Advisory Commission on Childhood Vaccines

September 1-2, 2011

Day One

Minutes

Members Present

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

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 called the meeting of the Advisory Commission on Childhood Vaccines to order, welcomed the commissioners and others present and on the phone, and called for approval of the minutes of the June 9-10, 2011 meeting. On motion duly made and seconded, those minutes were unanimously approved.

Ms. Drew announced that Chief Special Master Patricia Campbell-Smith was present and would make some brief comments. She added that Ms. Campbell-Smith was appointed to the U.S. Court of Federal Claims as a special master in 2004, and was appointed Chief Special Master on April 7, 2011.

Ms. Campbell-Smith greeted the Commission, introducing staff attorney Jocelyn Macintosh, who has been working to coordinate disposition of cases that were part of the Omnibus Autism Proceeding (OAP), which has been terminated. She announced that the Judicial Conference would be held in Berkeley, California on October 18th-19th, and invited members of the Commission, who were able, to attend. She noted that the agenda would include a discussion of the Institute of Medicine (IOM) report on vaccine adverse events, a review of the increasing reliance on alternative dispute resolution, and an update on the OAP and autism cases. She concluded by explaining that much of the proceedings would be recorded and would be available on the Court's web site at some time shortly after the meeting.

Ms. Drew expressed appreciation for her contribution to the meeting, and invited Dr. Evans to present his regular report.

Report from the Division of Vaccine Injury Compensation,
Dr. Geoffrey Evans, Director, DVIC

Dr. Evans welcomed those present in person and on the telephone to the 81st quarterly meeting of the Commission. After briefly reviewing the agenda, he turned to the statistics for the fiscal year to date, noting that the number of non-autism filings continues at a brisk pace, with about half alleging injury to adults, mainly from influenza vaccine. The recent ACIP recommendation for universal influenza

immunization for everyone over age 6 months should result in significantly more than100 million flu vaccinations annually, ensuring that influenza vaccines will continue to be prominent part of the VICP program. Claims adjudications are similar in number and distribution, with autism claims being dismissed at a similar pace the past year, the result of termination of the Omnibus Autism Proceeding.

In response to the previous Commission requests for more details on compensated claims, Dr. Evans noted that about eight percent were the result of concession by DVIC, 17% resolved through a hearing and decision by a special master, but most (75%)through a negotiated settlement. Those proportions have remained consistent for the past several years. The alleged injuries in these settled cases will be discussed in the Department of Justice presentation. One aspect of the increased reliance on settlement has been a shortening of the time the total process takes for claims to be compensated, down from an average of 4 years, overall, to an average of about 18 months for claims filed over the past several years.

Dr. Evans explained that total awards to petitioners could be more than $200 million in FY 2011, up from $180 million last year. Although petitioner awards and attorney's fees are up, the Trust Fund balance has increased to just over $3.3 billion, in part as a result of the large number of flu vaccine doses subject to the excise tax.

Turning to DVIC activities, Dr. Evans announced that he and Dr. Charlene Douglas would attend the National Vaccine Advisory Committee (NVAC) meeting in Washington on September 13-14; and that he would be the HRSA ex-officio representative at the Advisory Committee on Immunization Practices (ACIP) in Atlanta on October 24-25. Finally, Dr. Evans provided contact information for those interested in getting in touch with the program.

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 September 1, 2011 Department of Justice Power Point Presentation (DOJ PP), as part of his presentation.

Statistics

Mr. Matanoski began his presentation with a discussion of DOJ's statistical report from the time period of May 16, 2011, through August 15, 2011. He explained that DOJ typically presents statistical information for three-month time frames, reflecting activity in the Program since the last meeting. DOJ uses that information to report on the development of any trends in the Program. In this reporting period, 83 new cases were filed. (DOJ PP, p. 2). As has been noted in past meetings, the majority of these cases (55) were adult petitioners. There were slightly fewer new cases filed this reporting period compared to the last. Commenting on this trend, Mr. Matanoski explained that in litigation, there is an "ebb and flow" of activity throughout the calendar year, with slower periods in the summer and around the holiday seasons in December and January. He remarked that the number of petitions filed in this fiscal year was expected to be slightly less than the number filed in the previous year.

This reporting period, 66 cases were compensated. (DOJ PP, p. 3). Of those case, the majority (53) were resolved through settlement. However, most cases (587) were dismissed without an award of compensation, many of which were Omnibus Autism Proceeding (OAP) cases. This large number of OAP dismissals was expected, and is reflective of the number of petitioners who chose to dismiss their cases because they did not have enough scientific evidence to move forward with their claims. Only a small number of cases (9) opted to voluntarily withdraw from the Program in this reporting period. (DOJ PP, p. 4). Mr. Matanoski acknowledged that there are still differences between DOJ's statistics and HHS's statistics but that they have been working together to identify the reason for the gap. He hopes to narrow that gap by the next meeting.

Ms. Hoiberg also asked about the term “stipulation” versus “settlement” noting that DOJ’s presentation reports on the number of decisions adopted by “stipulation.” Mr. Matanoski explained that stipulations can be used for a variety of things but in terms of reporting here, the word stipulation is being used in the narrow sense of settling a case. This information is meant to distinguish the three types of decisions issued by a special master for damages. Mr. Matanoski reiterated that another type of resolution is through a proffer, which reflects the parties’ agreement to the damages as a factual matter, and results in a decision by the special master adopting the proffer. Here, the term stipulations means settlement, which involves a meeting of the minds to resolve the matter for less than full-value of what either party was seeking. Mr. Matanoski also noted that most of the cases for this period were not compensated, with 587 decisions dismissing a petition. These were in the autism proceedings. He also reported that voluntary withdrawals constituted a small number of dismissals, as the majority of cases go through the process and obtain a decision. Mr. Matanoski next discussed the glossary of terms, which is provided as part of DOJ’s presentation. (DOJ PP, pp. 5-7). As requested at the previous meeting, four new terms [affirmed, reversed, remanded, and vacated] were added to the glossary. Noting that the glossary and the wire diagram are familiar to the ACCV members, Mr. Matanoski offered to answer any questions. Ms.Hoiberg suggested that those slides be discussed in more detail at future meetings, when new members are present.

Appeals

Since the ACCV’s last meeting, the Court of Appeals for the Federal Circuit (CAFC), sitting *en banc* (all judges) issued its decision in Cloer v. HHS. On the narrow issued of the statute of limitations, the CAFC held, consistent with past decision, that the statute of limitations begins to run three years from the occurrence of the first symptom or manifestation of onset of the injury. This is an objective standard. While there is a chance that the parties could seek *certiorari* to the United States Supreme Court as the time-period for that is in effect, the *en banc* decision is the law. In addition, the CAFC certified a couple of questions to the parties, one of which was equitable tolling. Responding to Dr. Herr’s question seeking a definition of that term, Mr. Matanoski explained that “tolling” refers to stopping the running of the statute while “equitable” refers to the event/situation that stops the statute clock. Equitable tolling is a very narrow exception to the statute of limitations. In the federal claim scenario, one would need to show that he/she was misled or suffering from duress as a reason for not filing a timely claim. This would encompass some type of fraud. The CAFC was clear in that equitable tolling would not apply where a claim was not filed because the claimant was not aware that a claim existed. Another example that would not constitute equitable tolling would be where an attorney did not file a timely claim. A potential scenario of equitable tolling would include facts that a claimant was misled into not filing a claim using an example where government physician told a veteran that he was not injured and willfully misled a veteran into not filing a claim. Ms. Hoiberg asked about the specific cases that were overturned when the CAFC issued its decision in Cloer. Mr. Matanoski replied that a previous CAFC overturned a panel decision in *Brice v. HHS*, which held that equitable tolling was unavailable under the Vaccine Act. Mr. Matanoski commented that before the Brice decision, equitable tolling was permitted under the Act, but of the approximately 60 cases that sought to apply equitable tolling, none met the narrow set of circumstances under which the statute would have been tolled. Drawing from past experience before Brice, Mr. Matanoski predicted an increase in litigation surrounding the application of equitable tolling even though few, if any cases, will meet the standard. Mr. King asked if Mr. Matanoski could give another example, in addition to fraud, of when equitable tolling would be available to a petitioner. Mr. Matanoski suggested that if a petitioner was threatened not to bring a claim, noting that the impediment must be in place during the entire limitations period. Attorney neglect would be insufficient. Another issue raised by the Cloer decision involves its effect on attorneys’ fees, which will be evolving as cases raise the issue of equitable tolling.

Next, Mr. Matanoski highlighted other Vaccine Act cases pending before the CAFC. Two cases, *Hammitt v. HHS and Stone v. HHS* both deal with the medical issue, Dravet’s Syndrome. Following genetic testing, the children in both cases were found to have a genetic mutation, which is known to cause Severe Myoclonic Epilepsy of Infancy. That was considered a factor unrelated, and petitioners claims were denied by the special master. Responding to a question from Ms. Hoiberg, Mr. Matanoski recalled that he did not believe there was an aggravation claim alleged by the petitioner in either case. He also observed that the cases raised the question of which party bears the burden of proof to demonstrate a factor

unrelated. Regardless of which party bears the burden of proof, the ultimate decision by the special master includes a review of the totality of the evidence to determine more likely than not a vaccine caused the injury. In Mr. Matanoski's view, in actual causation cases, the question remains whether or not the vaccine more likely injury was vaccine-related regardless of how the evidence is introduced. This differs from a Table claim which involves a presumption of causation and respondent becomes the burdened party once petitioner gains the benefit of the presumption. Ms. Hoiberg asked whether the genetic testing was ordered by the court or if the testing was done before the claim was filed. Mr. Matanoski was uncertain but he did not think that the court had ordered the testing. Mr. Matanoski also discussed the cases of *Caves v. HHS* and *Hager v. HHS*, which are both pending at the CAFC. These cases are similar inasmuch as the special masters in each case made factual findings that are entitled to deference. On review to the Court of Federal Claims (CFC), the judge in Caves affirmed the special master's decision, and petitioners appealed. In Hager the CFC judge reversed the special master's findings, and DOJ appealed on the basis that the special master's findings should have been accorded deference and not overturned. The case, *Kennedy v. HHS* is unusual case because it was filed 1990, when the petitioner was a child and represented by his parents. Now, the child has returned as an adult alleging that his case should not have been dismissed, and that his parents did not adequately represent his interests. The special master reviewed this case under Rule 60, which says that a case can be revisited for matters of justice to determine whether the judgment should be vacated. The special master decided that the judgment should not be vacated, and the CFC judged agreed. The cases of *Knight (Rotoli) v. HHS* and *Porter v. HHS*, were appealed by respondent on the basis that the CFC should have deferred to the special master's factual findings. Turning to the CFC cases, the cases of *Snyder v. HHS* and *Harris v. HHS* are also Dravet's Syndrome cases, and were appealed by petitioners. The case, *Figueroa v. HHS*, involves jurisdiction. The issue in *Broekelschen v. HHS* involves a disagreement over the amount of attorneys' fees that the special master awarded to petitioner's attorney. The case, *Ricci v. HHS*, was appealed by petitioner and relates to a special master's discretion. In *McKellar v. HHS*, the special master awarded interim attorney's fees, respondent appealed. Respondent disagreed with the special master's interpretation of *Avera v. HHS* and the statute, as well as whether the claim was brought and maintained with a reasonable basis. The case, *Rickett v. HHS*, was discussed previously and will be argued at the CFC on September 7, 2011.

Adjudicated Stipulations

Mr. Matanoski turned to claims that were recently resolved by stipulation - settlement. (DOJ PP pp. 14-19). During this reporting period there were 53 cases adjudicated by stipulation, as opposed to 74 previously; while slightly less, Mr. Matanoski did not expect to see a downward trend in settlements. Regarding processing, the average case (excluding outliers from a hepatitis B omnibus proceeding) took 21.1 months, as opposed to 19.2 months, reported at the last meeting. DOJ is monitoring this for possible trends considering the tightened resources to ensure that there is sufficient manpower to process claims efficiently and consistently in the interest of justice. Responding to Ms. Hoiberg's question about a case that took 8 years and 4 months to process, Mr. Matanoski explained that petitioners in that case needed extra time to collect medical records and other information. It entered the OAP in 2003, then opted out in 2006, which added to the delays. Two other cases took over 12 years to process were part of the hepatitis B omnibus proceeding. Regarding the cases that took over five years, both cases were litigated with one claim going to an entitlement hearing before moving to settlement.

Questions and Comments

Mr. Matanoski expressed appreciation to the ACCV for the opportunity to present at the meeting and offered to answer any questions. There were no questions. Ms. Drew thanked Mr. Matanoski for his presentation.

Report on the Institute of Medicine Project on Vaccines and Adverse Events
Dr. Ellen Clayton, Chair, Institute of Medicine Committee on Vaccines and Adverse Events

Dr. Clayton explained that the Committee's charge was specifically to review existing peer-reviewed scientific literature addressing a number of adverse events in eight vaccines, which were specified by

HRSA. The Committee added ten additional adverse events. The Committee did not address efficacy or benefits of the vaccines. The Committee was selected by the IOM and was composed of scientifically qualified individuals from various disciplines – several epidemiologists, a pediatric neurologist, an internist, a pediatric immunologist and a basic science researcher. The vaccines examined were: MMR (measles, mumps, rubella), varicella zoster, influenza, hepatitis A and B, HPV (human papillomavirus), meningococcal vaccine, diphtheria toxoid-tetanus toxoid-and acellular pertussis-containing vaccines, and diphtheria toxoid-tetanus toxoid-and acellular pertussis-containing vaccines. The Committee met 8 times, including 3 information-gathering open sessions. A medical librarian conducted three comprehensive searches, developing a list of over 12,000 papers, which was whittled down to about slightly more than a thousand papers dealing with new evidence. The list of papers was published on the IOM web site and the public was invited to make additional suggestions. The papers accepted for review by the Committee had to have been published in a peer-reviewed journal, and there had to have been documentation that the vaccine was actually administered and that the adverse event was confirmed by a health care provider (e.g., physicians, nurses, etc.). The adverse event also had to have occurred in an appropriate timeframe – some are known to occur within hours or days, some at more distant times.

To assess causation, the Committee established complex criteria. The adverse event was examined in light of evidence developed through epidemiology, data on populations who received the vaccine versus populations who did not, comparing the incidence of adverse events in both groups. Then the Committee looked at mechanistic evidence, biological and clinical data that might explain how the adverse event develops. Epidemiological evidence had to prove that the exposure occurred (that the vaccine was administered), and that a specific adverse event occurred and was validated. That evidence also had to take into account confounding issues and bias -- some adverse events may have multiple causes and the research must try to differentiate those causes. Finally, the quality of the study was considered – adequate power to arrive at valid conclusions, proper follow-up of subjects, proper eligibility (inclusion criteria) for subjects in the study, etc.

Then the Committee assigned weights to the epidemiological evidence for each adverse event. A high confidence value was placed on evidence from two or more high quality studies that were similar in results. One such study would merit a moderate confidence value. One or more studies that did not have the depth, consistency or precision of the high and moderate value studies were deemed of limited confidence value. If no satisfactory epidemiological studies were located, the adverse event was labeled "insufficient."

Dr. Clayton emphasized that the Committee focused significant attention on the biological mechanisms for each adverse event, and included detailed information on each. Biological mechanisms could be related to immune mediated responses, tissue responses, the injection itself, and changes in total body coagulation. A weighting description similar to those for epidemiologic evidence was applied to biological mechanisms – "strong" for a high quality study that supported the connection between the adverse event and the biological mechanism; "intermediate" for two or more studies that "suggest" a significant connection; "weak" for studies that lack sufficient data to connect the adverse event with the biological mechanism. A fourth category was "lacking evidence of a biological mechanism," when no evidence was available in the literature.

Finally, the Committee developed a score based on the combined epidemiological evidence and biological mechanisms that was used to define the Committee's conclusions regarding each vaccine and related adverse event:

> *Evidence convincingly supports a causal relationship.*
> *Evidence favors acceptance of a causal relationship.*
> *Evidence favors rejection of a causal relationship.*
> *Evidence is inadequate to accept or reject a causal relationship.*

Dr. Clayton cautioned that the last category does not suggest that the Committee did not find sufficient evidence that the vaccine does or does not cause an adverse event, but only that there was not enough information to come to any conclusion. She summarized the conclusions reached by the Committee for each vaccine and for specific adverse events.

Evidence convincingly supports a causal relationship

Varicella: Disseminated Oka VZV without other organ involvement; Disseminated with pneumonia, meningitis, or hepatitis; Reactivation; Reactivation with meningitis or encephalitis
MMR: Febrile Seizures; Measles Inclusion Body Encephalitis (immunoincompetent only)
Anaphylaxis: MMR; Varicella; Influenza; Hepatitis B; TT; Meningococcal
Injection-related: Deltoid bursitis; Syncope

Evidence favors acceptance of a casual relationship

MHPV: Anaphylaxis
MR: Transient arthralgia in women and in children
Influenza: OculoRespiratory Syndrome

Evidence favors rejection of a causal relationship

MMR: Autism; Type I diabetes
DT,TT, aP: Type 1 diabetes
Influenza: Bell's palsy; Asthma exacerbation or reactive airway disease episodes in children and adults (TIV only)

Some evidence is present but inadequate to accept or reject a causal relationship based on epidemiological evidence

Influenza: Seizures; GBS; LAIV-asthma/RAD (moderate null); Stroke, MI, all cause mortality (moderate decreased risk; only 1 study each)
MMR: Meningitis (moderate null)
Hepatitis B: First demyelinating event (moderate null); Type 1 diabetes (moderate null)

Some evidence is present but inadequate to accept or reject a causal relationship based on biological mechanistic evidence

MMR: Chronic arthralgia and Chronic arthritis in women; Hearing loss
Hepatitis B: Acute Disseminated EncephaloMyelitis, First demyelinating event, vasculitis
Injection-related: Chronic Regional Pain Syndrome

Dr. Clayton commented that an individual's susceptibility to an adverse event involves a number of parameters, some of which are age related: present and past environmental exposures, intercurrent illness, personal behavior, personal genome and the microbiome. Concerning the microbiome (microbial communities at various sites in the body), as much as 95% of the DNA found is bacterial or viral, not human. All the non human DNA factors can change over the individual's lifetime. An individual may have an illness (e.g., mononucleosis) that causes an adverse reaction to a drug (amoxicillin) that in the healthy state would not cause such a reaction. One's personal genome can favor adverse reactions at one age that would not occur at another age (febrile seizures occur in infants but rarely in adults), or between the sexes (women appear to be more vulnerable to side effects of MMR than are men). Finally, individuals, especially children, may have metabolic, genetic or immune system traits that predispose to adverse events.

Dr. Clayton noted that there is a significant amount of information in the report for every vaccine and every adverse event, discussions that are two to six pages in length for each. The information includes detail on the various studies that were considered, and a complete discussion of the strengths and weaknesses of the evidence reviewed. She added that the report was also designed to support decision making by providing information to researchers and policy makers. Finally, she briefly discussed the

IOM's commitment to reaching consensus in every report, noting that discussion may become extensive in order to attain that consensus – and that this report was unanimously approved by every member of the Committee. She provided the IOM's web address specific to the report: www.iom.edu/vaccineadverseeffects.

Dr. Evans expressed appreciation for the IOM's efforts in producing the detailed report, and added that Dr. Rosemary Johann-Liang was the HRSA Project Officer for the contract.

Public Comment

Ms. Drew invited public comment.

Mr. Louis Conte, representing himself as a parent of children with autism, stated that he was a co-author of Unanswered Questions from the Vaccine Injury Compensation Program, a paper published by the Pace Environmental Law Review. He noted that the paper was discussed at the last ACCV meeting, and he clarified that the authors were concerned with the causes of autism, including whether or not vaccines may cause or contribute to the onset of the condition. He commented that his investigation for the paper revealed 21 VICP published decisions describing autism as being the result of a vaccine, and 62 cases that compensated a child for encephalopathy or seizures that are features of autism.

Mr. Conte noted family members he interviewed indicated that no one from the federal government had contacted them following resolution of their claims, which led to the recommendation in the paper that an independent review of the data submitted in the compensated cases should be undertaken. He also stated that the paper recommended a congressional review of VICP's adherence to the mandate of the original legislation. Finally, he invited the Commission members to view "Mixed Signals," a presentation of HDNET which would be on the EBCALA web site within a few days of the meeting. That program compares two claims, one for Kimberly Sue Leteure, which was compensated, and one for Michelle Cedillo, which was not.

Mr. James Moody, representing the National Autism Association, commented that the IOM study should be commended for identifying the limitations of epidemiological research and the lack of data for many adverse events, and for pointing out how little is known about immune and autoimmune responses to vaccines. He suggested that the report should have recommended that research be undertaken that includes both individuals immunized with vaccines and those who do not receive vaccinations. The report should also have cited studies at the University of Pittsburgh that has looked at those two populations. Finally, he felt the report should have included a discussion of the effects of mercury (thimerosol) as a preservative

Noting that there were no other individuals interested in making a public comment, Ms. Drew recessed the meeting until the following day.

(The meeting recessed at 4:30 p.m., to reconvene the following morning, September 2, at 9:00 a.m.)

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Charlene Douglas, Ph.D.
Kristen Feemster, M.D.
Thomas Herr, M.D.
Sarah Hoiberg
David King
Ann Linguiti Pron, MSN, CRNP, RN
Jason Smith, J.D.
Michelle Williams, JD (via telephone)

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Staff Liaison

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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. There being none, Ms. Drew invited Dr. Dan Salmon to comment on the activities of the National Vaccine Program Office.

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

Dr. Salmon reminded the Commission that NVAC had been mandated to prepare a white paper on the national vaccine safety system, addressing ways to take advantage of new technology and advancing science, and to make the safety system as robust as possible. A final draft of the white paper was discussed at the last NVAC meeting, and the final version will be voted on at the September 2011 NVAC meeting, bringing to a conclusion the two-year project. The white paper will be published on the NVAC web site after final approval.

Update on the Center for Biologics Evaluation and Research, Food and Drug Administration, Dr. Marion Gruber, CBER, FDA

Dr. Gruber announced that FDA had not approved any new vaccines since the last ACCV meeting, except for approving the 2011-2012 influenza vaccine formulation on July 18, providing authority for the six manufacturers in the U.S. that supply the vaccines. There are a number of vaccines under review, most already licensed for some age groups and under review for licensing to additional age groups – a

meningococcal vaccine for infants 2 to 16 months of age, a pediatric pneumococcal vaccine for possible administration in older adults, and a quadrivalent flu vaccine.

Dr. Gruber announced that the current director of the Office of Vaccines Research and Review will retire after six years as director, and after more than 20 years with CBER, and that she had agreed to serve as Acting Director until a permanent replacement could be appointed.

Review of Vaccine Information Statements
Ms. Jennifer Hamborsky and Mr. Skip Wolf

Led by Ms. Hamborsky and Mr. Wolf, the Commission extensively discussed three vaccine information statements (VIS's) – rotavirus, meningococcal, and hepatitis A.

Rotavirus

Ms. Hamborsky noted that only one change had been made since the Commission last reviewed the rotavirus VIS, the addition of a history of intussusception as a contraindication. Ms. Hoiberg suggested that, under section 2, the wording of the first paragraph, about the nominal effect of improved hygiene and sanitation, be improved. She felt the description of the effect should be "not significantly reduced" rather than "not reduced very much."

There was a discussion of section 6 concerning advice to call "a doctor, or get the person to the doctor immediately." She suggested adding the term "or emergency services" to emphasize the urgency of making such a contact. Mr. Wolf explained that consultants had agreed that the advice should remain limited to contacting a physician, and specifically not include others, such as other health care providers, ERs, dialing 911 and so forth. Ms. Williams requested that the consultants provide a written rationale for that recommendation for review by the Commission. Mr. Wolf agreed to pursue that request.

Ms. Drew noted that, in section 7, a previously agreed on change to amend the statement that an individual "may file a claim" by calling the VICP was not made in this VIS. Mr. Wolf agreed that it was an oversight and that the paragraph would be corrected to conform to other VIS's.

Hepatitis A

Ms. Hamborsky explained that two bullets had been added since the last ACCV review: Under section 2, who should receive the vaccine, "Unvaccinated people who have been exposed to hepatitis A virus, to prevent infection;" and "Unvaccinated people who plan to adopt a child, or care for an adopted child, from a country where hepatitis A is common."

Ms. Hoiberg took exception to the statement in section 3 stating that, although safety for the vaccine has not been determined, there is no evidence that the vaccine may be harmful to pregnant women. Dr. Gruber explained that there had been no pre-licensure trials in pregnant women, and that the pregnancy category C had been assigned, not as a contraindication, but as a statement that if the vaccine is clearly indicated (e.g., through known exposure) the vaccine may be administered. She added that the decision would be the result of a risk/benefit analysis by the provider, not the pregnant woman. She noted that the package insert also includes the category C limitation. The package insert also has a similar limitation for nursing mothers, based on the lack of hard data. Dr. Gruber agreed that the wording might be re-evaluated if "no evidence" means "no data." Mr. Wolf agreed to check with the ACIP about the rationale for the statement.

There was a brief discussion of the sequence of administration as described under section 2, concerning the use of immune globulin (IG) as a stop gap measure for travelers who do not have time to take the two-dose regimen taken six months apart. It was noted that the single IG injection should provide temporary immune response through a travel period, but that an individual who wants extended immunization should then take the two-dose regimen. Mr. Wolf agreed to review the wording to make

those options clearer. Dr. Feemster suggested that the paragraphs discussing this issue be reordered in the next VIS in a more logical sequence, perhaps in a box labeled "For Travelers."

Under section 4, Ms. Williams expressed concern that some of the "mild problems," such as headache, that last more than the indicated one or two days, might belong in the "severe problems" category as well. Mr. Wolf agreed to look into whether or not such symptoms that last more than one or two days should be addressed in a different way.

There was agreement that section 2, in the bullets describing who should be vaccinated, could be confusing, since all children between their first and second birthdays should be vaccinated. There was a suggestion that the wording should indicate that older children and adolescents not previously vaccinated should be vaccinated if they live in a high risk area. Ms. Hamborsky explained that this concerned the "catch up" issue. The previous recommendation was to vaccinate all children between ages 1-2 *if they lived in a high risk area*. At that time many children did not receive the vaccine who are now in the "through 18 years of age "category. The current recommendation is to vaccinate only those in that group who live in high risk areas. Ms. Hamborsky agreed to look into clarifying the wording of that section.

Dr. Gruber asked about section 1 and the statement that three to five deaths per thousand occur, suggesting that the denominator of that statement be clarified – hospitalized cases, reported cases? She felt the number seemed too high. Under section 2, describing "other people" who should receive the vaccine, Dr. Gruber recommended change to the second bullet to read: "Unvaccinated people who have been exposed to hepatitis A virus *no more than two weeks prior*, to prevent infection."

Ms. Williams noted that the logical sequence of section 1 could be improved by grouping the transmission potential and symptoms separately -- by moving the last sentence to the first paragraph. And the symptom of jaundice would be clearer if the word "eyes" was revised to be "yellow eyes."

In section 2, there was a brief discussion about the term "street drugs." Mr. Wolf commented that street drugs was the wording in the ACIP recommendation, used because it was felt that it would be more universally understood. It was noted that using the term "illicit" drug might not be understood at all reading levels, and that "illegal" drugs would be inaccurate. Dr. Douglas and Ms. Williams commented on the importance of maintaining an appropriate reading level, usually accepted as an eighth grade reading level. It was noted that there are tests for readability, but Ms. Hamborsky commented that those tests are not helpful in assessing a VIS, which contains some multi-syllable words by necessity, such as meningococcal. Mr. Wolfe added that the wording is regularly tested in focus groups of parents, who seem to find them understandable.

Meningococcal infections

The Commission reviewed the VIS in section sequence. In section 1, asked about the term "college freshman" rather than "college students," Ms. Hamborsky stated that the risk is specifically linked to college freshmen living in dorms, and not all college students. In section 2, Ms. Hamborsky noted that two statements were deleted. The first referred to a statistic that the vaccine protects 90% of those who receive the vaccine. The FDA pointed out that those results vary by lab. The second was the removal of the statement that MCV4 was better than MPSV4 at preventing person-to-person exposure – a recommendation by a CDC subject matter expert (SME). In another FDA recommendation, to describe the two brands of vaccine, Menactra and Menveo, was not accepted because it was felt that it would unnecessarily confuse the issue, especially since the brand of vaccine is selected by the provider and not the parent. Dr. Gruber pointed out that the two vaccines are actually produced by different manufacturing processes. Mr. Wolf commented that the issue of how much information to include is always a challenge to resolve. Ms. Hamborsky noted that, in focus groups, parents usually comment that the selection of one of two or more vaccine options is the responsibility of the physician. Dr. Herr agreed that in trying to explain such differences the VIS can become unnecessarily technical.

Finally, in section 2, there was a suggestion that the last sentence be clarified to explain that the vaccines protect against specific forms of meningococcal infections, and not all.

In section 3, Ms. Williams suggested rewording the increased risk of microbiologists to include any individuals who work in labs where they might come in contact with meningococcal bacteria. Dr. Feemster commented that the recommendation for children 9 to 23 months of age who have complicating medical conditions does not include asplenic children. Dr. Wolfe agreed to check the ACIP minutes but believed that the ACIP specifically did not vote on that issue. There was also a comment that the wording in that paragraph should not break out "older" adults, since the recommendation should apply to all adults. Dr. Feemster suggested clarifying who needs two doses at the outset and who needs a booster at a certain age.

Ms. Hamborsky commented that, in section 4, information was added about the pregnancy registry. Ms. Hoiberg asked whether a parent should be able to identify the components in a vaccine, since there is a warning about allergic reaction to such components. Mr. Wolf explained that the wording recommended informing the provider about any allergies; the provider should be able to identify the components in a vaccine. Dr. Herr brought up the issue of allergic reaction to latex, which is not technically a vaccine component but may be part of the packaging (e.g., the tip of the syringe or the container stopper). Mr. Wolfe agreed that it was an important issue, but not one that was relevant to the VIS since it is a provider issue. He added that the VIS could be revised to include a phrase such as "any allergies, including an allergy to latex." Ms. Pron noted that some VIS's, such as the one for hepatitis A, include a description of vaccine components, while others don't. She suggested that there should be consistency from VIS to VIS.

In section 5, Ms. Hoiberg asked whether or not the description of fever as a mild problem should be clarified to read "low-grade fever," since a high fever might indicate a more serious problem. Dr. Herr suggested that it was really a subjective concept with parents, and even a matter of medical judgment among physicians. The condition of the child is often more significant than the level of the fever.

Ms. Drew commented that the box describing the risk of fainting spells appears to be part of the serious problems paragraph. Mr. Wolf agreed that the box should be moved so that it follows the first paragraph under section 5. Ms. Williams suggested that the warning be included on all VIS's. Ms. Hamborsky commented that it was included in this VIS because teenagers, who are more prone to syncope after an injection, receive the meningococcal vaccine. There was a suggestion that there also be information about the proper administration of the injection (both parties seated) and an observation period of at least 15 minutes for syncope or anaphylaxis. Mr. Wolf agreed to forward the recommendation, although ACIP's recommendations pertaining to that issue are directed at providers and not parents. Ms. Hamborsky commented that parents may not understand the technical differences between methods of administration (intramuscular versus subcutaneous), and that there are other ways to convey recommendations related to the injection other than through the VIS.

DVIC Clinical Update
Dr. Rosemary Johann-Liang

Dr. Johann-Liang presented a review of medical review cases for the third quarter of FY 2011, noting that the annual number should be close to that of FY 2010. The new cases for the third quarter were all non-autism cases with a distribution of about one-third pediatric and two-thirds adult. Dr. Johann-Liang explained that the what actually happened to the claimant may be quite different after the completion of medical review from what was alleged by the claimant. and effect of each alleged adverse event.

The vaccines named in the claims were mainly influenza (35%), human papillomavirus (19%), meningococcal and tetanus-containing (about 10%), and MMR, varicella, hepatitis A and B, and rotavirus, all between 2% and 6%. Dr Johann Liang said that adverse events that were determined by the medical review were primarily demyelinating disorders accounting for 43% of all injuries. GBS was the leading injury, accounting for 26% of all injuries alleged. Injection-related injuries accounted for 11% of injuries, followed by rheumatologic (7%), genetic and other underlying disorders (6%), psychiatric (3%) and a catch-all, including SIDS, intussusception, cardiac, infectious diseases, dermatologic, gastrointestinal, and muscular injuries (17%). Finally, 7% of cases reviewed were deaths. Of interest is the recent

appearance of claims of pseudo-seizures which are not confirmed on EEG, and claims for injuries related to genetic and underlying disorders that turn out to be temporally related to the vaccinations, but not caused by them. Finally, there were two recent claims of intussusception related to rotavirus vaccinations.

Dr. Liang turned to the IOM report and the presentation by Dr. Clayton, chair of the review committee. The charge to review the existing scientific literature related to specific vaccines and adverse events was delivered to the IOM in April 2009. It required that the committee look at epidemiological studies and studies of the mechanism of action of certain vaccines. The final report of the IOM committee was released on August 25, 2011.

The purpose of the study was to develop supporting evidence for revision of the Vaccine Injury Table. Over time, the VICP has received more and more claims for injuries that were not on the Table, and to expedite the claims process the Table needed to be updated. During the study the committee reviewed 158 vaccine-adverse event combinations. The DVIC worked hard to accumulate, analyze and publish data on adverse events that were included in the IOM study to provide additional new information to the committee. One such paper that was important to the review process was the DVIC report on shoulder injury-related vaccine administration (SIRVA). There was also work on injection-related injuries, such as syncope, and anaphylaxis.

Dr. Johann-Liang explained that the IOM report would be an important component of the review of the Vaccine Injury Table, but that other studies within DVIC and information from the various surveillance systems would also be included.

Rotavirus Vaccines and Intussusception
Dr. Candice Smith, Medical Reviewer, DVIC (via telephone)

Dr. Smith demonstrated the importance of rotavirus disease on national and international public health. Rotavirus is the most common cause of acute gastroenteritis, which causes severe diarrhea accompanied by fever and vomiting. Previously nearly all children would experience the disease before age 5. Even now the disease causes over 500,000 deaths in developing countries, and in the U.S. there are over 300,000 ER visits and 50,000 hospitalizations because of the disease. Until 2006 when vaccination began in the U.S., there would be a significant peaking of the disease in the winter. Since then, as the vaccination program became more established, the number of cases dropped dramatically, and the previous winter peaks became less pronounced.

The first rotavirus vaccine, a rhesus-strain live oral vaccine, was named Rotashield. The risk of intussusception was almost immediately identified, and by spring 1999 it was estimated that there was a 30-fold increased risk. In mid-1999 the vaccine was removed from the market, slightly more than a year after its first appearance.

Dr. Smith described the naturally-occurring intussusception, a telescoping of the bowel into itself, causing a reduction or stoppage of the blood flow, resulting in tissue damage. The cause has not been definitively ascertained, and its occurrence is uncommon (only 1,400 children in the U.S. have the condition annually). Those children are usually 4 to 10 months of age, more often male, and more commonly Hispanic or African American. It is treated with contrast enema to reduce the telescoping or, if that fails, with surgical intervention. Morbidity and death are infrequent, and intussusception recurs in about 10% of cases.

There are two rotavirus vaccines available in the U.S., Rotateq (licensed in 2006) and Rotarix (licensed in 2008). The pre-licensure trial for Rotarix was much larger than most new drug trials, involving 12 countries and over 60,000 subjects. During the trial 26 cases of intussusception were identified, 11 from the vaccine cohort and 16 from the control cohort. In the first 31 days after vaccination the vaccine cohort had 6 and the control cohort 7, suggesting that there was no increased risk of intussusception as a result of the vaccine. Interestingly, in the full year follow-up there was a lower risk of intussusception in the vaccine cohort, suggesting a protective effect of the vaccine.

After these pre-licensure studies, the manufacturer of Rotarix, the attenuated human strain vaccine, conducted a very large study of over a million infants, which resulted in an incidence of 1.8, a very slight increased risk from taking the vaccine. There were studies in Brazil and Mexico, the first of which showed no significant risk with the first dose, an increased risk with the second dose (an incidence of 2.6). The Mexico study showed the reverse, an incidence of 5.3 with the first dose and no increase with the second dose. It was noted that the policy in Brazil is to give oral polio vaccine with the first dose of rotavirus vaccine, which may affect the immune response of the rotavirus vaccine.

There was a brief discussion about why the Brazilians would use oral polio vaccine, no longer used in the U.S., and Dr. Smith explained that the oral vaccine provides a more rapid herd immune response and that when the vaccine rates increase Brazil would probably consider switching from the oral vaccine.

Turning to the pre-licensure trials for Rotateq, Dr. Smith explained that Rotateq is a human-bovine vaccine that protects against five strains of rotavirus. This vaccine has much lower amounts of shedding in humans, which is important to note as one theory of the cause of intussusception is the immune response to the amount of shedding from the vaccine. There were 72,000 subjects from 11 countries in the initial trial (80% from Finland and the U.S.), which resulted in 32 cases of intussusception. Analysis of the time periods was similar to the Rotarix trials – 6 vaccine, 5 placebos in the first 42 days; 7 vaccines and 10 placebos in the period from 42 days post-vaccination to one year. Like Rotarix, there appeared to be no increased risk of intussusception.

After the pre-marketing studies, the Vaccine Safety Datalink (VSD) has conducted three studies, involving near a million subjects, and none indicate any increased risk. Finally, the Australians conducted a study of 295,000 doses and found and increased risk of intussusception within 7 days of vaccination with the first dose (found three cases when expected 0.6). This study highlighted that is was only with the first dose and with the later doses; the vaccination appears to be protective against intussusception. The CDC evaluated the studies and recommended the Rotateq vaccine despite the minimal risk revealed by a few of the studies. The recommendation is based on the decision that the benefits far outweigh the risks of encountering intussusception after vaccination.

Dr. Johann-Liang commented that rotavirus vaccine is included in the Vaccine Injury Table, but that no injuries have been identified with the vaccine. She said there were 12 claims by the end of 2010, nine girls, three boys, and aged 8 to 31 weeks. Almost two-thirds of these children had alternative factors (like malrotation of the gut) that could have contributed to the condition. Although Rotateq is the predominant rotavirus vaccine in the U.S., in the future Rotarix will be increasingly distributed. Dr. Johann-Liang stated that, at the upcoming December meeting, the Commission may be asked to consider adding intussusception as an adverse event for rotavirus vaccines, something which may be considered by the Department on a separate track versus future proposed changes to the Table based on the IOM Report. Concerning the process for the Table update following IOM Report, small working groups composed of representatives of the DVIC, CDC Immunization Safety Office and the Office of the General Counsel will look at individual vaccines and develop recommendations for next steps in updating the Table.

Update on the Immunization Safety Office (ISO). CDC
Dr. Jane Gidudu, ISO, CDC

Dr. Gidudu discussed the current trivalent influenza vaccine that includes the monovalent 2009 H1N1 virus strain. The CDC recommends the vaccine to all individuals 6 months of age and older, preferably received before the beginning of the flu season. There is a new intradermal vaccine, Fluzone Intradermal, which can be administered to those between the ages of 18 and 64. Although rare, an allergic anaphylactic reaction can occur because of a number of components in the flu vaccine. Four deaths were recorded in the last 15 years. Prior severe allergic reaction to flu vaccine is listed as a contraindication, although if an allergic reaction to a main component, eggs, is mild (such as a breakout of hives), an individual may consider getting the vaccine. It should be administered only by a provider familiar with and prepared for the manifestations of egg allergy, including anaphylaxis.

Dr. Gidudu explained that the VSD followed over 200,000 children who received the trivalent inactivated vaccine (TIV) and PCV13 at the same time during the last flu season. There was an increased risk of febrile seizure, especially in those children between 12 and 24 months of age.

At its last meeting in June, the ACIP agreed that providers should institute a program to provide Tdap vaccination to women in their late second or third trimester (after 20 weeks gestation) or immediately postpartum.

With regard to meningococcal vaccine, children between 9 and 23 months of age, who are at increased risk, should receive the vaccine in a two-dose regimen. Increased risk includes those with complement component deficiencies, those in defined risk groups for a community or institutional outbreak, and those who travel to areas where meningococcal disease is endemic. Children who are asplenic were excluded.

Dr. Gidudu briefly mentioned three publications. Petro Moro published a paper analyzing adverse events related to administration of H1N1 in pregnant women as reported through the Vaccine Adverse Event Reporting System (VAERS). The most prominent pregnancy-specific adverse event was spontaneous abortion with no new concerns. Lee et all monitored about 4.5 million doses of flu vaccine in the VSD system and found no safety issues following administration of H1N1 or the seasonal flu vaccine. Glanz et al studied 66,283 children 24 to 59 months of age in the VSD system, who received 91,692 doses of TIV, concluding that there were no medically attended events related to the vaccinations. There were no serious adverse events, although there were statistically significant associations with gastrointestinal conditions and fever.

Update on the National Institute of Allergy and Infection Disease, NIAID, NIH
Ms. Jessica Bernstein

Ms. Bernstein described the goals of the NIH vaccine research and development program:

- To identify new vaccine candidates especially for diseases for which no vaccines exist.
- To improve safety and efficacy of existing vaccines
- To develop novel vaccine approaches and strategies
- To support research on vaccine safety

The vaccine safety program announcement, supported by five NIH institutes and CDC, was originally released in 2008. The program announcement includes a variety of research topics, and allows applicants significant flexibility to develop ideas. Some examples of topics; immunology research, including optimizing immune response to vaccines; comparing vaccine schedules and using genomics to develop predictors of adverse events; and identifying biomarkers of adverse events. Ms. Bernstein added that, although the program announcement was scheduled to expire in September 2011, it has been extended to January 2012.

Future Science Workgroup Report
Michelle Williams

Ms. Williams reported that the workgroup met several times since the last ACCV meeting. The charge to the workgroup by the Commission was to consider the potential of medical information contained in the records of VICP claims, regardless of outcome, to provide data to investigators interested in research into advancing the goals of public health to future vaccine recipients. Inherent in that charge is identification of barriers to accessing that data and, if they exist, whether they can be overcome. Ms. Williams observed that, although the information has been called a “database,” in fact the information is basically a disparate collection of files.

A second task mentioned by the Commission was in response to the recommendations made during the public comment period that a moratorium be declared to suspend action on all pending autism cases until

the science on causality is more complete. Chief Special Master Campbell-Smith commented that the Omnibus Autism Proceeding (OAP) was the most generous stay in the history of the VICP. It allowed more than five years for the science of causality to develop. Two theories of causation, the MMR vaccine and vaccines containing thimerosol, were argued during the OAP and both were rejected. Now the OAP had effectively ended and petitioners involved in that proceeding, who have received a significant number of communications about how to proceed, must develop cases to support their claims, normally not including the arguments heard during the OAP. To date no petitioner or counsel for petitioner has requested a further scientific stay. She added that, although autism would not be appropriate, other scientific issues related to the cases being developed may qualify for a scientific stay if proper evidence of the validity of the request is presented.

Ms. Williams expressed appreciation for the Chief Special Master's comments and concluded her report.

Nomination/Election of New Chair

Mr. Smith proposed that Ms. Drew consider serving as acting chair for the next meeting, at which time the Commission could elect a chair from the more experienced members, and a vice chair from among the new members. That would allow a plan of succession that would allow a new member to gain experience in the leadership position of vice chair in anticipation that he or she might become the chair for the ensuing terms of office. Ms. Drew agreed to serve through the December meeting. Dr. Evans informed the ACCV that the Department had just received approval for replacement of the 3 remaining ACCV members whose terms are expiring. All have accepted and are prepared to attend the next quarterly meeting in December. Since 6 of the 9 ACCV just began serving in March, it may be better to have the three outgoing members remain on the Commission, and, as was done this past March, have the 3 incoming members attend the orientation session and full meeting, as observers, and be officially sworn in once the meeting is adjourned. No one raised an objection to this approach.

Ms. Drew agreed to the extension of her term as acting chair, suggesting that the Commission elect an interim vice chair, whose term would end upon the election of the chair, at which time a vice chair would be elected to serve a regular term of office with the chair. Ms. Drew stated that Ms. Williams had indicated that she was not able to serve in such a capacity, but that Mr. King was amenable. On motion duly made and seconded, Ms. Drew was unanimously elected interim chair, and Mr. King was unanimously elected interim vice chair, to serve until a regular election of chair and vice chair could take place.

Public Comment

Mr. Jim Moody, representing the National Autism Association, noting that a number of scientific studies of autism as it relates to vaccines are ongoing, expressed the hope that the pending OAP cases would go forward at some time in the future. He reiterated his feeling that studies include cohorts of both vaccinated and unvaccinated individuals should be conducted, in part to establish baseline data on unvaccinated individuals. He added that the IOM was convening a committee to specifically address this issue, a project that might take up to three years.

Future Agenda Items

Ms. Drew invited suggestions for future agenda items, noting that the issue of injection practices, dosage issues related to Gardasil, and labeling of latex components in vaccine packaging and delivery systems were mentioned during the meeting. She announced that Ms. Hoiberg, Mr. King, Ms. Pron and herself would constitute the Agenda Committee for the next meeting.

Adjournment

There being no other business, on motion duly made and seconded, the meeting was adjourned by consensus at 11:40 a.m.

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Sherry K. Drew, Acting ACCV Chair

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Geoffrey Evans, M.D.
Executive Secretary, ACCV

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Date