

Advisory Commission on Childhood Vaccines (ACCV)

October 28, 2010

Minutes

Members Present

Charlene Gallagher, J.D., chair
Sherry K. Drew, J.D., Vice Chair
Tawny Buck (via teleconference)
Magdalena Castro-Lewis
Margaret Fisher, M.D.
Thomas Herr, M.D.
Sarah Hoiberg
Jeffrey M. Sconyers, J.D.
Tamara Tempfer, RN.-C., M.S.N., P.N.P.

Executive Secretary

Geoffrey Evans, M.D., Director, Division of Vaccine Injury Compensation (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 welcomed all in attendance in person and by teleconference to the 78th meeting of the ACCV. After calling for approval of the September meeting minutes, on motion duly made and seconded, the minutes of the September 2010 meeting were unanimously approved.

Review of Vaccine Information Statements (VIS)

Ms. Gallagher invited comments on the draft VIS documents related to rotavirus and oral polio vaccines. Joining the call were Centers for Disease Control and Prevention (CDC) staff, including Mr. Skip Wolfe, Ms. Jennifer Hamborsky, and Mr. Kevin Malone.

Dr. Fisher stated that rotavirus does not cause severe diarrhea as suggested in section 1. Before the availability of the vaccine, almost all children under five were infected and few developed severe diarrhea. The statement should indicate that it may cause diarrhea or that symptoms include diarrhea.

Mr. Sconyers said that although there may be no evidence that the vaccine causes illness, the statement in the VIS should be less emphatic since there is also no evidence that the vaccine does not cause illness in recipients.

Ms. Buck and Ms. Hoiberg commented that in the last paragraph of section 2, the words “remarkably” and “dramatically” are emotionally charged words that make the paragraph sound like a sales pitch. There was a suggestion that a more objective description of efficacy would be consistent with statements in other VIS documents. However Dr. Fisher commented that the rotavirus vaccine has had a significant effect on reducing incidence. Mr. Wolfe suggested including statistics to illustrate point, and perhaps using the word “significantly” as the adjective describing the reduction in incidence.

Ms. Hoiberg suggested including the two brand names of the available vaccines (since the schedule of administration is different). In response, Mr. Wolfe pointed out that brand names are rarely used in VISs and that other brand names may appear in the marketplace over time. Mr. Malone added that recipients rarely know the brand names of vaccines and that including brand names in VIS discussion might suggest an endorsement by CDC. Mr. Sconyers suggested adding a statement that there is more than one brand and the parents should ask the provider which brand is being administered.

In section 4, under the paragraph mentioned “moderately or severely ill” babies, Ms. Buck suggested that parents are not in a position to differentiate between the two and the paragraph should be simplified to simply state that if a baby is ill the parents should ask the provider whether the vaccine should be delayed. Mr. Sconyers commented that, in the first sentence, changing the word “should” to “can” (probably wait) would give the parents a better choice.

There was a brief discussion about the warning in Section 4 about severe combined immunodeficiency (SCID) and the fact that at the age when the vaccines are administered most parents would not be aware of such a diagnosis. Although a very rare disorder in infants, Dr. Fisher noted that most states are now recommending a SCID screen at birth. Mr. Wolfe stated that, even if parents are not specifically aware of the condition in their child, SCID is a significant contraindication to taking rotavirus vaccine and the statement must be in the VIS.

Mr. Sconyers commented that the sentence about informing the provider if a child has had intussusception should include some indication that the condition is potentially a severe side effect. Dr. Herr suggested that the sentence should be more forceful, perhaps using the words “inform your doctor” rather than just “check with your doctor.” Mr. Wolfe added that at the time a history of intussusception is a precaution and not a contraindication.

Concerning section 5, there was agreement that the heading for mild problems should be more clearly identified as a subsection. Mr. Wolfe explained that the first sentence concerning serious problems is standard in most VISs and that, since there have been no severe side effects identified for the two rotavirus vaccines currently available, no additional emphasis is placed on serious risks in the statement (therefore no such subheading in the section).

Mr. Sconyers expressed concern about the estimated risk of intussusception in the VIS of 0 to 4 cases per 100,000 inoculations, since those figures could range from no additional risk to as much as 15% increased risk. Ms. Hamborsky stated that the estimate had been changed in the VIS (not yet indicated in the version being reviewed) to one per 100,000 inoculations. The explanation was offered that the original figures were derived from a single study in Mexico and that since there have been three additional studies for the two vaccines, an estimate of one event in 100,000 inoculations was considered the best estimate of this very rare side effect. There is no evidence from U.S. experience that supports an estimate of side effects as high as 4 per 100,000. Dr. Evans mentioned that Dr. Marion Gruber might offer some comments later in the meeting about the Food and Drug Administration’s (FDA) current thinking about the risk and product labeling.

In sections 6 through 8, the Commission members had no additional recommendations.

Mr. Wolfe invited comments concerning the multi vaccine VIS covering an infant’s first series of vaccines (DTaP, polio, Hib, rotavirus, Hepatitis B and PVV13). There was a brief discussion about the best way to communicate to parents that a vaccine produces immunity in the same way having the illness produces immunity. It was noted that the issue is not clear cut, and that in either case an individual may or may not develop antigens or antibodies and therefore immunity to a disease. There was a suggestion for wording as follows: “A child’s immune system makes antibodies to a vaccine the same way that it would make antibodies if the child had the disease.” This means they may develop immunity in the same way – without having to get sick first.” Mr. Wolfe commented that the level of scientific content must be carefully considered, since some parents will not know what terms like antibodies, antigens, and so on mean.

Ms. Buck commented that the sentence, “Combination vaccines are as safe and effective as these vaccines given separately,” may not be accurate since there is at least one vaccine that causes higher rates of febrile events. Mr. Wolfe agreed that, since that particular vaccine was not included in the combination being considered in this VIS, that the sentence should begin, “These combination vaccines,” to clearly exclude other vaccines that may cause such side effects.

Finally, concerning the introductory paragraphs, it was noted that the illnesses have not been completely eradicated and that “in other parts of the world” they have reappeared. Ms. Jessica Bernstein noted that

such an event also happened in California so that the sentence should indicate that possibility. Mr. Wolfe noted that those California cases of pertussis were in children too young to be vaccinated, but that he would take the comment into consideration.

Turning to the individual vaccines, Mr. Sconyers noted that the statistics on IPV in the combination VIS did not agree with the statistics in the individual IPV VIS, and Mr. Wolfe agreed that they should be checked and made consistent. Mr. Sconyers also suggested alternative wording for the tetanus section, which currently has the word "victim" as part of the discussion. His wording: "About one in five people who get tetanus die from it." Others suggested substituting "person", "patient" or "infected person" for the word "victim." Finally, Mr. Sconyers suggested adding a clarification to the statement under the rotavirus section (section 8) that the 70,000 cases occur within the U.S.

Asked to comment on the table of routine baby vaccines included in the VIS, Mr. Sconyers suggested that the comments about additional doses of hepatitis B and polio are less emphatic than in the individual VISs.

Finally, Ms. Castro-Lewis suggested that, when formatting the final VIS, that the items mentioned in the introductory section match subheadings later in the document so that a logical order is maintained.

Under the section on precautions, Mr. Sconyers noted that in the first paragraph, the decision to vaccinate or not is made by the parent, not by the physician. Under the following section, Risks, Ms. Hoiberg took exception to the comment under serious DTaP events, that long-term seizures, "have been reported so rarely that it is hard to tell whether they were actually caused by the vaccination of just happened to occur afterward." She requested that the sentence be deleted. Finally, in the additional section on polio history, Mr. Sconyers suggested it would be helpful to indicate that the number of cases cited were cases per year.

**Communications and Outreach Workgroup Report
Banyan Communications, Ms. Sally Deval, Ms. Merrell Hansen
Altarum Institute, Dr. Namratha Swami**

Ms. Merrell Hansen commented that DVIC had awarded a contract to Banyan Communications in the fall of 2009 to create a communication plan for the National Vaccine Injury Compensation Program (VICP). She said that her presentation would bring the Commission up to date on research, an overview of the plan, a description of the proposed target audiences, and recommendations strategies and tactics to accomplish the plan. Ms. Sally Deval noted that the latest detailed communications plan had been distributed to Commission members and that the presentation would be a summary. The Banyan contract involved a series of steps to arrive at the point where the plan was considered implementable. The first was formative research, conducted by the Altarum Institute, during which initial foundational information was gathered from what was considered to be the potential target audiences of the outreach program. In terms of implementation, first drafts of materials are developed and submitted to DVIC for vetting, approval, clearance and compliance (with various federal regulations, such as Section 508 dealing with access by individuals with disabilities). Final message materials for the program are developed and tested in focus groups by potential recipients. When those materials are deemed appropriate and effective, the program is implemented, at which time a process of tracking and evaluation begins. Ms. Deval stated that the primary outcome or objective of the plan is to inform target audiences that VICP exists.

Dr. Namratha Swamy described the formative research that relied on a literature search, an environmental scan to better understand target audiences, discussions with subject matter experts from the government and academic areas, and the conduct of six focus groups in two cities. The process confirmed that there is limited awareness of the VICP; that the CDC focuses on both health care providers and consumers in educational efforts; and that consumers rely mainly on health care providers for information about vaccines. It was also clear that whatever messages are created must be relatively neutral in terms of either encouraging or discouraging information. Finally, the research revealed different attitudes between health care providers and consumers with regard to the content and dissemination of material related to vaccines, a question that needs to be examined.

Ms. Deval explained that the research pointed to five important audiences – health care providers, who most directly impact the consumers, who are parents (or prospective parents), older adults, Spanish-speaking adults, and individuals in the lower social economic status (SES) categories. Noting that in marketing terms a secondary audience is an audience that can carry the message to the primary audience – primary and secondary is not related to importance of the audience, but to the function of the audience – a secondary audience must have either direct access to the primary audience, the trust and confidence of the primary audience, or both. In this program the secondary audiences are the health care providers, direct-to-consumer outreach (any channel not covered elsewhere that has direct contact with users), partners (associations, health departments, federal agencies, etc.) and broadcast media. In terms of broadcast media, the plan does not anticipate expensive media campaigns, but carefully planned and executed programs that target very specifically the primary audience.

Ms. Deval outlined the key attributes of the plan – accessibility, so that information is readily available and easy to find; responsiveness, so that VICP or any other partner responds to inquiries in a timely way; practicality, such that the plan will not try to change attitudes (a major challenge) but will focus on information availability; empowerment, so that health care providers and others can be confident that they have the right information at the right time; cost-effectiveness, including a formula that allows scaling of the program if funding changes; partnership opportunities, that allow interested partners to join the effort at whatever level of commitment is appropriate to the partner; and sustainability, a plan than can be managed by different entities over time.

Developing strategies is a product of establishing the overall objective (to make people aware of VICP), defining objectives and then fleshing out strategies and later tactics that will make the program effective. Ms. Deval described six strategies. The first strategy is to educate, then motivate and empower, health care professionals to make the VICP message available to patients and their peers. The second strategy is to provide that education through organizations and other entities that the providers trust. The third strategy, which comes from focus group feedback, is to raise awareness of the VICP through online channels of communication. The fourth strategy is to develop the same online opportunity for health care providers. The fifth strategy is to help individual's access information, not only through online sources, but through contact with peers, partners and community organizations. Finally, the sixth strategy is to develop awareness among those who are not even aware of vaccine injury, to push messages to that audience in a targeted way that will expand awareness of the VICP and its web site.

Ms. Hansen briefly discussed the development of the messages and tactics for getting those messages to the proper audiences. Messages should be simple and clear, constructed in a user-oriented way, factual, and culturally compatible with the targeted audience. Language should avoid legal phrases and have easy to understand explanations of scientific concepts. The use of statistical information is helpful if presented in a non-technical manner.

One important recommendation is the improvement of the VICP web site, including simple, intuitive navigation (clear indications of where information is and minimal click to get there), one-click transition of any content to a Spanish version, and search engine optimization (VICP should appear in the first few pages of results). Content should be composed in culturally-compatible ways, especially for Spanish-speaking readers and those in the lower SES groups. The program should include carefully selected access to social media, including blogs, and should offer some educational webinar sessions, especially for the health care providers. Finally, there should be consideration related to developing seminars and establishing a Speakers' Bureau.

Discussion of Banyan Presentation

In terms of the highest priority issues, Ms. Hansen stated that the best return on the investment would come from a revamped web site, which serves all audiences, and that effort must include an aggressive program to drive users to the web site – enhancing the search engine response, encouraging institutional partners (such as associations) to add a VICP link to their web sites, using radio PSAs to reach older individuals. Ms. Deval said the second priority might be education through online training and webinars targeted at health care providers. A third area of importance is focusing on parents, since they are very sensitive to the health needs of their children.

Concerning the web site, there was an observation that rather than a click to reach a translation page, the web site should have a language preference on its home page which would lead to a parallel web site totally constructed in the selected language. It could begin with Spanish but include other major foreign languages in the future.

There was a brief discussion about how doctors might respond to the program and how they are currently treating the issues of vaccine-related injuries. Dr. Fisher commented that those who are aware probably provide information about vaccine issues, and there are groups such as the American Academy of Pediatrics and the American Academy of Family Physicians that are willing to add vaccine information to their publications and communications to members. However, it was observed that most physicians rarely see vaccine-related injury, seldom consider the possibility when a patient presents with a problem, focusing on treating the problem first.

Concerning the effort to inform the general public, Dr. Daniel Salmon commented that with 300 million people in the United States, such a project would be daunting, and especially considering the rarity of vaccine-related adverse events a challenge when justifying allocating resources to the effort. Considering that, he suggested that the most efficient use of such resources would be to focus on specific health care providers, who are either involved in administering vaccines, or who are most likely to treat injuries that may have originated in a vaccine dose. Ms. Buck added that, since most physicians are going to be focused on the problem, and not the remote possibility that it arose from a vaccine, education about that possibility would be appropriate; something that would prompt a physician to inform a parent or patient about the program early on, even if he or she does not consider vaccines the probable cause of the problem.

Physician focus group feedback revealed some are reticent to inform patients about serious adverse effects of vaccine because the patient may choose not to be vaccinated. That suggests a barrier that may be difficult to overcome when relying on health care providers for information dissemination. Another observation derived from the focus groups was that patients often can recall receiving vaccine information, specifically the VIS, but either forgot the about information or were overwhelmed by the amount of information on the form. With regard to the physician informing every patient about vaccine issues, and considering the rarity of adverse events, there was a comment that the physician's time counseling the patient during an appointment could be considered better spent on topics such as childhood obesity and diabetes. Dr. Herr also noted that if physicians rely on diagnosis by exclusion, that is, ruling out possibilities, the possibility of a vaccine-related reaction may be well down on the diagnostic list.

Mr. Sconyers said the plan as described relies too much on targeting general audiences and should focus mainly on health care providers, specifically physicians, who need to know the importance of recognizing the symptoms of a vaccine-related injury and how to advise their patients about the alternatives, including the VICP. He added that the plan's reference to social media, blogging and twittering, most of which are personalized avenues of communication, may not be practical because of vaccine program privacy requirements that may severely restrict any use of those alternatives. Finally, Mr. Sconyers noted that in two places in the presentation there had been mention of "positive VICP messages" and he felt that the Commission's job usually concerned issues that were not so positive, so that marketing of VICP might not be an appropriate approach.

Ms. Tempfer asked about the possibility of providing continuing education credits with the webinar and online training, and Ms. Deval said that CDC offers such accreditation and it would be possible to explore the mechanism for that.

Ms. Gallagher closed the discussion, noting that there would be opportunities at future meetings of the Communications and Outreach Workgroup to discuss the plan further.

Report from the Division of Vaccine Injury Compensation

Dr. Geoffrey Evans, Director, DVIC

Dr. Evans provided a report of DVIC activities and statistics since the recent last meeting of the ACCV. Total claims filed hit a record mark of 429, higher than even 1999 when a bolus of hepatitis B claims were filed at the 2-year deadline for filing retroactive claims (dating back 8 years) whenever a new vaccine is added to the program. The trend in adult claims continues accounts for more than half of the claims filed. The increased access to flu vaccines and a greater awareness of the VICP could account for the record number of filings to date. Eighteen autism claims were filed this fiscal year versus 109 last year. Adjudications are fairly consistent with previous years, and settlements continue to slightly increase; now standing at just over over 80%. Petitioner's awards were also significantly higher in the last year, partly because of higher awards. Of the ten highest awards in program history, four were in 2010. Finally, the trust fund balance stands at about \$3.25 billion, growing at slightly less than \$100 million in 2010. Concerning activities since the last meeting, Dr. Evans noted that he and Ms. Castro-Lewis attended the September 14 and 15 National Vaccine Advisory Committee meeting, providing updates on the program and the Commission. He said he also attended a one-day workshop in Philadelphia on September 21 on Science, Ethics and Politics of Vaccine Mandates (Dr. Salmon also attended and made a presentation). Dr. Evans attended the annual meeting of the American Academy of Pediatrics in San Francisco in early October and visited the Department of Justice's booth, being told that a number of pediatricians had stopped and confirmed their awareness of the VICP. He noted that staff from the Office of General Counsel and his office had attended the *Bruesewitz v. Wyeth* hearing before the Supreme Court on October 13. A decision is expected sometime before June of 2011. Finally, he presented an overview of the VICP to graduate students in the Department of Immunology at Children's Hospital in Philadelphia, Pennsylvania on October 14.

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 referenced the Power Point materials, entitled October 28, 2010 Department of Justice Power Point Presentation (DOJ PP), as part of his presentation. Mr. Rogers said he hoped to give the ACCV a recent, "real-time" snapshot of the litigation in the Program.

Personnel

Mr. Rogers announced that two replacement paralegals had been hired since the last meeting, bringing the total number of paralegals in the office to seven. The office is looking to hire one more.

Statistics

In the last reporting period (August 3, 2010 to October 3, 2010), there were seventy-nine petitions filed (seventy-eight non-autism and one autism). (DOJ PP, p. 3). Mr. Rogers reported that the number of petitions being filed was increasing, and noted that those ACCV members who attended the Court of Federal Claims Judicial Conference heard about this trend. Newly-filed petitions are primarily adult, non-autism claims. Mr. Rogers commented that if the number of petitions continues at the same level of this past reporting period, 468 petitions will be filed in the fiscal year. Turning to statistics regarding adjudicated claims, Mr. Rogers reminded the ACCV that DOJ tracks judgments as soon as they are issued, but does not send the judgments to HHS until the claim is ready for payment. As a result, statistics between the two agencies may vary. In the last reporting period, thirty-three adjudicated claims were compensated. (DOJ PP, p. 4). Two of those claims were conceded, with one resolved by a proffer and one by a stipulation. Mr. Rogers reiterated that a proffer involved both parties agreeing on the

evidence (usually involving only one life care planner). In cases involving a stipulation, the parties don't agree on the evidence, but still resolve the case with a compromise. Of the thirty-one cases not conceded by HHS, one was resolved by a proffer, one was a decision awarding damages, and twenty-nine were resolved by stipulation. (DOJ PP, p. 4) In the last reporting period, sixty-eight claims fell under the "Not Compensated/Dismissed" category. (DOJ PP, p. 4). Twelve were non-autism petitions. Mr. Rogers noted that four of these twelve were not involuntary; they were requested by petitioners. Fifty-six adjudicated petitions were autism dismissals. (DOJ PP, p. 4). In the last reporting period, there were four petitions voluntarily withdrawn from the Program. (DOJ PP, p. 5). Mr. Rogers explained that petitioners have a right under the Vaccine Act to withdraw their claim if a decision hasn't been issued within a certain time period. He noted that it is unusual for a petitioner to pull out of the Program before the case is resolved with one of the resolutions he discussed on pp. 3-4 of the DOJ PP. Mr. Rogers noted that a glossary of terms, along with a flow chart depicting case processing in the Program, were provided. (DOJ PP, pp. 6-8). Mr. Rogers commented that the most common pathway to compensation in the Program is through a final decision awarding compensation based upon a settlement (the pink box on the left side of the flow chart). Mr. Rogers noted there was some discussion at the Judicial Conference regarding this common pathway to compensation, and whether it was what the Framers of the Vaccine Act intended. Mr. Rogers stated that DOJ believes this common pathway to a settlement decision is a good thing.

Autism

There were no changes to the status of the Autism cases since the last ACCV meeting. The Theory One and Theory Two cases are resolved, and the appeals process is complete. (DOJ PP, pp. 9-10). The Office of Special Masters has told those petitioners remaining in the Omnibus Autism Proceeding that they can move forward with their claims, but will need additional evidence to obtain an outcome different from the OAP test cases.

Appeals

Mr. Rogers stated that the most significant update he had for the ACCV was regarding the status of Cloer, a case pending at the U.S. Court of Appeals for the Federal Circuit (CAFC). Since the last ACCV meeting, the CAFC vacated the earlier panel decision in Cloer and granted en banc review. (DOJ PP, p. 11). This means that the original decision is vacated, and the full panel of judges will rehear the case and issue a new decision. The case is now in the briefing stages. Mr. Rogers briefly discussed other appellate activity at the CAFC. Four new entitlement decisions were recently appealed. (DOJ PP, p. 12). Mr. Rogers later clarified in response to Ms. Hoiberg's question that, in fact, two appeals Knight v. HHS (formerly known as Rotoli v. HHS), and its companion case, Porter v. HHS, were filed by respondent. Turning to appellate activity at the U.S. Court of Federal Claims (CFC), Mr. Rogers stated there were no cases decided at the CFC this reporting period. (DOJ PP, p. 13). Veryzer v. HHS and Hammit v. HHS are new appeals at the CFC brought by petitioners. (DOJ PP, p. 14). Mr. Rogers then discussed upcoming oral arguments. (DOJ PP, p. 15). Masias v. HHS and Riggins v. HHS are both attorneys' fees and costs cases. McCollum v. HHS is a damages case that questions the court's authority to change judgment after judgment has been entered.

Settlements

Mr. Rogers directed the ACCV's attention to a chart showing recent stipulations in the Program (DOJ PP, pp. 16-19). Most cases took three years or less to be resolved. There were many cases that took one to two years to be resolved. One case took only one year, which requires nearly perfect coordination by all parties in the process.

Questions and Comments

Dr. Salmon asked if petitioners who voluntarily withdraw from the VICP can file a civil suit. Mr. Rogers explained that voluntary withdrawal preserves, and does not prejudice or diminish, a petitioner's right to a future civil action. This issue is at the center of the Bruesewitz case pending before the Supreme Court. Dr. Salmon asked additional questions about the nature and timing of the voluntary withdrawal process. Mr. Rogers explained that generally, a petitioner must remain in the Program at least 420 days before withdrawing.

Adjuvants in Vaccines

Dr. Mark Walderhaug, Center for Biologics Evaluation and Research (CBER)

Dr. Walderhaug discussed CBER's program to develop risk data on vaccine adjuvants and to establish a positive line of communication with the science community and the general public concerning the risks and benefits of these additives which are intended to improve the efficacy of vaccines. The first is what is planned to be a series of white papers on adjuvants concerns aluminum, which has engendered some concern about potential neurotoxicity.

Concerning the rationale for adding aluminum to vaccines, Dr. Walderhaug explained that its presence in some vaccines significantly enhances immune response by increasing the rate at which cytokines are secreted thereby increasing interaction with B cells and T cells, which drive the immune response to the target antigen, whether from the vaccine or the actual illness. Without the aluminum adjuvant the body would need higher levels of antigen exposed over a longer time to attain the same immune response.

The Agency for Toxic Substances and Disease Registry conducted research in 2002 on risk levels for aluminum in infants. Infants are exposed to aluminum to a limited extent in utero, and after birth from either breast milk or formula. The result of the research established a minimal risk level based on a mouse model, from which the exposure in humans was calculated to be a hundredfold lower than was considered safe in the mouse. The maximal level of exposure in infants based on available aluminum in either breast milk or formula was calculated to be well below the minimal risk level, and even when aluminum exposure from the infant vaccine series was included in the calculation the minimal risk level remained below the maximal level of exposure acceptable. Recent research has revised the both the maximal level of exposure and the minimal risk level to even more conservative levels.

Dr. Walderhaug also explained that consumed aluminum is non-soluble and therefore is poorly absorbed. However, when there is a brief time when it enters the small intestine that it becomes soluble and can be absorbed. Once absorbed, it is distributed throughout the body in extracellular fluids and blood and in soft tissue, like the lungs, heart and liver. However, aluminum is rapidly eliminated from the body in urine and to a lesser extent in feces, but some parts of the body, specifically bone, it is incorporated at low rates. Bone is a safe place for aluminum to accumulate and this is the location of almost all of the residual aluminum in both infants and adults. The recent research mentioned before also showed that injected aluminum may take more than 20 days to be transferred from muscle tissue to the rest of the body, and this slow rate of transfer keeps even the maximal level of exposure curve well below the minimal risk curve.

Ms. Buck asked whether background exposure was considered, in addition to vaccine exposure. Dr. Walderhaug indicated that they had not included background exposures, noting it was possible some infants could have higher exposure to aluminum. This has not been looked at and probably should be to see the range of exposure in some formulas, and perhaps other external exposures. In addition, Ms. Buck asked whether the guidelines were based on ingesting or inhaling versus injection. Dr. Walderhaug replied that the minimum risk level was based on oral exposure; that the oral exposure was adjusted to the blood exposure by using a known factor by which oral aluminum gets absorbed in the body. Aluminum is insoluble, and other than a brief period in the stomach when acid makes it soluble, once aluminum passes into the small intestine and gets precipitated, there is little opportunity for it to get absorbed in the body.

In summary, Dr. Walderhaug stated that even under maximal exposures, aluminum never exceeds the minimal risk level for infants and provides the benefits of enhanced immune response based on the inclusion of the adjuvant with vaccines. Therefore, the risk level is well below that set by federal standards and justifies the adjuvant in appropriate vaccines.

Update on Rotavirus Vaccines

Dr. Marion Gruber, Center for Biologics Evaluation and Research, FDA

Dr. Gruber announced that the November 16 and 17 Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting would address two interesting issues, the pathway to licensure for a new anthrax vaccine for post-exposure prophylaxis indication, which will be done under the animal rule since

anthrax cannot be the subject of an efficacy study in humans, and an additional indication for Gardasil, as a vaccine for prevention of anal dysplasia and anal cancer in males and females.

Turning to rotavirus, Dr. Gruber reminded the Commission that the disease causes severe diarrhea and dehydration in infants worldwide. In the U.S., before vaccine was available, there were over 70,000 hospitalizations annually and in the poorer countries around the world rotavirus still accounts for half a million infant deaths annually. By 2008, after the introduction of Rotateq and Rotarix the hospitalization rate in the U.S. decreased dramatically. Since intussusception was linked to a previously licensed rotavirus vaccine, Rotashield, it is important to assess the risks of intussusception with any rotavirus vaccine. Of note, intussusception can occur spontaneously, without the presence of a vaccine, at the rate of about 33 cases per 100,000 in the U.S.

Dr. Gruber explained that Rotarix is derived from a human rotavirus strain and is administered in two doses, orally. Only about 3 million doses are distributed within the U.S., although worldwide an estimated 76 million doses are distributed. The original safety/efficacy study was conducted in a number of foreign countries involving more than 60,000 infants who received either Rotarix or a placebo. No increased risk of intussusception following administration of Rotarix was observed within a 31 day period following any dose, and rates were comparable to the placebo group. Moreover, in a subset of about 20,000 infants followed up to one year after dose 1, there were 4 cases of intussusception with Rotarix compared to 14 cases in the placebo group. However, after Rotarix was approved in 2008 and began to be administered broadly, VAERS identified reports of infants with intussusception occurring days and sometimes weeks after vaccination. This information was included in the product labeling. For some reason, Dr. Gruber said, the VIS for Rotarix did not include this information. The manufacturer, GSK, was asked to perform a postmarketing study to assess the potential risk of intussusception in Rotarix recipients. The study was begun in 2009 with 50,000 subjects. Interim results are expected by April 2011. GSK also conducted a study at the request of the European Medicines Agency, the Mexican PASS study – post authorization surveillance study – the final results should be available in 2011. However, interim data was analyzed and GSK announced that the interim data suggested a small increase in risk for intussusception within 31 days after the first dose of vaccination. For the U.S., these findings translate to potentially zero to four additional cases of intussusception hospitalizations per 100,000 infants within 31 days of receiving the first dose of Rotarix. As a precautionary measure, the FDA added this information to the already existing intussusception subsection of the labeling. No changes were made to the contraindication section of the labeling. Dr. Gruber noted that there are other studies under way, one in Brazil that is not completed but interim data shows no increase in risk for intussusception. A more complete picture of the risk must be deferred until that study and others now under way are completed.

Turning to Rotateq, Dr. Gruber explained that the vaccine contains live reassortant rotaviruses isolated from human and bovine hosts, and is also administered orally, but requires three doses. This vaccine is widely distributed in the U.S., more than 30 million doses annually. The manufacturer, Merck, conducted a large pre-licensure trial of 72,000 infants, about half of whom received the vaccine and the other half a placebo. Excellent efficacy was demonstrated. In that study, subjects were monitored by active surveillance to identify potential cases of intussusception. There were six cases among the vaccine cohort and 5 cases in the placebo cohort within 42 days of any dose, suggesting no increased risk of intussusception relative to placebo. A post-licensing study of 85,000 infants was recently completed and data are under review. Additional studies are ongoing and will provide additional safety information and help to better understand the potential risk of intussusception with Rotateq. Notably, the labeling of Rotateq mentions that cases of intussusception have been reported. This information was received by VAERS. The Rotateq labeling was not changed because the Mexico study did not use Rotateq and information available to date does not suggest an increased risk of intussusception from Rotateq. Currently, the benefits of rotavirus vaccines outweigh the suggested increased risk for intussusception or any other potential risks. Dr. Gruber noted that FDA and CDC will continue to closely monitor the safety of both currently U.S. licensed rotavirus vaccines.

There was a brief discussion of the formula for arriving at the power needed for a study to identify a rare adverse event after vaccination. Dr. Gruber commented that usually safety studies are designed to detect adverse events at the rate of one per thousand, requiring about 3,000 subjects. The Rotateq and

Rotarix studies enrolled a much higher number of infants based on background rate for intussusception and experience gained with the Rotashield vaccine.

Rotavirus Vaccines and the Vaccine Injury Table

Dr. Vito Caserta, Countermeasures Injury Compensation Program (CICP), HRSA

Dr. Evans introduced Dr. Vito Caserta, noting that he had been the Chief Medical Officer for DVIC when intussusception was added to the Vaccine Injury Table (Table). Dr. Caserta briefly described the process required to add an adverse event or a vaccine to the Table, explaining that the Secretary of the Department of Health and Human Services (HHS) has the ultimate responsibility under the National Childhood Vaccine Injury Act of 1986 for adding items to the Table. Anyone, including the ACCV or its members, may petition the Secretary to add an injury to the Table. The petitions are considered by certain federal entities, including the ACCV, and when a decision is made by the Secretary a Notice of Proposed Rulemaking is published in the *Federal Register*, followed by a 180-day public comment period and a public hearing, usually conducted following a regularly scheduled ACCV meeting. After considering the comments from those two sources, a final rule is published, and after 30 days the injury is usually placed on the Table. Dr. Caserta explained that after the injury is added an individual may file a claim for an alleged injury that may have occurred during the preceding eight years. That claim may be filed within the next two years, after which the statute of limitation would expire.

Dr. Caserta explained that a vaccine may also be added to the Table if it is (1) recommended by CDC for routine use in children through publication in the Morbidity and Mortality Weekly Report (MMWR); and (2) imposition of an excise tax by Congress. When both requirements are satisfied the vaccine is added to the Table, as of the effective date of the excise tax.

Turning to the rotavirus vaccines, Dr. Caserta commented that the first such vaccine, Rotashield, was licensed in August 1998. Distribution began by October of that year, and within two months an unusual spike in reported cases of intussusception was detected by surveillance systems. CDC initiated a study in May 1999 and by late summer confirmed that there was a statistically significant relationship between the increased risk of intussusception and Rotashield. By the end of 2000, over 100 cases had been reported, half of which required surgical intervention. The general category of rotavirus vaccines was added to the Table in July 1999.

Dr. Caserta noted that there was an impediment to filing a claim for intussusception. The enabling legislation for the VICP required that a claimant have six months of residual effects of the adverse event to be eligible for compensation. In most cases, either the surgical or non-surgical treatment corrected the disorder and complete recovery occurred before the end of the six month period, making the claimant technically ineligible. Therefore, Congress amended the legislation in 2000, allowing claimants to file if there was inpatient hospitalization and surgery. A second category of rotavirus vaccines, specifically "live, oral, rhesus-based" (Rotashield) was added to the Table in 2002 with the associated injury of intussusception (onset interval up to 30 days after vaccination). The first claims based on intussusception were received in 2000. Ultimately, 31 were filed, of which 31 were compensated. Since then Rotateq and Rotarix have been licensed and there have been 15 claims filed.

Only the general category of rotavirus vaccines (without any condition specified), remains on the Vaccine Injury Table. The "live, oral, rhesus-based rotavirus vaccine" category was removed in 2008 since Rotashield vaccine has not been given in the US since 1999 and the 3-year statute of limitations for filing has ended

Dr. Evans commented that the ACIP is involved in looking at the post-marketing data for Rotateq and Rotarix and an update on the analysis of the data will be presented at the March 2011 ACCV meeting. Dr. Evans noted that, although intussusception is no longer on the Injury Table, such injuries related to the vaccine are still eligible for compensation and the program has received claims. He added that a petition was submitted by a claimant to add influenza vaccines and Guillain-Barré Syndrome (GBS) to the Table and ACCV will review the petition after the Institute of Medicine (IOM) study results have been released.

Dr. Caserta commented that there is a significant body of research concerning the possible relationship of the H1N1 vaccine to GBS that is now being reviewed by the National Vaccine Program Office (NVPO). The data analysis will help determine how to handle the H1N1 vaccine, which is not covered under the CIRC. Dr. Evans noted that the IOM report would not include recommendations for H1N1 since the data was so new.

During discussion, Mr. Sconyers commented that the program compensation policy for intussusception when the disorder was on the Table, which he explained covered perhaps 80% of claimants whose conditions were not attributed to the Rotashield vaccine versus 20% "legitimate" vaccine injuries simply because intussusception was on the Table. Dr. Caserta explained that because GBS is rare, a background rate of one in a million populations, it is more difficult to define the increased risk that may be superficially related to the vaccine. The sample sizes must be very large. The much more common intussusception allowed smaller sample size studies to determine that the increased risk was 20-30 times the background rate for the condition to occur as a result of vaccination up to two weeks after the inoculation. Dr. Evans added that the reason that the current vaccines are not considered in the Table is that, unlike the relative risk of intussusception from the Rotashield vaccine (greater than 20 times the background rate) the relative risk of Rotarix is only 1.8 times greater than background. The epidemiological data does not support an assumption that the vaccine is more likely to be the cause of the intussusception. The same has been true for GBS and the variety of demyelinating diseases.

Update on the Immunization Safety Office (ISO), CDC

Dr. Jane Gidudu, ISO, CDC

Dr. Gidudu outlined three recent publications, the first from the Vaccine Safety Datalink (VSD) published in *Pediatrics*. The study by Price et al adds more comprehensive scientific evidence to the existing science on the safety of thimerosal in vaccines and immunoglobulin products, which should help to further lessen concerns regarding children's vaccines. The study shows that receiving vaccines with thimerosal did not increase the risk of autism. The second published article by C. Vellozzi et al., reported on adverse events related to H1N1 influenza vaccine in the first four months after inoculation, showing that over 90% were non-serious, and that GBS, anaphylaxis and death were rare outcomes (each not higher than 2 per million doses distributed). The adverse event reporting profile after the 2009 H1N1 vaccines was consistent with that of seasonal influenza vaccines. The third paper by P. Moro et al., published in the *American Journal of Obstetrics and Gynecology*, addressed Vaccine Adverse Event Reporting System (VAERS) reports in pregnant women submitted from July 1990 to June 2009. The data showed no unusual patterns of pregnancy complications or adverse fetal outcomes after administration of either the Trivalent (TIV) or live (LAIV) vaccine, and there were no deaths reported during that period.

Dr. Gidudu commented briefly on the Australian experience with rotavirus vaccines, and the fact that World Health Organization (WHO) had announced that the benefits of the vaccines greatly outweigh the potential risks involved, but that further data collections and data analysis would continue using data from a number of surveillance systems in several foreign countries. She explained that 33.5 million doses of Rotateq had been distributed in the U.S. between March 2006 and August 2010, resulting in 5,511 reports to VAERS, of which 487 related to intussusception, 214 of which claimed the disorder had occurred within 21 days of inoculation, and 121 of those within seven days of inoculation. Comparatively, 2.8 million doses of Rotarix were distributed in a shorter time periods (April 2008 to August 2010) resulting in 285 reports, 22 of which claimed intussusception, 14 within 21 days of inoculation.

Noting that the VSD continues to monitor intussusception events in the 1 to 30 day period after inoculation, comparing children who received Rotateq and children who received other vaccines, but not Rotateq. Thus far the data have shown no increased risk of intussusception associated with the Rotateq vaccine. However, she added that the study had limited power to detect risk because of the size of the population involved in the study.

Turning to human papillomavirus vaccine (HPV), Dr. Gidudu explained that VAERS reports on 33 million distributed doses of HPV vaccine resulted in 16,423 adverse event reports, of which 8% were classified as serious. A subset of reports by males of adverse events included non-serious events such as dizziness, syncope and nausea, but also included a small number of serious events including GBS,

severe diarrhea, myocardial infarction, pulmonary embolus, and syncope with seizure-like activity. A VSD active surveillance study showed no increased risk of any pre-specified adverse event and no incidence of GBS within 40 days of HPV vaccine administration.

For the current influenza season, CDC surveillance systems will continue high priority surveillance for GBS, seizures (especially in children), narcolepsy, and adverse events that may be associated with high dose influenza vaccines. The VAERS surveillance of the 2010-2011 flu season began in September and VSD rapid cycle analysis is also under way for the flu vaccine.

Update from the National Vaccines Program Office (NVPO)

Dr. Dan Salmon, NVPO

Dr. Salmon described progress in developing the National Vaccine Plan, which has been reviewed by various Federal departments, the Rand Corporation, Institute of Medicine and the National Vaccine Advisory Committee (NVAC). The target is to release the final plan at the February 2011 NVAC meeting.

Dr. Salmon turned to the Vaccine Safety Work Group, noting that the final report, first planned for release at the February NVAC meeting, would probably be released at the June meeting. The Work Group is developing a White Paper on the US vaccine safety system, and is planning a closed meeting in November and a public stake-holders engagement meeting, perhaps in the early spring.

Next, Dr. Salmon updated the ACCV on the NVAC Vaccine Safety Risk Assessment Working Group, which is conducting an ongoing review of all data related to the H1N1 flu vaccines. The Working Group is currently receiving end-of-season data from all surveillance systems. One method of analysis is the VSD's Rapid Cycle Analysis, which calculates the rate of adverse events during previous flu vaccine programs and compares that to the incidence of adverse events during the vaccine program of interest, to reveal any variation in the rate of adverse events that might signal an increased risk. Since the H1N1 vaccine has a different formulation each season, a new risk might be indicated by this method. The Working Group anticipates releasing a final report at the February 2011 NVAC meeting.

Dr. Salmon noted the increased risk of GBS with the 1976 swine flu vaccine, which was confirmed in a 2002 IOM evaluation of the medical and scientific literature, but data from subsequent flu vaccination programs have not revealed similar epidemiological evidence. For the H1N1 flu vaccine, the Emerging Infections Program, with active surveillance for GBS in ten states, suggests a signal for GBS existed in those surveillance programs, which means that further investigation is indicated. The research challenge is the rarity, with a risk of one in a million background rate. If an increase in risk is associated with H1N1 vaccine, it would be very small. Designing a study that would provide the power required for a confident conclusion requires a very large number of subjects. Dr. Salmon indicated that his office is in the process of developing a meta-analysis of existing data from several surveillance programs, such as the VSD, Environmental Protection Agency (EIP), Department of Defense (DoD), Centers for Medicare and Medicaid Services (CMS), involving a very large number of persons. It is planned that the results of the analysis should be available in about 90 days.

Asked about progress in identifying a denominator for improving risk analysis of vaccine use, Dr. Salmon agreed that, except for some surveillance programs (like VSD), it is sometimes difficult to know exactly how many vaccine doses are administered, and who receives them. He described one method, called a self-control case series, which follows individuals for a period of time after receiving a vaccine and then again at a later date. The subjects therefore serve as both controls and study subjects, which does have the benefit of avoiding the confounding effect of study controls who do not receive vaccinations and who may not have the same characteristics as subjects who receive vaccines, two groups of subjects who might be quite different. This is the basis of the GBS analysis.

Update on the National Institutes of Health (NIH) Activities

Ms. Jessica Bernstein, National Institute of Allergy and Infectious Diseases (NIAID), NIH

Ms. Bernstein briefly mentioned two programs of research recently established at NIH. The first is a study of health outcomes in children with autism spectrum disorder (ASD), including observations about the influence of the disorder on the child's family. The study will develop data from a large database of

medical claims as part of the objective of developing a profile of basic health and social characteristics of the children and their families compared to children and families with no diagnosis of ASD. She noted that a stakeholders meeting was scheduled for October 29th.

Ms. Bernstein described the second study of advanced magnetic resonance imaging (MRI) scans to chart brain maturity with the objective of improving diagnosis of developmental delays and psychiatric disorders that do not display obvious structural abnormalities in the brain. If the concept is valid the accumulation of data on brain activity with maturation may provide a “normal” profile against which individual brain scans can be compared – something like the growth charts that pediatricians use to assess a child’s early height and weight development. The technique might provide a way to diagnose and monitor psychiatric and developmental anomalies to facilitate earlier treatment.

Public Comment

Ms. Gallagher invited public comment and announced that there were two individuals who had requested the opportunity to speak.

Ms. Rebecca Eastep, who stated she works with SafeMinds, read a statement which was prepared for presentation at a public meeting with the Special Masters. Noting that her son was a petitioner in the Omnibus Autism Proceeding (OAP), she stated that her son developed symptoms after a vaccination that was administered about ten years ago. She recalled contact by an attorney in 2002 who explained the VCIP to her, which he described as a swift, flexible and less adversarial alternate to the traditional tort process.

She expressed concern that the statute of limitation language starts the clock with the first symptom entered in a child’s medical record, even if the parent is not informed of the entry or the symptom by the physician. She noted that a child might not be formally diagnosed with ASD for a considerable period of time, which might extend beyond the three-year limitation. Ms. Eastep also expressed concern that the obstacles attorneys encounter in attempting to obtain vaccine safety data developed during other prior claims procedures which have been settled is challenging.

Finally, she stated she had attended the OAP test case and she was disappointed to observe that the proceeding were, in her opinion, quite adversarial in terms of the interaction between the Special Masters and the plaintiff’s attorneys. One result of that may be that claimants will find it more difficult to find willing legal representation and attorneys will find it more difficult to obtain expert witnesses. Ms. Eastep expressed concern about the program that she characterized as a government program, defended by government attorneys and judged by judges who work for the government.

Ms. Eastep expressed the opinion that two types of autism exist, the classic form that has been in existence since autism was first discovered, and a newer type, a regressive form related to vaccine injury. She also expressed the opinion that the incidence is greater than the currently published CDC estimate of one case per 110 children.

The second comment from the public was from James Moody, representing SafeMinds. Mr. Moody pointed out that the OAP resulted in a negative decision with regard to causation of autism, but that the recent settlement of the Poling case appeared to indicate that autism was related to the vaccine injury in that case. He expressed concern that the Court was sending 30-day notices to claimants in the OAP which in essence requires the claimants to develop new evidence if there is interest in continuing the claim. He added that autism science is basically an emerging one and claimants should be allowed to remain eligible for compensation until the science has become more definitive as to causation.

Mr. Moody then commented that, with regard to the information published in the vaccine information sheets, the studies referenced are usually conducted with subjects who are typically more healthy than the average vaccine recipient, and therefore the results may be biased. He suggested including a caveat in the VIS that parents should be aware that data from the post-licensure studies might be more accurate.

Finally, with regard to the product that might result from the Banyan contract, Mr. Moody noted that during the early phase of the VICP, most of the injuries were published in the Table which made it easier for attorneys to develop claims for compensation. Now that most of the injuries are not on the Table, the injury information is much less available. He urged that the Banyan report should encourage a more transparent treatment of the claims procedures and outcomes.

Future Agenda Items

Ms. Gallagher suggested that the next agenda be initially developed by the agenda work group for review by the members through e-mail exchange. She invited volunteers for the work group and Ms. Castro-Lewis, Ms. Tempfer, and Dr. Herr agreed to create the draft agenda. Ms. Hoiberg commented that she would call a meeting of the Outreach Work Group, probably before Thanksgiving, to discuss the Banyan presentation.

Charlene Gallagher, ACCV Chair

Sherry K. Drew, ACCV Vice-Chair

Geoffrey Evans, M.D.
Executive Secretary, ACCV

Date