Advisory Commission on Childhood Vaccines

June 10-11, 2010

Day One

Minutes

Members Present
Charlene Gallagher, J.D., Chair
Sherry K. Drew, J.D., Vice Chair
Tawny Buck (via teleconference)
Margaret Fisher. M.D.
Thomas Herr, MD
Sarah Hoiberg
Elizabeth Saindon
Jeffrey M. Sconyers, J.D,
Tamara Tempfer, RN-C, MSN, PNP

Executive Secretary

Geoffrey Evans, M.D., Director, DVIC

Staff Liaison

Andrea Herzog, Principal Staff Liaison

Welcome, Report of the Chair and Approval of Minutes

Ms. Gallagher called the meeting to order and, after introductions, she invited Special Master Gary Golkiewicz to introduce newly appointed Chief Special Master Dee Lord, who was appointed on April 8. Noting that Mr. Golkiewicz had served as Chief Special Master for over 21 years he explained that he would continue to be active as a Special Master. He noted that Chief Special Master Lord had been an attorney in private practice and had held federal appointments, including administrative law judge. Chief Special Master Lord commended Special Master Golkiewicz for his contributions to the Vaccine Injury Compensation Program. She invited Commission members to attend the upcoming Judicial Conference in October, noting that the Special Masters will conduct a session on autism cases.

Ms. Gallagher invited approval of the minutes of the March ACCV meeting with the change of a typographical error from a vaccine identified as ETaP that should be Tdap the motion duly made and seconded, the minutes were unanimously approved.

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

Dr. Evans welcomed Commission members, staff and guests to the 76th meeting of the ACCV. He reviewed the agenda and the meeting materials provided to Commission members prior to the meeting.

Dr. Evans began by updating program statistics since the last meeting. First, the filing of non-autism claims continues to increase. He estimated that up to 400 claims could be filed before the end of the Fiscal Year. The majority of claims are filed on behalf of adults, mainly involving seasonal influenza immunizations. To put this into perspective, over a hundred million influenza immunizations are

administered each year. In contrast, autism filings continue to decline – only 12 claims thus far this fiscal year.

Dr. Evans stated that adjudications would probably exceed those in the previous year. There have been 117 adjudications completed this year, with a slight percentage decrease in settlements (from 83% to 78%) and an increase in concessions (from 8% to 11%). In terms of awards, compensation will probably approach $125 million, the highest in program history, partly because there have been several awards exceeding $10 million. Similarly, attorney's fees have increased. The Trust Fund stands at over $3.2 billion, and net income for the year projected to be $122 million.

Dr. Evans reported on significant activities since the last ACCV meeting. Staff attended three major meetings, manning the VICP exhibition booth and distributing almost 300 VICP information packets – the 31st annual conference of the National Association of Pediatric Nurse Practitioners in Chicago (April 15-17); the 50th Annual Clinical Meeting of the American Congress of Obstetricians and Gynecologists in San Francisco (May 17-19); and the American Academy of Physician Assistants Annual Conference in Atlanta (May 31-June 2). Dr. Evans reported that he and former ACCV Chair Magdalena Castro-Lewis presented an update on ACCV activities at the National Vaccine Advisory Committee (NVAC) meeting (June 2-3). He added that ACCV Commission member Tawny Buck is a member of NVAC and serves as Co-Chair of NVAC's Working Group on Vaccine Safety.

Dr. Evans briefly discussed communications, mainly inquiries received from the public via e-mail and telephone contact. He noted there is significant interest in the childhood vaccines, followed by questions related to influenza vaccine use in adults. Issues related to the program usually involve filing a claim, the Act's statute of limitations, and information on the Omnibus Autism Proceeding and autism, in general.

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

Power Point Presentation Summary

Mr. Rogers, Department of Justice (DOJ) referenced the Power Point materials, entitled March 4, 2010, Department of Justice Power Point Presentation (DOJ PP), as part of his presentation.

Statistics

As in past presentations, Mr. Rogers emphasized that DOJ offers a short-term snapshot of what's happening in the Program. Since the last meeting, 73 petitions were filed. (DOJ PP, p. 3). Of those, 2 were autism petitions and 71 were non-autism petitions (39 reflected adults and 32 were on behalf of children under age 18). (DOJ PP, p. 3).

There were 54 petitions adjudicated, of which 22 were compensable. (DOJ PP, p. 4). Of those, 2 were concessions, and 20 were not conceded by the Department of Health and Human Services (HHS). Of those not conceded, 15 were resolved by settlement, 1 was decided by the special master, and 4 were resolved by proffer. Mr. Rogers emphasized that a proffer has many features of a settlement but differs in that both sides agree upon what the evidence on damages shows, whereas a settlement is a compromise between the two parties' positions. A settlement, unlike a proffer, requires extensive internal DOJ/HHS approvals. In a proffer, while the parties agree upon what the evidence shows, the special master still reviews the evidence (and can award more or less although that is unlikely), and issues a decision consistent with the evidence. The parties can still appeal that decision, although an appeal is unlikely if the decision is consistent with the proffer. Mr. Rogers explained that DOJ separates proffers from decisions in our reporting statistics because it offers some perspective on a substantial number of cases

where the special master decides the case based upon evidence agreed upon and submitted by the parties working together, as opposed to where the special master issues a decision based on competing evidence submitted by the parties.

Responding to an earlier question posed by Mr. Sconyers to Dr. Evans, HHS, during that presentation, Mr. Rogers said that he believed that HHS was counting proffers as decisions, and would confirm with Dr. Evans regarding their terminology. He referenced the proffer definition in DOJ's power point materials. Mr. Sconyers reiterated that it would be helpful for the agencies to use common terms.

Ms. Buck asked for clarification of proffer approvals. Responding, Mr. Rogers explained that a special master makes a decision based upon the proffer, which is different from a settlement. A settlement involves a different approval process within DOJ. The key to a proffer (unlike a settlement) is that the parties genuinely agree as to what the evidence demonstrates. In a settlement, DOJ thinks that the damages should be one amount and petitioner thinks differently but they agree to settle for a compromised amount. Further explaining a proffer, Mr. Rogers indicated that in a proffer scenario, the parties could use a joint life care planner and end up agreeing with that life care planner's recommendations. Those recommendations are the only and undisputed evidence in the case. That evidence is submitted jointly by the parties for the special master to review and approve by issuing a decision on the proffer. Ms. Drew further clarified that a proffer can result after entitlement is conceded, and then the parties move to damages and retain a joint life care planner. As noted by Ms. Drew, while the parties agree upon the damages, it is still not technically a settlement. Mr. Rogers emphasized that proffers are important and reflect quick and fair resolution of the cases.

Ms. Buck questioned why more cases are not resolved by proffer given the benefits of faster resolution than settlement. Mr. Rogers explained that proffers are faster because both parties agree upon what the evidence shows and present that agreement to the special master for a decision. When the parties cannot agree, i.e., where the respective life care planners disagree on terms of the life care plan, then the special master has to decide that case. Ms. Drew commented that all cases, whether they involve a proffer or not, result in a special master's decision. Mr. Rogers agreed and added that settlements also require a decision, which can confuse the statistics. For purposes of providing information to the ACCV, DOJ's goal is to clarify how the decision was reached – i.e., a settlement, proffer or dispute resolved by the special master.

Responding to Dr. Herr's question, Mr. Rogers clarified that proffers deal with the level of compensation, as opposed to entitlement. Mr. Rogers recalled no instance where entitlement was proffered, and emphasized that the proffer discussion relates to amount/level of compensation, as opposed to entitlement. Ms. Buck asked about the impact on public access to case information whether or not the case is resolved by settlement, decision, or proffer. Responding, Mr. Rogers said that he would have to check on decisions adopting proffers to see if the proffer is filed with a published decision. Referencing settlements, which are filed with published decisions, Mr. Rogers believed that proffers would be treated similarly but would need to confirm.

Returning to the statistics, Mr. Rogers stated that there were 32 non-compensable cases. (DOJ PP, p. 4). Of those, 21 were autism. DOJ tracks the autism cases separately because they mask the background performance of the program. Including autism, the Program would be at about a 40% compensation rate. Excluding autism, the Program numbers track HHS and reflect about 66%.

Mr. Sconyers asked about the status of individual autism cases. Responding, Mr. Rogers indicated that the individual cases are being activated. Mainly, the parties have been asked to categorize the cases involving jurisdictional problems and documentation needed so that they can move toward resolution. A certain number of cases are being activated monthly.

Turning to the DOJ PP glossary, Mr. Rogers noted the definitions. (DOJ PP, p.5-6). Viewing the case processing chart (DOJ PP, p. 7), Mr. Rogers emphasized that most cases continue to move through the decision chart along the settlement side with a few more as concessions this quarter.

Autism

The oral argument before the U.S. Court of Appeals for the Federal Circuit (Federal Circuit) took place on the morning of the ACCV meeting, June 10, in Cedillo v. HHS. (DOJ PP, p. 8). Cedillo is one of the two test cases on appeal for the Theory One autism claims (whether thimerosal containing vaccines combined with the MMR vaccine to cause autism spectrum disorders).

Responding to Mr. Sconyers question on the issues raised at oral argument, Mr. Rogers said that the presiding panel discussed processing issues including submission of the Buxton evidence. The second appeal to the Federal Circuit on Theory One, Hazelhurst v. HHS, was affirmed on May 13. (DOJ PP, p. 8). The third test case (Snyder v. HHS) for Theory One was not appealed.

As for the Theory Two autism claims (whether thimerosal-containing vaccines alone can cause autism), decisions in the three test cases were released March 12, 2010, and were not appealed. (DOJ PP, p. 9).

Appeals

The trend continues that the appellate practice is based on petitioner appeals. Recently, the Federal Circuit decided Doe 11 v. HHS, which was affirmed. In Moberly v. HHS, which was discussed at the last meeting, the Federal Circuit denied petitioners' request for *en banc* (full court) review was denied. (DOJ PP, p. 11). The Moberly decision is not final as petitioners are within the time-period to file a request for *certiorari* (review) to the U.S. Supreme Court. Responding to a question from Ms. Buck about the details surrounding the case, Cloer v. HHS, (a statute of limitations case decided by the Federal Circuit), Mr. Rogers said that he could not offer more details about Cloer as the time-period for seeking rehearing of the decision by DOJ had not expired. Ms. Buck asked about the effect of the Cloer case on other pending cases, including the Omnibus autism claims. Mr. Rogers responded that Cloer represents the law of the Federal Circuit right now. Regarding the Omnibus cases, Mr. Rogers indicated that DOJ would examine each case individually noting that Cloer would affect a case that is untimely based on the first symptom of onset inasmuch as Cloer found that the statue of limitations does not run until one of two events: the medical community recognizes a causal connection between the vaccine and the injury or petitioner is given notice by a medical practitioner of a causal relationship. Thus, Cloer affects cases involving those issues of timeliness. Responding to Ms. Buck's question on whether cases with a "Cloer issue" would be stayed, Mr. Rogers said that staying a case would be up to the presiding special master or court. While they could not ignore Cloer, they could stay the proceeding until the law is settled.

Dr. Herr posed a hypothetical question about the effect of Cloer on someone with a changed medical condition, to which Mr. Rogers responded that Cloer would address the issue but could not provide a definitive answer given that Cloer may be appealed. Mr. Rogers reiterated that Cloer issues would be addressed as required under the law in each case individually. Turning to the U.S. Court of Federal Claims (CFC), Mr. Rogers noted that there were five recently decided cases, and observed that the litigation on appeals is by petitioners. (DOJ PP, p. 12).

Settlements

In response to a request by the ACCV about settlements, Mr. Rogers presented a list of stipulations filed by DOJ in claims adjudicated between February 23, 2010 and May 24, 2010. (DOJ PP, pp. 15-18). The information is taken from filed stipulations, which DOJ tracks. Some of the stipulations have not yet posted on the Court's website although they will be. The chart reflects the vaccine and alleged injury (which derives from the petition). Responding to a Commissioner's request from the last meeting, DOJ added a column to include the time it takes from the date that a petition is filed until the date that the stipulation is filed. Mr. Rogers expressed the caveat that while this time-period is not reflective of the end of the case because judgment still has not issued, it offers a snapshot of timing.

Responding to Dr. Fisher's request to define stipulations, Mr. Rogers explained that stipulations reflect a settlement agreement that is signed by the parties. Once the parties and their representatives have signed the stipulation, it is submitted to the Special Master who issues a decision adopting the stipulation and its terms. A thirty-day period follows during which either party can appeal the special master's decision. Typically the parties waive that appeal period. Thereafter, judgment enters, and petitioner accepts the judgment. The claim goes to HHS for payment. Responding to a question from Dr. Evans, Mr. Rogers indicated that if a case is conceded and then settled on damages, the parties could do a proffer. Mr. Rogers confirmed a point made by Mr. Sconyers that stipulations resolve the entire case – entitlement and compensation (damages). The stipulations reflect the end of a case for which compensation is being awarded. Mr. Rogers indicated that the key point reflected by the stipulation time-frame is the period from filing the petitioner to filing the stipulation. Using the snapshot provided by this time-period shows the average to be about one year and half. Mr. Rogers reminded the Commission that the information provided is taken from the stipulation and not the docket because the stipulation, unlike the contents of the docket, is publically available. In order to know the details surrounding a particular case, one would need to review the docket, which is privileged. The parties can waive confidentiality, but without that waiver, Mr. Rogers is precluded from commenting further upon details of the stipulation.

Referencing the DOJ PP decision tree (DOJ PP. 7), if a case is not conceded, then it could take longer for a decision to issue. There may also be appeals, which would increase the pendency of a case. Mr. Rogers commented that several cases were resolved quickly, within months. (DOJ PP, p. 15-18). He attributed that to a case being filed with all documents, as opposed to an allegation and no records. Generally speaking, cases resolved in a five-month period as reflected by the stipulation would have been fully documented, with very clear and likely uncomplicated issues. Cases involving complicated life care needs on the other hand can be time consuming.

Other Issues

Mr. Rogers discussed the case, Bruesewitz v. Wyeth, Inc., 130 S. Ct. 1734 (cert. granted Mar. 8, 2010). (DOJ PP, p. 19). He noted that Certiorari was granted by the U.S. Supreme Court a few days after the last ACCV meeting. DOJ provided a copy of its brief in the case of American Home Products Corp., D/B/A Wyeth v. Ferrari, No. 08-1120, which was filed by the Solicitor General and contains the Government's arguments. This was not filed in Bruesewitz. It recommended that Certiorari be granted in Bruesewitz on the interpretation of the statute. Further, Mr. Rogers added that petitioner's brief in Bruesewitz has been filed recently, along with six amicus briefs.

Comment

Mr. Sconyers expressed appreciation for getting materials to the Commission in advance, and responding to the Commission's request for information. He also commented that the slides on stipulations provided a lot of insight into how the Program actually works. Mr. Sconyers observed that cases are for the most part being resolved pretty quickly, with some outliers. Ms. Gallagher also expressed appreciation for the information and presentation.

Ms. Buck asked about information on the Countermeasure Injury Compensation Program (CICP), noting that the H1N1 strain will be included in the year's seasonal flu vaccine, which would lead most people to believe that it will be covered under the Program. Dr. Evans responded that an update has not been provided, although it was listed on the agenda at the National Vaccine Advisory Commission (NVAC) meeting because that program is still being developed. Currently, the program has received more than 200 notices to file a claim. Over the next few months as the regulations are published and the CICP begins to process those claims, more information will be available. Dr. Evans acknowledged that H1N1 will be included in the 2010-2011 trivalent seasonal flu vaccine. He indicated that further information will be available at the September meetings for NVAC and ACCV. Responding to Ms. Buck's point about processing claims under the VICP and the CICP, Dr. Evans acknowledged the overlap

and indicated awareness of the CICP processing. Ms. Buck stated that there has been very little outreach to the public on the CICP and H1N1 campaign, noting a short - one year - statute of limitations period, and expressed hope for cooperation between the two programs.

Omnibus Autism Proceeding Update
Kevin Conway, J.D.

Mr. Conway explained that he represented several hundred autistic children, including Michelle Cedillo, who alleged vaccine-related injuries in Cedillo v. HHS. He noted that of the three Theory One cases, all of which were decided against the plaintiffs at the Special Master level, only Cedillo has not been finalized in appeal. He added that there were also a number of cases that alleged injury based on mercury alone as an additive to vaccines, all of which were decided in favor of HHS and the attorneys involved decided not to pursue appeal. Those cases are no longer active.

Mr. Conway commented that since most of the autism cases that have been decided have been against the plaintiffs, the attorneys for children with autism must determine on a case-by-case basis whether to pursue VICP claims. It may be that the attorneys will finally counsel their clients with regard to exiting the VICP and pursuing civil actions. Some may remain based on the fact that as science develops new bases for the claims may emerge. He added that the Cloer decision also presents a dilemma in that an earlier decision, in Wilkerson V. HHS, ruled that the statute of limitations begins to run when the first symptom is medically established. Mr. Conway suggested that the Cloer decision may be interpreted to mean that, since the medical community has not yet determined whether autism is a vaccine injury, there may in effect be no statute of limitations for autism. The conflict may have to be decided by the courts.

During discussion Mr. Conway commented that if an attorney decides to support a client's desire to leave the program and preserve the right to file a civil action the challenges are significant since, unlike the VICP, the claim must include evidence that the manufacturer was negligent. In any event, it may take many years for the science to develop to substantiate the relationship between vaccines and autism. On the other hand, in most states the statute of limitations is far longer than the VICP's three years, so there may be many cases put in abeyance until some developments occur in the science.

Update from the National Vaccine Program Office
Dan Salmon, Ph.D., M.P.H., NVPO

Dr. Salmon provided update comments on the NVAC's Vaccine Safety Working Group (VSWG) and Vaccine Safety Risk Assessment Working Group (VSRAWG). The VSWG completed its first charge to review the CDC Immunization Safety Office research agenda, providing recommendations with regard to content and prioritization of research projects. The VSWG's current efforts are directed at looking at the national safety system more broadly and developing a white paper addressing new opportunities and developments that might promote enhancements in the safety system, reduction of adverse events related to vaccines, developing a way to assess the safety of vaccines in a more timely way, and improving public confidence in vaccine safety.

The VSWG, a group of about 20 members, has held a number of meetings and early on established five subgroups, three of which are focused on content (governance and structure, epidemiology and surveillance, and identification of biological mechanisms. There are two process subgroups, one looking at stakeholder engagement and the other involved with developing an implementation plan. The VSWG has developed draft functions (like surveillance and communications) and key attributes that would apply broadly (efficiency, effectiveness, transparency, and equity). Although the original target for release of the white paper was September, since completion of the National Vaccine Plan will take longer than originally anticipated, the deadline for release has been moved to the February 2011 NVAC meeting.

Turning to the VSRAWG, Dr. Salmon explained that his office was aware with the advent of the H1N1 immunization program that the vaccine enterprise would expand dramatically. At that time the nature of the vaccine was not known – adjuvant or not, one dose or two, schedule, route of administration and so on – all of which impact safety monitoring. A small group put together by HHS Secretary Leavitt, the Federal Immunization Safety Task Force, developed a draft safety monitoring plan. A subgroup of NVAC reviewed the plan and made a number of recommendations – to establish data with regard to background rates of disease; to enhance surveillance to include active monitoring of specific populations, including subpopulations; to develop a communications plan to improve cooperation with the media; and the formation of an independent panel to review safety data and disseminate it on as transparent a basis as possible. That last recommendation was the seed that resulted in the VSRAWG, which was to look at safety data on a continuous basis and provide advice to the Secretary. Membership in VSRAWG included representatives of VPAC, ACIP, NVAC, NVSD and DoD's Health Board. Because the issues could be highly sensitive an exceptionally rigid conflict of interest policy was established.

The VSRAWG was briefed in depth at the outset – safety systems in place, information on relevant clinical trials and all of the systems that would contribute surveillance data as the program continued. For each monitoring system exceptional detail was provided – outcomes monitored, population size and description, number of doses administered, analytical procedures and results. Dr. Salmon commented that the data base relied on what was perhaps the largest surveillance effort ever undertaken in the area of vaccines. Every two weeks the VSRAWG received detailed briefings of completely analyzed surveillance data collected from all the federal agencies involved. Once a month the VSRAWG prepared a report, approved by the Assistant Secretary for Health, which was released at a public NVAC meeting.

Dr. Salmon presented data from the last report to the VSRAWG. About 105 million doses of inactivated H1N1 vaccine and about 21 million doses of live H1N1 vaccine have been distributed, which is not necessarily the same as doses administered. The report indicated that there had been two weak signals generated from individual surveillance systems. Dr. Salmon stated that a weak signal implies a low level of risk might exist that would warrant further investigation to see if an "association" might exist. If the association was established a final effort would determine whether there was a real causal relationship of adverse event to vaccine. So far only the two weak signals and a preliminary weak signal have been established.

Dr. Salmon mentioned that the detailed data analysis was related to 18 pre-specified adverse events (such as Guillain-Barré syndrome [GBS]) for which background levels are established, including levels that were associated with an earlier vaccination program (such as GBS in 1976). The surveillance process includes a new analytical method, Rapid Cycle Analysis, which is fast, sensitive and very likely to identify problems early on. A disadvantage is that it also identifies false positives, issues that turn out to be non-problems.

Asked about whether the two weak signals were related to each other, Dr., Salmon stated that the signals were independently identified, but that the epidemiological analysis is identical among the various surveillance systems. Asked about how criteria are established for identifying risk, Dr. Salmon briefly discussed the 1976 GBS surveillance that identified possible adverse events from day one to day 42, during which time it was established that the highest risk of GBS was between 7 and 21 days. That data was used to establish the parameters for the current surveillance, which is day one to day 42, and then occurrences of GBS from day 43 to day 84. It was noted that there are also seasonal effects for GBS occurrence and Dr. Salmon commented that the literature is not consistent as to whether there are seasonal effects or not, but that the data from the current surveillance would be analyzed for those who received vaccine and those who did not, and for whether a seasonal effect could be in play.

Dr. Salmon concluded by explaining that the various systems are currently working on "end-of-season analysis" which will bring together the data and improve the possibility of clarifying risks for rare events, such as GBS for which the risk is one in a million.

Review of Vaccine Information Statements (VISs)
Charles Wolfe, CDC

Mr. Wolfe explained that the ACCV is one of several review groups to consider the composition of the VISs. He noted that the Commission would review four including MMRV, HPV, Cervarix and Gardasil. The primary reviewer, Dr. Fisher, offered the following suggestions:

The claim that "many VIS are available in Spanish" is inaccurate. All VIS are available in Spanish along with other languages and the statement should express that. Dr. Fisher questioned the rationale for publishing two separate VIS for a single vaccine, such as the HPV vaccine. Mr. Wolfe commented that part of the rationale as that there are different adverse events for the two vaccines, as well as two distinct vaccination schedules. Developing a single set of specifications might confuse the recipient. Dr. Fisher also suggested that some of the language might be a little more complicated than necessary. As well, different VIS may have different versions of the same statement. That is, it might be more appropriate to express a specific concept the same way in all VIS.

Dr. Fisher commented that the ACCV review often takes place months after the VIS has already been released. She suggested that a more timely procedure would be helpful so that the ACCV's recommendations could be considered before the VIS's are printed and released. Dr. Wolf commented that the process is cumbersome, partly because of the need to get the documents published in a timely way while still going through the relatively onerous review process, that includes a Federal Register announcement and public comment period. There is also public pressure to get something out almost immediately after a product is licensed. Dr. Evans noted that the charge is to obtain ACCV review of new VIS's and VIS's undergoing revision before release. There was a brief discussion about whether the Commission could receive new and revised VIS's in a more timely way and if the review could take place via teleconference, between ACCV meetings. Asked about the legal considerations, Ms. Saindon stated that it might be possible to develop a process by which a teleconference or e-mail could be employed to review in a more timely manner as long as the deliberations were made public in some way.

Mr. Sconyers commented that the vaccination schedule of pneumococcal vaccine was confusing with regard to explaining different schedules for very young children, adolescents and children with co-morbid conditions. Mr. Wolfe conceded the point, noting that such recommendations are helpful when working with the subject matter experts. Mr. Sconyers also noted that the MMRV vaccine is available to adults but that sterility is not mentioned.

There was a brief discussion about how to handle the CDC preference that, in the absence of parental preference, MMR and varicella vaccine should be given separately for the first dose (which is now a specific recommendation by the ACIP). There was agreement that the language in the VIS should reflect the CDC's somewhat complicated stance on the issue. There was also a suggestion that wording should be included with regard to the need for an individual who has received one live vaccine to inform a provider who is administering a second live vaccine, especially now that individuals are obtaining immunizations from various sources (physicians, pharmacies, etc.).

Ms. Drew commented that a statement that "persons who believe they may have been injured by a vaccine may file a claim with the VICP by calling this number," is misleading since a claim may not be filed by phone or even by visiting the VICP web site.

Asked about a statement that anyone 13 or older should obtain a MMR immunization separate from a varicella immunization, there was agreement that it implied a possible risk which does not exist. The statement is made because the combination, MMRV, is not licensed for those over 13. The reason for the recommendation should be explained. Similarly, Dr. Fisher took exception to the statement that girls should get the HPV vaccine before first sexual contact since everyone is exposed to papillomaviruses (wart viruses). The term "genital human papillomavirus" would be more accurate.

Mr. Wolfe asked about the risks statement in the pneumococcal conjugate virus VIS, explaining that the complex data came from the manufacturer's package insert (multiple parameters, age, severity and dose). He asked if it would be appropriate to average the number to make the description of risk more understandable. Dr. Fisher agreed that such simplicity would improve the VIS.

Finally, Dr. Fisher expressed concern that the new rotavirus VIS was not included in the review, and Mr. Wolfe agreed that it could be distributed to the Commission and he would be available for a teleconference on the following meeting day. The review was inserted in the agenda for 9:00 a.m.

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

Dr. Mulach briefly discussed two initiatives at NIH that might be of interest to the Commission. In the first the National Human Genome Research Institute (NHGRI) sequenced the entire genome of a 40-year-old male, integrating the individual's personal medical history as well as medical information from family members. NHGRI scientists were then able to correlate gene analysis with the actual health history and develop potential health outcomes.

Dr. Mulach described the second initiative, the human microbiome project begun in 2008 to better understand the presence and function of microbes in the human being that probably outnumber human cells by a factor of ten to one. Many of these microbes are necessary for good health and if an imbalance occurs illness can ensue. Dr. Fisher agreed that the project is important and far reaching, adding that our bodies contain far more bacterial DNA than human DNA and understanding the implications of that fact is important.

Update on the Immunization Safety Office (CDC) Vaccine Activities
Jane Gidudu, M.D., M.P.H., ISO, and Karen Broder, M.D., CDC

Dr. Gidudu outlined the new recommendations from ACIP regarding the routine administration of measles, mumps, rubella and varicella vaccination of infants 12 to 15 months should receive the first does and upon reaching 4 to 6 years receive a second dose. For the first dose of either measles, mumps, rubella and vacicella (MMR plus a separate varicella) vaccination or a combination measles, mumps, rubella and varicella as a combined (MMRV)vaccine may be administered at age 12-47 months. If the first dose is administered after age 48 months , the use of the combination MMRV vaccine is generally preferred. A second dose may be administered between the ages of 15 months to 12 years.

On October 16, 2009 the FDA licensed human papillomavirus vaccine (HPV2 or Cervarix) for females ages 10 through 25. A quadrivalent HPV vaccine, Gardasil (HPV4), was licensed for use in females 9 through 26, and recommended for administration at age 11 or 12. In October 2009, the FDA expanded licensure of Gardasil to males 9 through 26 for genital warts. ACIP provided guidance that HPV4 may be given to males but not for routine use.

In an MMWR recently published results of an active surveillance of Guillain-Barré syndrome in individuals participating in an Emerging Infections Program (EIP). Preliminary results from an analysis comparing GBS patients who were hospitalized through March 31, 2010, who did not receive 2009 H1N1 vaccination showed an age-adjusted ratio of 1.77 comapred to patients who did and did not receive H1N1 Influenza A vaccine. In general about one person in 100,000 develops GBS annually. In the 1976 vaccination with swine flu, one study showed that ten in a million people may develop vaccine-related GBS. No federally-sponsored surveillance program has shown a statistically significant association between GBS and the 2009 H1N1 vaccine. If end-of-surveillance analysis confirms this finding, this would correspond to 0.8 excess cases of GBS per 1 million vaccinations, similar to that found in some formulations of seasonal influenza vaccines.

Dr. Broder discussed 6,165 non-serious reports received by VAERS for fiscal year 2010 through the end of January, 2010 which included both adverse events related to live and inactivated vaccine. Reports included rash, nausea, vomiting, dizziness, headaches, fever and pain. "Inappropriate schedule administration" was also reported, which indicated either an improper dosage or administration to an individual not licensed to receive the vaccine. There were very few actual adverse events related to improper schedule administration. There was also a category, contraindication for vaccine," which also was normally reported without an accompanying adverse event.

During the same period there were 466 reports of "serious nonfatal adverse events," those which require hospitalization or are considered life-threatening. For inactivated vaccine about one-third were neurological in nature (53 incidents of Guillain-Barré syndrome), and the remaining accounted for less than ten percent each – allergic reactions, respiratory complaints, pregnancy-related events, cardiovascular complications and others. For live vaccine the more common adverse events were respiratory (31%).

For perspective, Dr. Broder mentioned that there were slightly over 9,000 VAERS reports after the H1N1 flu season versus over 82 million doses distributed, not all of which were necessarily administered. The proportion of adverse event reported for the H1N1 series was similar to that reported for the seasonal flu. GBS incidence was about two in a million doses distributed. Asked about comparative data for unvaccinated individuals Dr. Broder explained that because of the nature of the VAERS reporting system no such data were available.

Update on the Center for Biologics Evaluation (CBER) Vaccine Activities
Overview of PCV in Rotavirus Vaccines
Phillip R. Krause, M.D,

Dr. Krause stated that there had been no new vaccine approvals since the last ACCV meeting. He noted that VRBPAC had met on May 7th and discussed the contamination of GlaxoSmithKline's (GSK) Rotarix rotavirus vaccine with porcine circovirus (PCV). The contamination was discovered by a researcher at the University of California, San Francisco, who was looking at most of the available live attenuated vaccines. GSK initiated tests and confirmed that the contamination exists at all stages of production. Dr. Krause explained that when FDA became aware of the contamination a recommendation was issued to suspend the use of Rotarix while further studies were conducted. A judgment call was made that the risk was not sufficient to order a recall.

Subsequently Merck, testing its own product, Rotateq, reported finding PCV, although at much lower levels than Rotarix. As a result of both discoveries, CBER launched a laboratory investigation and confirmed the presence of PCV DNA fragments as well as intact virus in Rotarix. The conclusion at CBER was that there was very little likelihood that the contamination would cause harm to any child receiving the vaccine. This was based on the profile of PCV, the smallest mammalian virus, a common virus in pigs, and a virus found in pork products sold in grocery stores to U.S. consumers who are commonly exposed to the virus and experience no infectious consequence. There is no evidence that PCV causes disease in humans and there is no evidence that PCV in any licensed vaccine poses any safety risk. Finally, GSK has completed preliminary serologic studies (blood before and after immunization) and there were no PCV antibodies detected, suggesting that no infection had occurred as a result of the vaccination.

Asked how the PCV made it into the vaccine, Dr, Krause explained that porcine trypsin, an enzyme, is used to facilitate moving cells that tend to adhere to the surfaces of flasks, from one container to another. In addition, trypsin is used to promote activation of infection in cell culture tests.

Asked about the potential for a broader testing program for vaccines, Dr. Krause explained that the challenge is the need to standardize tests for the regulatory setting. In fact, Dr. Krause stated that the second topic of discussion of the VRBPAC was the potential for such testing programs.

Dr. Krause discussed the proactive actions taken by FDA, including providing guidance to manufacturers on testing vaccines. Data from these tests are part of the overall application approval process. Since the FDA does not have a major in-house vaccine testing, data from manufacturers before and after licensing, and data from emerging data surveillance, are the main components in the process to develop assurance of vaccine safety. The populations involved in this safety surveillance network extend beyond U.S. borders and involve millions of vaccinations worldwide.

The process of developing new assays to the point of being useful standardized tests in the regulatory arena is a long and complicated process, Therefore, it is likely that CBER will arrive at answers related to the PCV issue long before arriving at a generic virus contamination detection scheme that can be applied more broadly. Regardless, despite the difficulty in standardizing tests, when a new test emerges, such as the tests for PCV, the manufacturers may be asked to integrate the test in ongoing research and development (R&D) as well as in monitoring existing products.

Dr. Krause explained that FDA's longstanding process for assuring vaccine safety relies on a risk benefit analysis based on data developed in pre-licensure clinical trials, clinical trials and research after licensing, and the standard post-marketing surveillance programs, and new and sophisticated data mining programs that examine, for example, insurance claims data. There is a constant monitoring process to ensure that the benefits of a vaccine far outweigh the risks of adverse events. Asked how FDA ensured that manufacturers followed approved formulations, manufacturing procedures and storage, handling and shipping procedures, Dr. Krause stated that there were reviews and inspections on the manufacturing side, inspections of clinical trial sites (including records and reports) and some testing of drug samples post-licensure.

Dr. Krause summarized the discussion at the VRBPAC meeting, noting that the members were convinced that the benefits of the two rotavirus vaccines significantly outweighed any theoretical risks. There was also agreement that the reporting of the results of the independent PCV tests that revealed the contamination should be transparent and available to the public. Although CBER continues to test for PVC in rotavirus vaccines, the original recommendation to suspend use has been withdrawn. The manufacturer is working on new labeling to include discussion of the PCV contamination, and looking at processes to remove the PCV contaminants.

Post-marketing Safety of U.S. Licensed Rotavirus Vaccines
David Martin, M.D., M.P.H., CBER, FDA

Discussing post-marketing surveillance, Dr, Martin mentioned several goals – to generate safety signals, to improve the reliability and quality of the signals, and to confirm valid association with specific adverse events. Data comes from pre-licensure clinical trials, post-licensure surveillance systems (like VAERS), and other sources. When reports are submitted to VAERS medical officers assess all those considered "serious" adverse events. In addition, current reports of adverse events in scientific literature are monitored and information is gathered from regulatory agencies outside of the U.S. Finally, there are studies conducted by independent academic researchers and by the manufacturers. Timeliness is important and surveillance systems like VAERS begin receiving reports as soon as the vaccine is released for use.

Dr. Martin pointed out, however, that there are limitations to the surveillance system. Clinical trials both before and after licensure are seldom sufficiently powered to detect rare adverse events or events that take a long time to become evident. Almost all studies are of limited duration, up to a few years. VAERS reports are voluntary and there are no limitations on how the adverse event can be described or attributed, and a report may or may not actually relate to a specific vaccine. There is no way to determine how many doses are administered that result in a particular number of adverse events, so rate of occurrence cannot be determined. There is also the possibility of over-reporting or under-reporting or of "stimulated reporting," a spate of reports that may result from a media event.

The Vaccine Safety Datalink VSD relies on rapid cycle analysis on a relatively limited population from eight managed care organizations, and the quality controls for that population are much higher than voluntary systems such as VAERS. Rapid cycle analysis can be affected by both false positives and false negatives, and the outcomes do not necessarily reflect the entire U.S. population. Finally, the quality of the independent studies conducted by industry and academia depend on the study designs

Addressing issues specifically related to rotavirus vaccines Dr. Martin commented that Rotateq was licensed in the U.S. in February 2006 with two labeled contraindications – hypersensitivity and history of severe combined immunodeficiency (SCID). The pre-licensure clinical trials for Rotateq involved more than 70,000 infants and the rate of adverse events among those who received the vaccines was similar to those who received the placebo. There was also a large population of nearly 70,000 who were tested for susceptibility to intussusception. Merck also sponsored a similar trial in 85,000 children who received Rotateq and the results were the same, no statistical association with intussusception. Over 37 million doses of Rotateq were distributed between licensing and March 2010.

Dr. Martin noted that the VSD registered only 207,000 doses of Rotateq administered from May 2006 to May 2008 and there was no evidence of increased risk of intussusception, seizures, meningitis, myocarditis, gram negative sepsis, bleeding or Kawasaki disease. Early VAERS reports identified several infants with post-vaccination gastroenteritis who were subsequently diagnosed with SCID, which prompted adding that as a contraindication on the labeling. Recently HRSA recommended screening neonates for SCID.

Turning to GlaxoSmithKline's (GSK) Rotarix vaccine, Dr. Martin noted that it was licensed in April 2008 and the contraindications were the same, hypersensitivity and history of SCID, but a third was added -- any malformation of the gastrointestinal tract that might predispose an infant to intussusception. Again over 70,000 infants were enrolled in pre-licensure clinical trials and the results were similar to the Rotateq clinical trials; no significant increased risk of adverse events. Through March 2010 about 2.5 million doses were distributed in the U.S. (although worldwide there were over 68 million distributed). GSK is conducting ongoing studies to monitor for intussusception, Kawasaki disease, convulsions, lower respiratory tract infection and death. Results of those tests are not yet available.

In conclusion, Dr. Martin stated that his office monitors all 72 licensed vaccines in the U.S. The level of resources devoted to each vaccine depends on the signals generated in the various surveillance systems.

Public Comment

Ms. Gallagher invited comments from the public. Mr. James Moody, representing SafeMinds, stressed the importance of comparing placebo vaccines to the active ingredient vaccines when developing a surveillance system. In addition, when setting surveillance parameters, the definitions of target adverse events should not be limited to a few specific events. For example, an individual who develops Guillain-Barré syndrome may not exhibit all of the symptoms required in a formal definition for research purposes and would therefore not be included in the data collected. Finally, over-aggregation of a sample population by sex or age might obscure safety signals. Mr. Moody recommended that studies should include all adverse events rather than a few preselected adverse events, and that the raw data from studies should be made available to independent researchers so that academic and industry researchers could conduct their own studies based on that data.

Concerning the Vaccine Information Statements, inclusion and exclusion criteria should be clearly explained and information should be included about comparability of study populations on which decisions are made concerning use. The VIS's should state whether there are comparable safety studies in the general population with regard to schedules, and schedules should be described as experimental until safety data confirms the validity of those schedules.

Finally, Mr. Moody stated his opinion that the rulings in the Omnibus Autism Proceeding underscored the evolving nature of the science related to the effects of vaccines on humans and that new science may more clearly explain the effect of vaccines on the human immune system and on the causation of adverse events. He expressed concern that claims that millions of doses administered support the notion that benefits outweigh risks and therefore demonstrate safety is not necessarily sound science.

The meeting recessed at 5:30 p.m., to reconvene the following morning, March 5, at 9:00 a.m.

Advisory Commission on Childhood Vaccines

June 10-11, 2010

Day Two

Minutes

Members Present
Charlene Gallagher, J.D., Chair
Sherry K. Drew, J.D., Vice Chair
Margaret Fisher. M.D.
Thomas Herr, MD
Sarah Hoiberg
Elizabeth Saindon
Jeffrey M. Sconyers, J.D,
Tamara Tempfer, RN-C, MSN, PNP

Executive Secretary

Geoffrey Evans, M.D., Director, DVIC

Staff Liaison

Andrea Herzog, Principal Staff Liaison

Welcome and Unfinished Business from Day One
Charlene Gallagher, ACCV Chair

Ms. Gallagher reconvened the meeting and welcomed Mr. Wolfe to continue review of the rotavirus Vaccine Information Statement (VIS). Dr. Fisher continued her primary review, commenting that the VIS should indicate that all, not some, VIS are available in Spanish. She noted that the sentence "your baby can become infected by being around other children who have rotavirus diarrhea," is self-evident and could be deleted. She added that another phrase, "babies who get the vaccine may be fed normally afterwards," might raise questions rather than provide assurance, and it also could be deleted.

Dr. Fisher suggested that web site link to information about porcine circovirus goes to the main FDA home page, on which there is no information about how to obtain such information. That link should take an individual directly to a page with information about PCV. She felt that a more forceful statement should be made about the contraindication for SCID and that it should be placed on the first page under a separate bullet.

Finally, Dr. Fisher suggested improving the syntax of several sentences to make the statements simpler and clearer. For example, "babies may be slightly more likely to be irritable," essentially says "babies may be irritable."

Mr. Wolfe invited comments on whether or not the reassurance that intussusception is not a risk factor in the new rotavirus vaccines (as it had been in Rotashield) should be deleted since so much time has passed since that issue. Dr. Fisher agreed that it was not necessary but should remain in the VIS for at least another five years.

DVIC Clinical Case Update
Rosemary Johann-Liang, M.D., DVIC

Dr. Johann-Liang discussed the medical review process that occurs when a claim is submitted to the National Vaccine Injury Compensation Program (VICP). She noted that the numbers of submissions requiring review have been increasing in the last few years. Non-autism reports, mainly flu vaccination events, have increased significantly while the numbers of autism claims have declined following the rulings on the recent omnibus autism proceedings. The majority of autism cases being currently reviewed are mainly from the thousands of cases suspended at the beginning of the Omnibus Autism Proceeding, a limited number of which are being activated each month at the direction of the Special Masters' office. These "activated" autism cases are being reviewed in terms of jurisdiction by the Department of Justice team, and in some instances, forwarded to DVIC for medical review.

Concerning the ages of the individuals who are the subject of the claims, before 2000 most were children, based on childhood vaccines. More recently the majority of claims are coming from adults who have received the flu vaccinations and, to a lesser extent, adolescents and young adults receiving the human papillomavirus vaccine. The shift has in part been the result of the huge number of flu vaccines distributed. Dr. Johann-Liang added that the increase in claims from adults age 30 to 49 may reflect the fact that many health care professionals are required to obtain influenza immunization.

In response to an inquiry about comparing the number of vaccinations actually administered (the denominator in the equation) to the number of claims submitted, Dr. Johann-Liang stated that no valid figures on actual vaccine doses administered are available (only distribution numbers)

Dr. Johann-Liang provided a profile of the cases reviewed since the beginning of the fiscal year. There were 498 medical reports generated based upon the review of submitted claims, 145 of which were related to the activated autism claims. About half of the cases filed were for adults, 45% related to influenza vaccines, 13% were filed by adolescents and young adults who received the HPV vaccine, and 12% involved claims that named two or more vaccines as the alleged cause of the adverse event. All other vaccines accounted for less than 10% of the reports.

Dr. Johann-Liang stated that in terms of specific adverse events, Guillain-Barré syndrome led the list with 30% of the reports, other demyelization conditions (12%) and skin conditions, shoulder/arm injuries, encephalitis, underlying disorder, immune and autoimmune responses (all between 5% and 7% of reports), and a catch-all miscellaneous grouping that amounted to 24% of reports. About 6% of the reports were related to death, with the majority of the cases showing underlying conditions as the cause of death.

Dr. Johann- Liang commented briefly on the HPV vaccine, for which 54 claims have been filed since 2008 in women age 12 to 27, who had one, two or three doses (about a third of the women in each category). One older male filed a claim. About 16% had other vaccines simultaneously but all are claiming that HPV caused the adverse event. Neurologic side effects were most common (nearly half of all events). Since syncope is more common after vaccination in the adolescent age group, 6% of the reports involved fainting, and the adverse event may have been injury related to fall or other mishap caused by the temporary loss of consciousness.

Concern was expressed about the timely processing of claims and Dr. Johann-Liang noted that the process may be slowed when the file is incomplete and additional information is required, most often from the petitioner. Also for allegations against newer vaccines, such as HPV cases, there is a lag time

between the time of injury and the time of filing due to the 3 year statute of limitations. The medical reviewers at DVIC have instituted process enhancers including templates for medical reviews (particularly with influenza cases since there are so many) to expedite the timely processing of claims from the medical review perspective.

Dr. Johann-Liang briefly commented on the reports related to shoulder/arm injuries, mainly caused by the mechanical process of the administration of the vaccine -- angle of entry, length of needle (too short, the vaccine may dissipate in fatty tissue' too long, the needle may injure bursa), possible difficulty in locating muscle tissue in older, frail individuals, etc. A detailed analysis of the shoulder injury case series is in progress and a resulting manuscript will be submitted for publication.

Finally Dr. Liang commented that the profile of adverse events is changing partly because of the demographics of the vaccinated populations – as older individuals become the majority of vaccine recipients, preexisting conditions play a more important role, as does physical condition.

IOM Committee on Vaccine Adverse Events Update
Kathleen Stratton, Ph.D., Study Director, Institute of Medicine

Dr. Stratton reminded the Commission that comment on IOM studies is limited until the study is complete, but that there were a number ways information could be shared. First, the committee roster, including biographical information about members, is available on the committee's web site. She noted that half of the members are epidemiologists, some of whom are practicing clinicians. There is a wide range of expertise among the other members – pediatric and adult neurology, rheumatology, and members who are specialists in allergies and internal medicine. The web site also includes a list of the adverse events that the committee will be assessing. The sponsor, HRSA, has charged the committee to look at the scientific literature with regard to epidemiology, clinical and biologic research related to specific vaccines and the specific adverse events. There are currently eight adverse events on the list and the committee has the option of recommending the addition of one or more additional adverse events if deemed appropriate. The committee is charged with providing the Secretary of HHS recommendations based on the relationship of the vaccines to the adverse events, and not recommendations as to what vaccines and adverse events should be added to or removed from the Vaccine Injury Table.

Also on the committee's web site is the bibliography of scientific literature that is available (over 12,000 entries), about 10% of which will finally be identified as relevant to the study. Public comment is welcomed concerning any aspect of the study, including recommending additional articles for review. The list will be periodically updated through refreshing searches until about the fall of 2010, when the report will begin to be developed.

Dr. Stratton commented that the committee has held three open information-gathering meetings, three closed meetings, and additional meetings, both open and closed, may be held, She added that there is a "public access" file into which anything contributed for consideration by the committee is added, and any member of the public may request access to items in that file. Currently there are 65 items in the file including contributed papers, e-mails and other information provided to the committee during any of its open meetings or submitted with specific approval to include in the public access file. If such permission not granted the item is not accepted by the committee. Some information considered proprietary by the IOM legal counsel may be redacted.

Asked about final release of the report, and whether it would be available in time for the June 2011 ACCV meeting, Dr. Stratton commented that although the report would be completed before that date, the Academies' review process is not fully predictable since it depends on volunteers. She assured the Commission that she would make every effort to meet that deadline and would keep the Commission informed of the progress toward release of the final report.

ACCV Communications and Outreach Workgroup Report

Sarah Hoiberg, ACCV member

Ms. Hoiberg reported that the Workgroup met before the meeting and discussed issues related to timely posting of minutes, transcripts and other Commission information. She commented on participating in the Banyan bi-weekly conference calls that provided updates on progress toward the outreach plan Banyan is preparing. They are on schedule and are providing sufficient information to ACCV. Ms. Hoiberg noted that one issue that must be addressed is the Americans with Disabilities Act, which requires compliance with Section 508 of the Act, which has to do with materials presented to the public on any web site. There are modifications to the data files that make it possible for individuals with certain disabilities to access the information in the files (e.g., an application that reads a text document aloud for individuals with impaired hearing).

Public Comment

Ms. Gallagher invited comments from the public. Mr. James Moody commented that the IOM committee should be advised to consider a program standard affirmed by the Court of Appeals in terms of biologic plausibility with regard to causation of adverse events. That standard is a five-part test of the biologic mechanism of action of an event. He added that it would be helpful if, in addition to making recommendation on whether or not evidence does or does not exist, the IOM study would identify gaps in the science that apply to the determination of causation of adverse events. The IOM's recommendations for future research would help congressional efforts to support research programs in the area of vaccine adverse events.

Future Agenda Items

There was a brief discussion about rescheduling the fall meeting of the ACCV such that it would coincide with the Judicial Conference. Dr. Evans agreed to look into it and make a change in the schedule, if possible.

Concerning agenda items for the next meeting, Dr. Fisher requested a report on the Countermeasures Injury Compensation Program, and Ms. Tempfer suggested including some of the regular updates, such as the report provided at the meeting by Dr. Johann-Liang. Ms. Gallagher noted that a process for the more timely review of Vaccine Information Statements was required, such as teleconference reviews between meetings. She asked Dr. Fisher to consider the issue and present a proposal at the next meeting. Dr. Herr invited members to contribute agenda items to the Agenda Committee, preferably at least two weeks before the next meeting.

Adjournment

There being no other business, on motion duly made and seconded, the meeting was adjourned by consensus at 11:30 a.m.

_____ _____

Charlene Gallagher, ACCV Chair Sherry K. Drew, ACCV Vice-Chair

_____ _____

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