

Advisory Commission on Childhood Vaccines

June 15, 2018

106th Meeting

Members Present

Karlen E. (Beth) Luthy, D.N.P., Chair ('18)

H. Cody Meissner, MD, Vice Chair ('19)

Kathleen F. Gaffney, PhD, RN ('19)

Tina Tan, MD ('19)

Alexandra Stewart, J.D. ('18)

Martha Toomey ('18)

Division of Injury Compensation Programs (DICP), Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services (HHS)

Narayan Nair, M.D., Acting Director, DICP

Andrea Herzog, Principal Staff Liaison, Advisory Commission on Childhood Vaccines (ACCV)

Welcome and Report of the Ms. Beth Luthy, ACCV Chair

Ms. Luthy called the meeting to order, welcomed the commission members, DICP staff, ex officio members, and guests on the teleconference call. A roll call confirmed a quorum of ACCV members and ex officio members on the conference call.

Public Comment on Agenda Items, Ms. Beth Luthy

Ms. Luthy invited comments from the public on agenda items. The conference operator informed the commission there were no requests to speak.

Approval of December 2017 and March 2018 Minutes, Ms. Beth Luthy

Ms. Luthy invited approval of the December 8, 2017 and March 8, 2018 meeting minutes. On motion duly made by Dr. Meissner and seconded by Mrs. Toomey, the minutes of the December 2017 meeting were unanimously approved. On motion duly made by Dr. Meissner and seconded by Ms. Toomey, the minutes of the March 2018 meeting were unanimously approved.

Work Group Update, Ms. Alexandra Stewart

Ms. Stewart announced that the ACCV Process Work Group agreed to revise the work group and add new commissioners to the membership. The work group met on April 11, 2018 and May 21, 2018 and officers were appointed at the May meeting: chair, Martha Toomey; vice chair, John Howie; and Ms. Stewart stated that she would serve as secretary. Ms. Toomey, was unable to attend either meeting, so Ms. Stewart agreed to present this meeting summary.

Mr. Howie suggested that existing recommendations (which can be found on the ACCV website) be identified and confirmed before discussion of new recommendations. He also suggested reviewing the funding and staffing issues that have caused the backlog in processing claims. There was some general discussion on how the commission interacts with the public, and some preliminary ideas related to increasing that interaction were briefly mentioned. The changes might include promoting inclusion, transparency and increased program education.

When the work group meets again it will clarify its mission, which would include consideration of process changes that the commission may submit to the new HHS secretary. The date and time for the next meeting has not been announced. It was observed that there has been a steady and dramatic increase in non-autism claims.

Report from the Division of Injury Compensation Programs, Dr. Narayan Nair, Director, DICP

Dr. Nair reviewed the agenda, which includes his report on the National Vaccine Injury Compensation Program (VICP), a report from the Department of Justice, and reports from the ex officio members (CDC, NIAID, FDA and NVPO). Dr. Nair presented VICP statistics, including data on the number of petitions filed in the current fiscal year, 783 as of June 4, 2018, and total annual filings since FY 2013. The average number of claims for Fiscal Years (FYs) 2008 – 2012 was 410. From FY 2013, following a decade of relatively stable claims, there has been a dramatic increase in non-autism claims filed with the VICP, so far peaking at over 1,200 claims in FY 2017.

Dr. Nair described the administrative funding approved for each fiscal year since 2013, when it was \$6.48 million and when there were 504 claims. Since then the annual claims have risen to 1,243 through FY 2017. In FY 2018 administrative funding increased to \$9.2 million, a 19% increase over the year before.

Dr. Nair discussed the VICP case backlog; all the claims with complete medical records filed in 2017 have been assigned for medical review. For FY 2018, the current backlog is 559 claims awaiting assignment to HRSA medical officers.

The awards paid through June 4, 2018, about 8 months into the current fiscal year, were slightly over \$130 million and attorney's fees and costs were \$19 million. For FY 2017, the amounts were \$252 million and \$30 million respectively. There were 877 adjudications in FY 2017, of which 696 were compensated (80%), and 181 were dismissed. To date in FY 2018, 405 cases have been adjudicated with 288 deemed compensable and 117 dismissed. Specifically, in FY 2017, 26% of adjudicated claims were resolved by concession, 7% by court decisions, 67% were settled by the parties to the case. There were 173 claims not compensated. To date in FY 2018, 35% were conceded, 19% decided by the court, 46 were settled and 100 were not compensated. These figures were slightly skewed by the fact that the reporting period was through June 14, instead of June 4.

In response to a question to clarify what a concession means, Dr. Nair explained that a concession is made by HHS when it is determined that, based on the evidence submitted in the case, it is more likely than not that the vaccine caused the injury or that the basis of the claim and the evidence submitted support the assumption that the injury is covered in the Vaccine Injury Table.

Noting the significant 19% increase in funding authorized for administrative purposes in FY 2018, Ms. Toomey stated that the work group would benefit by an explanation of how that dramatic increase came about. Dr. Nair explained that he did not know the specific detailed process that resulted in the increase, and that the program does not have direct input into the process, but he could look into it. Finally, asked about the term “non-autism,” Dr. Nair briefly explained the history of autism claims, the ultimate determination that the claims would be consolidated in an Omnibus Autism Proceeding (OAP), and the autism claims were separated from the reporting because of the potential of statistically misrepresenting the workload related to processing claims. He added that most autism claims have been dismissed, but that a very few, probably less than ten, are still pending.

Dr. Nair continued his report, noting that the Vaccine Injury Compensation Trust Fund (Trust Fund) stands at \$3.75 billion, and it was increased during the first part of FY 2018 (through March 31st) by \$168 million, \$137 million from excise tax revenues and \$32 million from interest on the fund’s investments.

Regarding program activities, on April 4, 2018, the Notice of Proposed Rulemaking (NPRM) proposing to add the category of vaccines recommended for pregnant women to the Vaccine Injury Table was published in the *Federal Register*. A public hearing is scheduled for September 17, 2018 and members of the public are encouraged to participate. On April 24, 2018 the DICP provided an overview of the program to managers of HRSA regional offices to help them inform grantees about the program.

During the discussion following Dr. Nair’s presentation, Ms. Toomey asked about the integrity of the Trust Fund. Dr. Nair explained that the statute limits disbursement of Trust Fund monies to administration the VICP by HRSA, and funding the Office of Special Masters of the U. S. Court of Federal Claims (CFC), germane programs in the Department of Justice, and compensating petitioners and paying their attorneys’ fees and costs. The statute can only be changed by act of Congress signed by the President.

Dr. Nair closed with an observation that the VICP is one of many programs within HRSA that provide benefits to the public. Other HRSA programs include: supporting poison control center; organ transplantation programs; contributions to the effort to reduce the effects of the opioid epidemic; funding for community health centers; and others. More detail is available on the HRSA web site.

Report from the Department of Justice, Ms. Catharine Reeves, Deputy Director, Torts Branch, DOJ

Ms. Reeves stated that her data covered claims from February 16, 2018 through May 15, 2018, which is a different reporting period than that discussed by DICP. Ms. Reeves stated that 263 claims were filed during this time period: 240 for adults and 23 on behalf of minors. The total number of cases adjudicated during this time period was 147: 113 compensated (43 conceded by HHS, 70 cases not conceded (68 decisions adopting a settlement; 2 decisions awarding damages)). There were 34 non-compensated cases, all of which were non-Omnibus Autism Proceeding claims. Finally, two claims were voluntarily withdrawn by the petitioners.

Turning to appeals in the U.S. Court of Appeals for the Federal Circuit (CAFC), Ms. Reeves stated that the CAFC issued three decisions during the reporting period: (1) *D’Tiole v. HHS* affirmed a ruling denying entitlement in a claim that flu vaccine caused narcolepsy; (2) *Anderson v. HHS* affirmed a ruling denying entitlement in a claim that flu vaccine caused autism;

and (3) *Galindo v. HHS*, petitioner unsuccessfully sought a writ of mandamus (an order from a court to an inferior government official ordering the government official to properly fulfill his/her official duties or correct an abuse of discretion). Six cases are pending in the CAFC.

In the Court of Federal Claims (CFC), the court issued four decisions following a motion for review filed by the petitioner (all involving entitlement issues), and two decisions following a motion for review filed by HHS. With regard to the motions for review filed by HHS, *McCulloch v. HHS* concerned attorneys' fees and costs, and *Fairchild v. HHS* involved an interim award of damages. The latter decision is of concern, as it has the potential to undermine the Vaccine Act's statutory scheme, which requires that a petitioner elect to accept or reject any compensation awarded on a Vaccine Act petition.

There are 12 motions for review pending in the CFC, 7 filed by petitioners and 5 filed by HHS. Oral arguments have been held in two of those cases. *Boatmon v. HHS*, argued on June 5, 2018 by the Deputy Assistant Attorney General, involved an allegation that a vaccine caused sudden infant death syndrome (SIDS). *Oliver v. HHS* was argued on June 6, 2018. A third case, *Depena v. HHS*, will have oral argument on July 9, 2018.

Finally, Ms. Reeves presented a history of adjudicated settlements showing the time required to reach final adjudication. Four cases took four or more years to reach final adjudication; 53 cases took one year or more; and 14 cases reached final adjudication in nine-to-twelve months. Ms. Reeves explained that in an "adjudicated settlement" the parties file a stipulation that sets forth the terms of their agreed upon settlement. That stipulation is then reviewed by the special master and, if found acceptable, the special master enters a decision that adopts the stipulation. A final judgment thereafter enters. A petitioner may either accept the final judgment and receive a damages award, or reject the final judgment and pursue a civil action.

During the discussion period, Ms. Toomey asked for more detail about *Anderson v. HHS*, the claim involving an allegation of vaccine-caused autism. Ms. Reeves explained that the petitioners in that case alleged that the MMR vaccine aggravated their child's underlying mitochondrial condition that resulted in autism. The special master denied entitlement because he determined that petitioners' evidence that their child had underlying mitochondrial disease was insufficient. In addition, the special master found that the medical records did not support petitioners' allegation that their child had suffered any reaction to the MMR vaccine. Both the CFC and the CAFC affirmed the special master's decision.

Update on the Immunization Safety Office (ISO), Centers for Disease Control and Prevention (CDC) Vaccine Activities, Dr. Jonathan Duffy, CDC

Dr. Duffy reported that the 48th National Immunization Conference was held May 15-17, 2018 in Atlanta, GA. The ISO staff made four oral presentations: 1) vaccine administration errors; 2) human papillomavirus (HPV) vaccination programs in the U.S.; 3) maternal vaccine safety monitoring at CDC; and 4) updates from the ISO. There were also several posters presented at the conference: 1) the healthcare providers' role in vaccine safety; 2) the safety of the currently licensed hepatitis B vaccine; and 3) the safety of Menactra based on Vaccine Adverse Event Reporting System (VAERS) data.

At the Preventive Medicine Conference on May 23-24, 2018, in Chicago, IL. The ISO had one presentation on unintentional administration of insulin instead of influenza vaccine in about 20 patients. It was deemed to be related to confusion between the two products.

Dr. Duffy announced the upcoming meeting of the Advisory Committee on Immunization Practices (ACIP) on June 20-21, 2018. At this meeting there will be a session devoted to a safety update on the 2017-2018 influenza season, and an update on the CDC-funded Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment (SOMNIA) study of narcolepsy following adjuvanted monovalent pandemic H1N1 flu vaccine. There will also be a pneumococcal session looking at the safety of 13-valent pneumococcal conjugate vaccine in adults 65 and older. Finally, there will be a session on herpes zoster vaccine, including a review of a new inactivated recombinant adjuvanted vaccine.

Dr. Duffy mentioned several recent publications:

- ,Kharbanda, et al. about first trimester influenza inactivated vaccination (IIV) and risks for major structural birth defects in offspring. It was published in the Journal of Pediatrics and was selected as Paper of the Year by the Health Care Systems Research Network (HCSRN). The authors concluded that first trimester maternal IIV exposure was not associated with an increased risk for selected major structural birth defects in a large cohort of singleton live births.
- Markowitz, et al. published a paper in Academic Pediatrics on HPV vaccination in the United States, a vaccine first introduced for females in the United States in 2006. The United States adopted a gender-neutral routine HPV immunization policy in 2011. The safety profile has been well-established from ten years of post-licensure monitoring. Vaccination coverage is increasing, although it remains lower than for other vaccines recommended for adolescents. Despite low coverage, the early positive effects of the HPV vaccination program have exceeded expectations.
- Irving, et al. published a paper in Academic Pediatrics entitled “Human papillomavirus vaccine coverage and prevalence of missed opportunities for vaccination in an integrated healthcare system.” The paper focused on coverage and less on safety.
- Glanz, et al. published a paper in the Journal of the American Medical Association on the association between estimated cumulative vaccine antigen exposure through the first 23 months of life and non-vaccine targeted infections from 24 through 47 months of age. The study looked at effects of vaccines on non-targeted conditions, and there was no significant difference in estimated cumulative vaccine antigen exposure through the first 23 months of life.
- Daley, et al. assessed potential confounding and misclassification bias when studying the safety of the childhood immunization schedule (Academic Pediatrics). The study found that data reported by parents versus EHRs did not differ significantly among children in the vaccination groups studied.
- Liang, et al. published recommendations by the ACIP regarding pertussis, diphtheria and tetanus vaccines.
- Miller, et al. published a comprehensive review of reports to VAERS on post-licensure safety surveillance of zoster vaccine live (Zostavax®). It covered ten years of reports and did not identify any new safety concerns.
- Donahue, et al. published a response to a letter to the Editor of Vaccine dealing with an association between influenza vaccine containing H1N1pdm09 and spontaneous abortion.

The original letter did not claim causation, only an association. It did prompt a response from the authors that included additional information about the study.

Dr. Duffy concluded his remarks. During discussion following Dr. Duffy's presentation, in response to a question about narcolepsy and the H1N1 flu vaccine, Dr. Duffy explained that the issue was first identified in Europe, and there were numerous articles published in that market. For the U.S., the ISO has looked at VAERS reports and found no association with narcolepsy, and the Vaccine Safety Datalink has similarly not identified any issues related to narcolepsy.

**Update on the National Institute of Allergy and Infectious Diseases (NIAID),
National Institutes of Health (NIH), Ms. Claire Schuster, NIAID, NIH**

Ms. Schuster reported that in March 2018, NIAID launched two clinical trials looking at the inactivated 2017 H7N9 influenza vaccine manufactured by Sanofi Pasteur. The two trials are being conducted by the NIAID-funded network of Vaccine and Treatment Evaluation Units (VTEUs) and participants are being enrolled at sites across the U.S. The Phase II trials will enroll up to 570 volunteers ages 19 to 64, and an additional 300 volunteers ages 65 and older. One of the trials is testing various dosages of the inactivated influenza candidate with or without the AS03 adjuvant (manufactured by GSK). This trial is being conducted at VTEU sites in Georgia, Iowa, Maryland, North Carolina and Washington. The second trial is testing the vaccine with adjuvant when co-administered with seasonal influenza vaccine. This trial is being conducted at VTEU sites and one affiliated site in Maryland, Alabama, Ohio and Tennessee. The new vaccine uses an inactivated form of the H7N9 virus collected in 2017 to increase the likelihood that the new vaccine will induce immunity against a newly-evolved strain of H7N9.

Research has revealed that influenza vaccines that effectively target an influenza surface protein, neuraminidase, could provide broad protection against various influenza strains and lessen the severity of the illness. Current vaccines target a more abundant surface protein, hemagglutinin. The new research builds on previous studies of neuraminidase and was conducted by a team of scientists including investigators from the NIAID-supported Centers of Excellence for Influenza Research and Surveillance (CEIRS) program.

At the last ACCV meeting, Dr. Mulach discussed NIAID's new strategic plan for developing a universal influenza vaccine, which would provide durable protection against multiple influenza strains. NIAID will pursue three objectives: 1) improve understanding of transmission, natural history, and pathogenesis of influenza infection; 2) achieve precise characterization of influenza immunity and correlates of immune protection; and 3) support rational design of universal influenza vaccines.

In May 2018, NIAID launched a clinical trial testing a candidate universal influenza vaccine. The trial is testing an experimental vaccine, M-001, developed in Israel, to assess its ability to produce a broad and protective response on its own or in conjunction with a licensed seasonal influenza vaccine. The vaccine contains components known as antigenic peptide sequences shared across a number of different influenza viruses. Six previous trials of M-001 conducted by Biondavax in Israel and Europe indicated that the vaccine was safe, well-tolerated, and able to produce an immune response in a broad range of flu strains. The new study, which will involve four VTEU sites in the U.S., will enroll up to 120 healthy volunteers between the ages of 18 and 49 years. Participating sites include Baylor College of Medicine, Cincinnati

Children's Hospital Medical Center and the University of Iowa. Lab support will be provided by Saint Louis University.

There are currently nine VTEU sites in the United States. The new structure to be launched in 2020, it will include a leadership group and operations center. A recent webinar on NIAID's vision for the VTEU structure can be viewed on YouTube at <http://www.youtube.com/user.niaid>.

In May, NIH opened national enrollment for the All of Us research program, that aims to enroll up to a million volunteers and oversample from communities that have been underrepresented in research. There is more information on All of Us at: <https://www.6youtube.com/watch?v=BSq08AduVGA>.

Finally, NIAID launched a Phase I clinical trial of an investigational vaccine developed by researchers and St. Jude Children's Hospital, designed to protect against respiratory syncytial virus (RSV). It will enroll a small group of healthy adults to assess the safety of the vaccine and its efficacy to induce an immune response.

Update on the Center for Biologics, Evaluation and Research (CBER), Food and Drug Administration (FDA) Vaccine Activities, CDR Valerie Marshall, CBER, FDA

CDR Marshall reported that in April 2018, the FDA approved a supplement to the Biologics License Application (BLA) for Zoster Vaccine Live, (Zostavax, Merck) to revise the package insert to include data from an interim analysis of an observational study that support longer-term effectiveness of Zostavax in individuals 50 years of age and older. To fulfill requirements of a post-marketing commitment, Merck conducted this study to assess the duration of protection against Herpes Zoster.

In April 2018, the FDA approved a supplement to the BLA for inactivated, adsorbed, Japanese encephalitis vaccine, (Ixario, Valneva) to update the package insert with immunogenicity and safety data from long-term pediatric clinical studies. The updated package insert will also include a recommendation for a booster dose at least 11 months after completion of the primary vaccination series for individuals less than 17 years of age who are at risk of continued exposure or re-exposure to the virus.

In April 2018, the FDA approved a supplement to the BLA for Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (Hiberix, GSK) to update the package insert to include safety and effectiveness data from the booster phase of Study Hib- 097, which verifies and describes the clinical benefit of Hiberix administered as a booster dose for active immunization.

The Vaccines and Related Biological Products Committee (VRBPAC) met on May 17, 2018 to discuss approaches for demonstrating effectiveness of Group B Streptococcus (GBS) vaccines intended for use in pregnant women to protect the newborn infant. GBS is a significant cause of early infant morbidity and mortality.

Finally, the FDA is engaged with interagency partners and medical product developers to advance the development of vaccines for Ebola. The FDA has been in close contact with interagency partners, medical product developers, the World Health Organization (WHO), and international regulatory counterparts, to help advance response efforts in the Democratic Republic of the Congo (DRC). FDA is supporting vaccination efforts in the DRC by primarily providing scientific and regulatory advice to WHO and supporting access to vaccine.

CDR Marshall concluded her report and there was no discussion.

Update from the National Vaccine Program Office, (NVPO), Dr. Karin Bok, NVPO

Ms. Luthy explained that there would not be a report from the NVPO, the last ex officio report on the agenda. She introduced Ann Aiken, who will replace Dr. Bok. Ms. Aiken introduced herself as communications director of the NVPO, stating that she would assume the duties of Karin Bok as ex officio commission member and would be providing reports about NVPO activities in the future.

Public Comment

Ms. Luthy suggested inviting public comment before considering future agenda items and new business. There was concern expressed because the agenda item was scheduled for 1:30 p.m., that this might adversely affect an individual's plan to make a comment. Ms. Andrea Herzog explained that the announcement in the Federal Register clearly stated that the opportunity to make public comment might be changed based on the flow of the meeting. It is also explained on the agenda published on the web prior to the meeting. Finally, public comment may be submitted in writing before or after the meeting, which provides ample opportunity to be heard.

Ms. Luthy invited public comments.

There were no requests to make comments.

Future Agenda Items/New Business, Ms. Beth Luthy, Chair

Ms. Toomey asked about the vacant position on the commission and Ms. Herzog indicated that nominations had been received and nomination packages would be prepared and sent forward for approval in the near future.

Ms. Luthy stated that the next meetings would be on September 6-7, and the last meeting of the year would be on December 6-7. Dr. Nair commented that either meeting could be an in-person meeting, depending on the needs of the commission. Ms. Toomey emphasized the importance of occasional in-person meetings. Dr. Meissner agreed, but also commented that the travel imposes a greater time commitment. Dr. Nair stated that there had been an attempt to hold at least two face-to-face meetings each year, particularly when a new commissioner is joining the ACCV.

Adjournment

There was a consensus to include in the record a special thank you to Ms. Herzog for her contribution and support for the commission, and her part in planning the meetings.

There being no further business, on motion duly made and seconded, the Commission unanimously approved adjournment.