Advisory Commission on Childhood Vaccines (ACCV)

December 2, 2016

102nd Meeting

Members Present
Kristen A. Feemster, M.D., Chair ('16)
Jason Smith, J.D., Vice Chair ('16)
Charlene Douglas, Ph.D. ('16)
Edward Kraus, J.D. ('16)
Luisita dela Rosa, Ph.D. ('16)
Karlen E. Luthy, ('18)
Martha Toomey ('18)
Alexandra Stewart, ('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., Director, DICP
Andrea Herzog, Principal Staff Liaison, ACCV

Welcome, Report of the Chair and Approval of Minutes, Kristen Feemster, ACCV Chair

Dr. Feemster called the meeting to order and completed a roll call, reflected above, for the record.

Public Comment on the Agenda Items

Dr. Feemster invited public comments concerning the agenda; there was none.

Approval of December 2016 ACCV Meeting Minutes

Dr. Feemster invited approval of the December 2016 meeting minutes. On motion duly made by Mr. Kraus, and seconded by Ms. Toomey, the minutes were approved unanimously.

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

Dr. Nair outlined the meeting agenda, noting that after his presentation Ms. Catharine Reeves would present information from the Department of Justice Vaccine Litigation Office; and Ms. Toomey, Chair of the ACCV Process Work Group, would provide an update; followed by update reports from the ACCV ex officio members from FDA, CDC, NIH, and NVPO.

Dr. Nair reported that for the years 2011 through 2016 the DICP received an average of 546 petitions per year. The yearly filings have increased annually and in fiscal year (FY) 2016,

1,120 petitions were filed, a significant increase over the prior year. The number of petitions received in FY 2017, through November 1, 2016, was 115.

Adjudications in FY 2016 totaled 837, of which 659 were deemed compensable and 178 were dismissed. So far in FY 2017 only 18 cases have been adjudicated, all of which were deemed compensable. In FY 2017, through November 14, 2016, 42 cases have been resolved: 10 through concessions by HHS; 1 decision handed down by the court; and 31 resolved by settlement agreement between the parties involved. Unlike previous years, all cases were non-autism claims. In FY 2016, the total petitioners' award was $228 million and attorneys received $21.6 million in fees and costs. To date in FY 2017, the total petitioners' awards are $17 million and attorneys' fees and costs are $2.5 million.

Dr. Nair reported that the Vaccine Injury Compensation Trust Fund (Trust Fund) stands at $3.6 billion. Excise tax added nearly $291 million and interest on the added nearly $99 million (25% of total revenues). In response to a clarifying question, Dr. Nair stated that, by statute, the money in the Trust Fund could only be used for petitioners' awards, attorney's fees and costs, and administrative expenses of the program.

Concerning program activities, Dr. Nair noted that a Notice of Proposed Rulemaking (NPRM) on revisions to the Vaccine Injury Table has reached the final rule stage and is being reviewed by HHS. Asked about a timeline, Dr. Nair said that the date of final approval is difficult to predict, but that his office is hopeful of an expeditious process.

Recent outreach activities included a presentation to the Association of State and Territorial Health Officials that resulted in the association mentioning the program in its regular newsletter, and adding a link on its web site so that interested individuals may look for information on the program. In September, an overview of the program was provided to the Public Health Service Physicians Professional Advisory Committee; and in October, the DICP participated in a webinar series entitled "Topics in Public Health."

Finally, Dr. Nair stated that a bill passed in the House of Representatives that would provide program coverage of vaccines recommended for routine use in pregnant women. That bill would have to clear the Senate as well, and then be signed into law by the President. He added that only the vaccines for pregnant women is included in the bill, and there were no other recommendations by the ACCV included in the bill (such as increasing the cap for pain and suffering, and expanding the statute of limitations).

There was a brief discussion about the timeline for nominations to fill the pending vacancies on the Commission and the appointment of a pediatrician to the Commission.

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

Ms. Reeves welcomed the commissioners. Ms. Reeves noted that the reporting period for the Department of Justice (DOJ) is different from that of the Division of Injury Compensation Programs. Ms. Reeves referenced the DOJ Power Point materials as part of her presentation for the three-month period from August 16, 2016 to November 15, 2016. During this reporting period, 355 petitions were filed, which is an increase of 79 petitions compared to last period. Of those 355, 34 were filed on behalf of children (10%) and 321 were filed by adults (90%). (DOJ PP at 2).

With regard to total cases adjudicated, Ms. Reeves noted that 222 claims were adjudicated this quarter. (DOJ PP at 3). There were 178 cases compensated. Of those 178

cases, 47 were conceded by HHS. Of those 47 conceded cases, all 47 were resolved by a decision adopting a proffer. Ms. Reeves noted that 11 fewer cases were adjudicated this period than last period. There were 131 cases compensated but not conceded by HHS. Of those, all 131 cases were resolved by a decision adopting a settlement stipulation. (DOJ PP at 3). There were 44 cases dismissed. Of those, 42 non-OAP cases were resolved by decisions dismissing the petition, and 2 were dismissed from the OAP. (DOJ PP at 3). There were 10 petitions voluntarily withdrawn, which Ms. Reeves remarked was a decrease of 3 compared to last period. (DOJ PP at 4).

Turning to appeals, four cases filed by petitioners at the U.S. Court of Appeals for the Federal Circuit (CAFC) were quickly voluntarily dismissed because they had not been heard by the Court of Federal Claims (CFC) and therefore the CAFC did not have jurisdiction to hear the appeals. (DOJ PP at 5). A fifth case, *R.V. v. HHS*, was also voluntarily dismissed by petitioners. In addition to four appeals filed by petitioners that are pending, three new appeals were filed by petitioners in *Murphy v. HHS*, *H.L. v. HHS*, and *Lasnetski v. HHS*. (DOJ PP at 6). In *Canuto v. HHS*, one of the four pending cases, a petition for panel re-hearing was denied, which effectively ended the appeal. Petitioners may choose to file for certiorari at the Supreme Court.

Ms. Reeves discussed appeals at the CFC, and noted that three appeals filed by petitioners were decided by the CFC. (DOJ PP at 7). One of the three appeals concerned attorneys' fees and costs and two concerned entitlement. The court affirmed the special master's decisions in the cases concerning entitlement. In *Reiling v. HHS*, petitioner's attorney filed a motion for review after he had withdrawn his appearance as attorney for petitioner, and the CFC dismissed the motion for lack of jurisdiction. Ms. Reeves reported that the CFC also decided three appeals filed by respondent. (DOJ PP at 7). In *Garrison v. HHS*, the special master's award of forum rates to petitioner's attorney was affirmed. In *Allicock v. HHS*, the CFC affirmed the special master's decision finding reasonable basis to award attorneys' fees and costs. In *Simmons v. HHS*, the CFC reversed the special master's decision finding reasonable basis to award attorneys' fees and costs. Ms. Reeves noted that petitioners filed six new appeals to the CFC, 4 of which involve entitlement, and 2 of which involve attorneys' fees and costs. (DOJ PP at 8). Nine cases remain pending at the CFC. (DOJ PP 8).

One oral argument is scheduled at the CAFC in *R.K v. HHS*. There was an oral argument in *Rich v. HHS* before the CFC and the decision is pending. (DOJ PP at 9).

Ms. Reeves noted the history of adjudicated settlements, which are listed in order of the time they took to resolve. (DOJ PP at 10-23). Most of the cases involved influenza vaccine and injuries related to Guillain-Barré Syndrome and shoulder injury related to vaccine administration (SIRVA).

Update from the ACCV Process Work Group, Martha Toomey, Work Group Chair, ACCV Member

Ms. Toomey reported that the Process Work Group recommendation regarding increasing resources did not specify when recommendation was submitted to the Secretary of the Department of Health and Human Services. Ms. Herzog commented that the cover letter and recommendation required signatures from the ACCV Chair and Vice Chair before submission and informed the ACCV that the recommendation was circulated for signatures. Mr. Jason Smith, Vice Chair, ACCV, stated that he had signed and sent the signed document to Dr. Nair's office via UPS the previous day, so the signed letter and recommendation should be ready for

delivery soon. Ms. Toomey informed the ACCV that the Process Work Group discussed other recommendations under consideration and agreed to delay submitting those recommendations until after the inauguration. Ms. Toomey stated that her report was concluded.

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

Dr. McNeil stated that he would review the recent October meeting of the Advisory Committee on Immunization Practices (ACIP), and briefly discuss several vaccine-related publications not previously addressed in ACCV meetings. The ACIP in a session on hepatitis B vaccine considered the recommendations of the American Association for the Study of Liver Disease. The modified ACIP recommendations included the following: 1) antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg+ pregnant women; 2) removal of permissive language for delaying a birth dose for all medically stable infants weighing 2,000 grams or more, noting that the hepatitis B vaccine should be administered within 24 hours of birth; and 3) hepatitis B vaccine for those with existing hepatitis C infection. There was a vote to accept the updated hepatitis B recommendations and the Vaccine for Children (VFC) resolution.

Turning to pertussis vaccine, Dr. McNeil commented that there was a vote to accept the updated statement in "Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States," as recommended by ACIP. There were no new vaccine recommendations. There was discussion of timing of vaccinations and, although there is variance in other countries, the ACIP agreed that the current recommendation should be followed – Tdap administered between 27 and 36 weeks of gestation. There is some data that indicate that vaccination in the early part of that time window will maximize passive antibody transfer to the infant.

The ISO has assessed data from three surveillance systems with regard to maternal Tdap safety. The Vaccine Adverse Event Reporting System (VAERS) conducts ongoing monitoring through voluntary reports of adverse events from several sources – clinics, physicians, and private individuals. The Vaccine Safety Datalink (VSD) has provided data on preterm delivery and small for gestational age infants, other vaccine-related adverse events, obstetric adverse events and birth defects. The VSD has access to electronic medical records from several large healthcare services for their statistical analysis. The Clinical Immunization Safety Assessment (CISA) project monitors vaccine safety in pregnant women and assessed the safety of simultaneous Tdap and inactivate influenza vaccine (IIV) immunization in pregnant women.

In summary, data to date are reassuring, VAERS shows that the pattern of adverse events in women receiving Tdap is consistent with expectations. In the VSD, a study of 50,000 women who received Tdap during pregnancy showed no increased risk. In the CISA project, Tdap was well tolerated in both pregnant and non-pregnant women.

Moving to human papillomavirus vaccines, the ACIP work group proposed a dose modification in the recommendation for young people who initiate inoculation age 9 to 14 years. The FDA approved a 2-dose series of 9vHPV for that population, and trials of the immune response with that schedule proved as good as the prior 3-dose regimen (although the recommendation stands for a 3-dose regimen for individuals beginning immunization after age 15). There was a vote in the ACIP to endorse 2 dose HPV immunization regimen before the 15th birthday, with the second of two doses administered 6 to 12 months after the first dose. For those 15 years and older the recommendation is for three doses, with the second dose at 1-2 months and the third at 6 months. There was a brief discussion about the rationale for a two-

dose regimen for those under 15 and a three-dose regimen for those 15 and older. Dr. Feemster commented that trials had shown that the immune response in the younger individuals reached about the same efficacy level as the immune response in the older group for those respective vaccine schedules. Therefore, it indicated that a third dose was not constructive for the younger individuals.

With regard to meningococcal vaccines, Dr. McNeil noted that there were two licensed vaccines in the U.S. for people 10 to 25 years of age. The ACIP modified its recommendation for Trumemba (Pfizer), which is licensed as a three-dose regimen for individuals at higher risk of meningococcal virus infections and for anyone who is in an outbreak area; to allow for it to be given as a two-dose regimen for healthy adolescents. There was a vote in the AICP to accept the recommendation and Vaccine for Children resolution.

Dr. McNeil commented on a new herpes zoster vaccine developed by GSK, an adjuvanted, subunit zoster vaccine with a two-dose schedule (0 and 2 months) for persons 50 years of age and older. GSK will submit a biologic license application (BLA) by the end of the year. Efficacy is excellent – 97% in the 50-59 age group, 91% for those 80 and older. Efficacy of greater than 85% is maintained through four years for all ages. Adverse reactions are relatively common, but are mainly minor injection site problems and nonspecific systemic effects.

An interagency working group has been established to address the Zika virus issues. It will evaluate candidate vaccines with an objective of developing one or more candidate vaccines that would be available by 2018. There are several candidate vaccines in preclinical development or Phase I trials now, and Phase II studies are scheduled for 2017. The ACIP will include a session on Zika virus at its February 2017 meeting.

The ACIP called the development and use of pneumococcal vaccine PCV13 a success story. Introduction of PCV13 in 2014 in the childhood schedule had markedly reduced the incidence of invasive pneumococcal disease in adults 65 and older, and the reduction suggests that benefits observed to date are largely due to indirect PCV13 effects. Most of the remaining burden of disease in adults can be traced to non-PCV13 serotypes.

The ACIP addressed influenza vaccines, noting that there is a low level of influenza activity in the US and the infections are mainly H3N2 strains (90%), although the pandemic H1N1 and H3N2 continue to circulate worldwide. The recent recommended components of the 2017 Southern Hemisphere vaccine include an updated H1N1 component, the first change for that strain since the 2009 pandemic. Labs worldwide continue to indicate that most currently circulating virus strains are antigenically similar to the vaccine viruses included in the 2016-2017 vaccines, which is good news. There are two newly icensed flu vaccines – Afluria quadrivalent (Seqirus) and Flublok quadrivalent (Protein Science). The latter is an insect cell line formulation and considered egg free.

The ACIP discussed respiratory syncytial virus. Respiratory syncytial virus (RSV) is an important factor in lower respiratory tract infections causing hospitalization in older adults. Novavax developed an RSV F-protein recombinant nanoparticle vaccine that fared well in Phase II trials in older adults, but failed to show efficacy in a subsequent Phase III trial. The company is trying to discover the reason for that failure. There is also a different RSV formulation prototype vaccine with an aluminum adjuvant being tested in pregnant women.

Dr. McNeil briefly mentioned a number of recent publications.

- Grohskopf et al. published in the MMWR updated ACIP recommendations on prevention and control of seasonal flu with vaccine recommendations. (MMWR Recomm Rep. 2016; 65 (5): 1-54)

- Bardenheier et al evaluated anthrax vaccine adsorbed given to US military personnel, and found an association with recent onset rheumatoid arthritis (RA); however, it did not increase the risk of RA in the long term. Nor was it associated with onset of systemic lupus erythematosus. The vaccine may have triggered RA earlier than expected, but it is thought likely that the condition would have eventually developed even without the vaccine. (Mil. Med. 2016; 181(10):1348-1356)

- Lauren et al. published a case report of subcutaneous nodules and sterile abscesses due to delayed type hypersensitivity to aluminum-containing vaccines. Anaphylaxis is a risk for any inoculation, but the delayed type hypersensitivity is relatively rare. (Pediatrics 2016. Epub ahead of print)

- Baxter et al. looked at acute demyelinating events following vaccination and found no association between transverse myelitis and prior immunization, although there was a possible association of acute disseminated encephalomyelitis (ADEM) with Tdap vaccine (probably no more than 1.16 cases per million vaccines administered). (Clin Infect Dis. 2016. – Epub ahead of print)

- DeSilva et al published a report based on Vaccine Safety Datalink data that showed that maternal Tdap was not significantly associated with increased risk of microcephaly for inoculations occurring at less than 14 weeks of gestation. (JAMA 2016; 316(17): 1823-1825)

Dr. McNeil concluded his report.

Update from the National Institute of Allergy and Infectious Diseases (NIAID, NIH), Vaccine Activities, Claire Schuster, NIAID, NIH

Ms. Schuster announced an early stage investigational trial of Zika Purified Inactivated Virus (ZPIV) vaccine that is based on technology that was developed at the Walter Reed Army Institute of Research (WRAIR) in Maryland. The technology is based on earlier work in 2009 by WRAIR to develop a vaccine for another flavivirus, Japanese encephalitis. The inactivated Zika virus vaccine cannot replicate and cause infection in humans. WRAIR, NIAID and the HHS Biomedical Advanced R&D Authority (BARDA) have established a collaboration to pursue development of the vaccine. A Phase I trial is underway at WRAIR to test the vaccine's safety and ability to generate an immune response. It will recruit individuals from 18 to 49 years of age with no previous infection by a flavivirus (e.g., Zika, yellow fever, dengue, Japanese encephalitis, and West Nile virus).

Another Phase 1 trial of this investigational vaccine is being conducted at the NIAID-funded Vaccine and Treatment Evaluation Unit at St. Louis University. In addition, a WRAIR-funded trial at the Center for Virology and Vaccine Research, part of Beth Israel Deaconess

Medical Center, and Harvard Medical School, is recruiting participants for a trial. Additional trials of the ZPIV vaccine are being planned.

Recent Zika-related publications include a paper by Dowd et al, Rapid Developments of a DNA Vaccine for Zika Virus (Science October 14, 2016); and Marston et al, Considerations for Developing a Zika Virus Vaccine (New England Journal of Medicine September 29, 2016).

NIH is supporting research to develop a patch to administer flu vaccine. The patch contains tiny microneedles that contain the vaccine, which dissolve in the skin. After application, the patch is removed and discarded. Nearly a hundred individuals participated in a trial to assess the appeal of the patch. Of participants who had not planned to get a flu vaccine, 35% opted to accept vaccination using the patch. The patch can be self-administered, requires no refrigeration, and remains stable until used. The November 4th issue of the NIH Record described the patch.

Another patch was developed that delivers a small amount of peanut protein through the skin to treat peanut allergies. The treatment is called epicutaneous immunotherapy and was shown to be effective, safe and well-tolerated. Seventy-four peanut-allergic volunteers between 4 and 25 years of age participated in a randomized placebo controlled trial that consisted of a low-dose and high-dose cohort. After one year, the investigators tested tolerance of each individual to consume ten times the peanut volume than before treatment. The study found that 46% of the low-dose group and 48% of the high-dose group achieved treatment success compared with 12% of the placebo group.

A different NIAID-supported study involves the hypothesis that the infant gut microbiome may influence the immune response to allergies and asthma in early childhood. Researchers at the University of California – San Francisco and the Henry Ford Health System in Detroit, studied microbiota that reside in the infant digestive tract. They identified a type of microbiota composition that appears to play a role in this process. The high-risk group identified by the researchers had a relatively lower abundance of certain bacteria and an increased abundance of specific fungi. Fujimura et al. in Nature Medicine reported the study.

Finally, Ms. Schuster reported that a large study of HIV vaccine efficacy (HVTN702) is being launched in South Africa, with support from NIAID, the Bill and Melinda Gates Foundation, and the South African Medical Council. It will build on the modest success of another HIV vaccine study (RV144) completed in Thailand. Ms. Schuster ended her report.

Update from the Center for Biologics, Evaluation and Research (CBER), FDA, Vaccine Activities, LCDR Valerie Marshall, CBER, FDA

LCDR Marshall addressed FDA vaccine supplement approvals. In September, the FDA approved a supplement to the biological license application (BLA) for Daptacel to add immunogenicity and safety data to support the co-administration of Meningococcal (Groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine (Menactra) with a fifth dose of Daptacel for children 4 through 6 years of age. Also in September, FDA approved a supplement to the BLA for Q-Pan to extend the age range of the vaccine to include persons 6 months through 17 years of age at increased risk of exposure to influenza A virus H5N1 subtype contained in the vaccine. The vaccine was previously approved for use in persons 18 years of age and older. The vaccine is not intended for commercial availability and was purchased for the national vaccine stockpile to be distributed in the event of a pandemic.

LCDR Marshall discussed two FDA publications. The first, by Khurana et al, in Nature Medicine (October 2016), was entitled "Human antibody repertoire following VSV-Ebola vaccination identified novel targets and virus neutralizing IgM antibodies." The FDA researchers demonstrated novel immune system targets on Ebola virus and identified the major type of vaccine-triggered antibodies that neutralize the virus. The findings also demonstrate that selection of the appropriate assay may be important for evaluating effective vaccines against the Ebola virus.

The second publication, "Zika (PRVABC59) infections associated with T-cell infiltration and neurodegeneration of the central nervous system in immunocompetent neonatal mice," looks at the use of neonatal C57Bl/6 mice to explore potential activity of Zika virus vaccines and therapeutics. This mouse model provides a platform for potentially improving and expediting studies to understand the causes and effect of the Zika virus. LCDR Marshall concluded her presentation.

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

Dr. Bok provided an update on the NVPO's pilot project on cooperative agreements for vaccine safety and the decision to extend the agreement based on initial positive results. The rationale for the agreement is to strengthen vaccine safety research in areas for which national surveillance system intervention or pre-clinical funding would not be suitable. The program funds exploratory research and early programmatic interventions that might influence scientific advancement and policy. It supports the objectives of the Assistant Secretary for Health in defining public health policy, and links NVPO with the vaccine safety community to address vaccine safety research hurdles and gaps.

NVPO funded two cooperative agreements for $250,000 each to help determine safety profiles of new vaccines in early development; modifying existing vaccines to improve their safety profiles; support applied research that will inform the current vaccine safety monitoring system; and conduct research that will promote consensus definitions of vaccine safety outcomes. One of those agreements, creation and analysis of a maternal-neonatal vaccine safety database, was awarded to Kaiser Hospital Foundation in Oakland. They have published one study and are currently completing a second analysis of alternative benefits of influenza vaccine during pregnancy. The cooperative agreement will also fund, at a different branch of the Kaiser Foundation in Portland, a program to prevent injection site pain and syncope associated with pre-teen and teen vaccinations.

Based on the success of the pilot program, a decision was made to renew the program with the FY 2017 Cooperative Agreement Program, with increased funding up to $750,000 per award. The objectives of the FY 2017 Cooperative Agreement Program is:

1. Research to better understand immunization safety in older adults; prediction of safety profiles of vaccines during early development before testing in humans;
2. Improvement of safety of existing vaccines; research to improve vaccine surveillance systems;
3. Research to improve the safety of currently marketed vaccines; and
4. Support for the Assistant Secretary for Health in analyzing bio-specimens to understand differences in genetic or metabolic profiles that may correlate with an individual's predisposition to immunization-related adverse outcomes.

The invitation to submit proposals will be released in January with responses due in March.

Finally, Dr. Bok announced that on September 20, 2016 the National Vaccine Advisory Committee voted on new recommendations to the Assistant Secretary for Health related to overcoming barriers and identifying opportunities for developing maternal immunizations.

Dr. Bok concluded her comments.

Public Comment

Dr. Feemster invited public comment. Hearing no requests to speak, she moved to the agenda item inviting Commission members to suggest new agenda topics for the next meeting.

Future agenda items and New Business, Dr. Kristen Feemster, Chair

Dr. Feemster invited comments. Mr. Kraus suggested adding time for a report on legislation that amends the Vaccine Act to include the maternal immunization changes. There was a suggestion that a presentation on the vaccine manufacturing process might be of interest, since the Commission generally focuses on post-licensure issues. There was consensus that the discussion would be helpful, and Mr. Smith, the ACCV member who serves as the vaccine manufacturer's attorney, offered to inquire about the possibility that his company could provide support for the discussion. Dr. Nair expressed interest in whether the presentation should focus on the FDA perspective or from the industry perspective. There was a comment that combining both would be more informative. There was a suggestion that including a brief discussion about the patch device discussed earlier in the meeting would be appropriate. Finally, there was a comment that a briefing would be informative on the transition in the White House and changes in Congress, and the prospects for future legislation.

Adjournment

There being no other comments from Commission members, on motion duly made by Mr. Kraus and seconded by Ms. Toomey, the Commission unanimously approved adjournment.