Dr. Gruber stated that since the last ACCV update was given, FDA has approved Menactra, manufactured by Sanofi Pasteur, on April 22, 2011, to include safety and immunogenicity data to support use in children 9 through 23 months of age to prevent invasive meningococcal diseased caused by. N. meningitidis serogroups A, C, Y and W-135. In addition to disease causing pathogens belonging to the serogroups contained in the vaccine, there are additional meningococcal bacterial pathogens including group B meningococcal bacteria. These bacteria are responsible for about a third of all invasive meningococcal disease, and about half of the disease in children less than one year old. The incidence rate for meningococcal group B disease in the U.S. is very low, which makes it infeasible to conduct efficacy studies with a disease endpoint. Therefore, CBER convened its Vaccines and Biological Products Advisory Committee on April 7, 2011 to present to the committee potential pathways to licensure of vaccines to protect against meningococcal group B disease and to obtain input from experts.

Dr. Gruber turned to another subject, taking the opportunity to clarify some inaccuracies and misconceptions regarding the FDA review of product labeling that were imbedded in a statement made by Mr. Wolfe during the ACCV meeting of September 17, 2010 when the VIS for rotavirus vaccines were discussed.

Dr. Gruber stated that FDA would like to clarify that it must comply with binding regulations regarding information that is included in product labeling. Specifically Title 21 Part 201.56 states that:

(1) The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.

(2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

(3) The labeling must be based whenever possible on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness.

Furthermore, the regulations state that for biological products, any clinical study that is discussed that relates to an indication for or use of the biological product must constitute or contribute to substantial evidence and must not imply or suggest indications or uses or dosing regimens not stated in the “indication and usage” or “dosage and administration” section of product labeling.

Therefore, FDA would like to stress that the information that is included in product labeling is driven by data derived from studies conducted by the sponsor. Before approving a biologic license application for a product including vaccines, FDA undertakes a detailed review of the proposed labeling, allowing only information for which there is a scientific basis to be included in the FDA-approved labeling. Under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act (the PHS Act), and FDA regulations, the agency makes approval decisions based on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling [See, e.g., 21 U.S.C. 355(d); 42 U.S.C. 262; 21 U.S.C. 360e(d)(2).] FDA's comprehensive scientific evaluation is embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal conclusions regarding the conditions under which the product can be used safely and effectively.

Public Comment

Ms. Drew announced that there was one individual from the public who wished to make a comment, Mr. James Moody, representing the National Autism Association.

Mr. Moody referred to a recently published study in the Pace Environmental Law Review, authored by directors of the Elizabeth Birt Center for Autism Law and Advocacy, entitled " Unanswered Questions from the Vaccine Injury Compensation Program: A Review of Compensation Cases of Brain Injury". Mr. Moody stated that the study dealt with 83 cases of injury compensated by the Program involving, at some point, a diagnosis of autism or autism-like features. He said the cases bring into question the federal government's claim that there is no evidence that vaccines cause autism. He noted that HRSA has stated that compensation was based on cases in which children had encephalopathy or a general brain disease. Mr. Moody urged the ACCV to review the connection between autism and vaccines.

On a second point, Mr. Moody stated that the Association had received a large number of inquiries about the Omnibus Autism Proceeding (OAP), including several hundred individuals who are involved but not represented by counsel. He commented that the Justice Department is bringing pressure on individuals to either dismiss cases or present new evidence or a new theory in order to continue the case in the Program. He added that new science has been developed, and that the CDC has conceded that baseline data is needed with regard to children who have never been vaccinated. He expressed concern that the OAP cases may prevent the injured parties from having the opportunity to receive compensation for what may turnout to be true vaccine injuries.

Mr. Moody asked that the ACCV request that the Secretary of DHHS declare a moratorium on dismissing further OAP cases until the scientific issues can be properly addressed.

There being no other requests for public comment, Ms. Drew ordered a recess until the following day.

(The meeting recessed at 4:30 p.m., to reconvene the following morning, June 10, at 9:00 a.m.)

Advisory Commission on Childhood Vaccines

June 9-10, 2011

Day Two

Minutes

Members Present

Sherry K. Drew, JD, Acting Chair
Charlene Douglas, Ph.D.
Kristen Feemster, M.D.
Thomas Herr, MD
Sarah Hoiberg
David King
Ann Linguiti Pron, MSN, CRNP, RN
Jason Smith, J.D.
Michelle Williams, JD

Executive Secretary

Geoffrey Evans, M.D., Director, DVIC

Staff Liaison

Andrea Herzog, Principal Staff Liaison

Welcome, Ms. Sherry Drew, Acting Chair

Ms. Drew called the meeting to order and invited comments on any unfinished business from the first day of the meeting.

Unfinished Business

Ms. Hoiberg commented on the statement made by Mr. James Moody during public comment the previous day, noting specifically his reference to the article in the Pace Environmental Law Review entitled, "Unanswered Questions in the Vaccine Injury Compensation Program: A Review of Compensated Cases of Vaccine-Induced Bran Injury." She explained that she had come to the Commission as a parent with a vaccine injured child. After her child was injured as a result of a DTaP vaccination, she ultimately filed a claim with the Program, which was judged favorably and compensation for the child's care was established, including applied behavior analysis (ABA) therapy, a type of therapy highlighted in the Pace University article. Although her child does not have autism, she has greatly benefited from ABA therapy.

Ms. Hoiberg expressed her feeling that the individuals interviewed for the study described in the Pace article had been treated appropriately by the Program, and had been awarded compensation for neurological injury that may have been a sequella of the vaccine administered. She stated her opinion that the Pace article was misleading in suggesting that these cases were diagnosed as autism and that publication of the study was a disservice to the positive aspects of the VICP.

Mr. King commented that Mr. Moody had requested that the Commission recommend to the Secretary there be a moratorium on the dismissal of cases filed under the Omnibus Autism Proceeding to allow time for ongoing scientific studies to be completed, and permit continuation under a new theory or with new evidence. Ms. Drew noted that such a recommendation would have to be made promptly since the process is well under way. Ms. Williams commented that the Commissioners had not had time to consider the ramifications of such a request, and questioned whether or not it was appropriate for the Commission to submit recommendations to the Office of the Special Masters. Dr. Herr agreed that if there were legal procedures that would accomplish the same, it would not be appropriate for the Commission to intercede. Ms. Hoiberg added that, as at the beginning of the Program when filing of older claims was permitted, it would seem logical that if circumstances warranted (such as new science) then Congress would respond to those new circumstances. Dr. Evans agreed that, in addition to the eight-year look-back period that applies to all injuries added to the Injury Table, Congress could extend that period, if appropriate. He suggested that the issue could be considered by the Future Science Workgroup, scheduled to meet immediately after adjournment of the Commission meeting. On motion duly made and seconded, the Commission unanimously approved referral of the issue to the Future Science Workgroup.

DVIC Clinical Update

Dr. Rosemary Johann-Liang, Chief Medical Officer, DVIC

Dr. Johann-Liang explained that, with regard to previous discussions about timelines and cases, her office follows the fiscal year, and have been presenting groups of cases by FY quarters (in order to maintain petitioner confidentiality), and requires that sufficient information be included in the case file for proper medical analysis. She added that she would be focusing on cases from the second quarter of FY 2011, and the discussions would pertain to the medical aspects of the claims.

Dr. Johann-Liang commented that the caseload for FY 2010 was higher than previous years, over 400 cases, and it appears that 2011 will see about the same number of cases. Asked about staffing versus the relatively significant increase in workload, Dr. Johann-Liang replied that appropriate staffing is always the goal with efforts under way to increase staffing, but in spite of the increased number of cases, the work product was being delivered in a timely manner. She added that because of the requirement that enough medical records are filed and available to review, this at times delays consideration of a case. For example about two-thirds of case reviews in the quarter under discussion were cases filed in FY 2010. Nonetheless, the processing time for most cases is about 2 - 4 weeks. The recommendations for each case may change over time as new information is received.

Turning to statistics, Dr. Johann-Liang provided data on the age distribution of claims showing that 68% were adults, and the vaccines alleged to have caused injury (with influenza at 40%, HPV at 19%, tetanus at 12% and infant vaccines at 9%). Varicella, hepatitis A and B, MMR, meningococcal and polio were 5% or less. There was a request that the flu claims be broken down as to type, TIV or LAIV, for the next meeting. Asked about whether some feedback is being sent to CDC or DHHS about the high level of claims for flu, Dr. Johann-Liang responded that the fact that a claim alleges injury from a specific vaccine does not necessarily hold true after the medical analysis. In addition, the concerned agencies are very active in monitoring all aspects of vaccine safety. Although there is communication between the medical analysis group and other agencies, information is not formally reported outside of DVIC since the purpose of the medical analysis is to adjudicate individual cases for potential compensation, a different focus than other agencies under the umbrella studying vaccine safety.

Dr. Johann-Liang showed the injuries alleged in claims, with GBS as the predominant injury (24%).Neurologic injury, which includes complex regional pain syndrome (CRPS), is the second largest injury category at 20%, followed by other demyelinating disorders at 16%. Other categories of injury, which each comprise 3% to 7% of injuries, included genetic or underlying disorders, psychiatric disorders, rheumatic disorders, newly filed autism cases and injuries ending in death.

Dr. Johann-Liang briefly discussed the upcoming Institute of Medicine report that is looking at 8 vaccines – HAV, HBV, HPV, influenza, meningococcal, MMR, tetanus-containing and varicella vaccines. She explained that the study recommendations would be an important consideration in updating the Vaccine Injury Table. Review of H1N1 pandemic influenza vaccine was not included in the original charge to IOM but H1N1 is now folded into the 2010 seasonal influenza vaccine, which the VICP does cover.

Dr. Johann-Liang then invited Dr. Shaer to discuss VICP's experience with CRPS.

Complex Regional Pain Syndrome
Dr. Catherine Schaer, Medical Officer

Dr. Schaer explained that the symptoms of CRPS have been recognized for over 150 years, under a number of names – reflex sympathetic dystrophy, causalgia, algodystrophy and sympathetic overdrive syndrome. She noted that it affects about one in 20,000 individuals, can occur at any age (mean age 42), is diagnosed three times more frequently in women, and is increasingly being seen in adolescents. The term "chronic regional pain syndrome" came out of an effort by the International Association for the Study of Pain (IASP) to better define the various conditions under one nomenclature for consistency of diagnosis.

CRPS is most commonly associated with a prior trauma (fracture, surgery, infection) and medical procedures, including injections. There are two subcategories of CRPS, CRPS I in which no specific nerve injury can be identified, and CRPS II that can be traced to a specific nerve injury. In up to 20% of cases no cause can be confirmed.

For diagnostic purposes the IASP arrived at four criteria. First, there must be an identifiable event that could cause the injury. Second, there must be pain that is disproportionate to any known inciting event. Third, evidence at some time of edema, changes in skin, blood flow, or abnormal sweating in the region of the pain. Finally, fourth, no other conditions may be present that could account for the degree of pain and dysfunction. One aspect of the diagnosis is that the pain is regional and not associated with a specific muscle or bone, nor does the pain conform to a nerve pathway. The pain can also express itself in different locations of the body, although usually in a general region.

The onset of CRPS may be minutes to months after injury, though most often within hours or a few days. The pain can be described at a shooting pain, a burning or tingling pain, a muscle spasm, and movement often exacerbates the pain. In the late stages of the disorder the affected limb may begin to atrophy, and skin appearance and texture can change. There are no known lab procedures or imaging techniques that effectively identify CRPS. The diagnosis is often made by exclusion because, standard tests reveal no other basis for the pain. Effective treatment is elusive, currently consisting of pain medications, muscle relaxants, physical therapy (disuse of the limb can cause further problems), nerve blocks and even surgery to sever nerves. Finally, chronic pain can cause psychological issues, such as anxiety and depression.

Dr. Shaer provided a number of citations for articles and studies on CRPS. She described the VICP experience with eight claims filed alleging CRPS injury. All were female, ages ranging from 8 to 54 years (four children, four adults), and the vaccines alleged to have caused the injury were influenza alone, influenza plus Tdap, hepatitis B alone and hepatitis B with Td, MMR alone and MMR with hepatitis B. Two reported onset in less than a day, six within a week, and two more than a month. Five of the eight met the IASP diagnostic criteria.

Dr. Shaer summarized, noting that there is very little information in the scientific literature about vaccination as a cause of CRPS, only six case reports. By adding the information developed in the VICP experience there is reason to believe that the vaccine injection may lead to CRPS. It was added to the IOM charge and a recommendation from that report, plus the VICP experience, will be useful in considering CRPS as a candidate for the Vaccine Injury Table.

There was a brief discussion about the lack of information about the condition, the fact that it probably affects around 15,000 individuals in the U.S. and the presumption that only rarely would an individual surmise that CRPS was associated with a vaccination. Dr. Shaer added that individuals seeking medical help because of pain are seldom diagnosed with CRPS, partly because onset is often distant in time from the cause. Mr. King suggested that it was appropriate for the ACIP to look at CRPS, since they are the scientific review body. Dr. Johann-Liang agreed, but added that they must rely on peer-reviewed research, of which there is very little. The IOM study may identify additional references that may enhance the opportunity for the ACIP to consider CRPS. Mr. King expressed the opinion that, even though causation is not proven, that it might be appropriate to include some brief discussion of CRPS in vaccine information statements. Dr. Evans commented that issues such as CRPS appear, groups such as ACIP become aware and become amenable to including consideration of those issues, and as more data develops there can be consideration of including a comment in the VIS. But he added that there are many "may cause injury" issues that could be included in a VIS that has only one or two pages available for information. Dr. Gidudu agreed that pain is a very difficult symptom to work with, especially when the onset may be distant in time from the cause. She added that there were efforts under way, including consideration by the General Recommendations Working Group, to look at pain.

Asked about whether the VICP covers injuries that relate only to the effect of the vaccine or to injuries that may be caused by external events, Dr. Johann-Liang explained that SIRVA was a compensable injury caused by the method of injection, as is syncope.

Ms. Drew closed the discussion and announced that there was one individual from the public who wished to make a comment, Mr. James Moody, representing the National Autism Association.

Mr. Moody reiterated his request that the Commission recommend to the Secretary DHHS that a moratorium be put in place for pending Omnibus Autism Proceeding cases. He submitted that such authority is granted to the Commission in its duty to advise the Secretary on the implementation of the VICP.

Concerning the cases reported in the Pace article, he stated his belief that all had either a specific autism diagnosis or symptoms that were related to autism. Since autism is a behavioral disorder, Mr. Moody suggested that the government agree that vaccines may cause brain injury leading to a diagnosis of autism or features of autism. He noted that he had located 16 studies that deny any link of vaccines to autism, but five studies that affirm such a link. The controversy will continue until the science can demonstrate which stance is correct. Therefore, the moratorium on autism claims should be established.

Finally, Mr. Moody commented that government data has not been published about birth cohorts after the 2002 ban on mercury in vaccines. Since it sometimes takes a number of years before the diagnosis of autism can be confirmed, it would be appropriate to make that data public so that research can be pursued that could shed some light on the issue.

Adjournment

There being no other business, on motion duly made and seconded, the meeting was adjourned by consensus at 11:00 a.m.

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Sherry K. Drew, Acting ACCV Chair

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Geoffrey Evans, M.D. Date
Executive Secretary, ACCV