

Advisory Commission on Childhood Vaccines Meeting Conference Call

June 5, 2008

Minutes

Members Present

Jeffrey M. Sconyers, J.D., Chair
Tawny Buck
William P. Glass, Jr., J.D. (via teleconference)
Tamara Tempfer, RN-C, MSN, PNP (via teleconference)
Margaret Fisher, M.D., FAAP
Charlene Gallagher, J.D.
Magdalena Castro-Lewis
Jaime G. Deville

Executive Secretary

Geoffrey Evans, M.D., Director, DVIC

Staff Liaison

Michelle Herzog

Introduction and Approval of Minutes

Mr. Sconyers convened the 69th quarterly meeting of the Advisory Commission of Childhood Vaccines (ACCV) at 12:08 p.m. He invited a motion to approve the minutes of the March 6 - 7, 2008 meeting. Ms. Buck commented that, pursuant to a discussion of the availability of thimerosal-free vaccines to practitioners, she had asked about the cost compared to vaccines that contain thimerosal. That question and the response from staff that the information would be provided was not reflected in the minutes. Mr. Sconyers stated that the minutes would be so amended. On motion duly made and seconded, the minutes of the March 2008 meeting, as amended, were unanimously approved. Ms. Buck added that it would be helpful to provide access to ACCV meeting transcripts on the program's web site. In addition, she suggested that contact information be provided in a visible manner on the web site.

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

Dr. Evans welcomed members and guests in attendance and reviewed the agenda for the two-day meeting.

Financial and Statistical Report

Dr. Evans reported that the large bolus of influenza claims that were anticipated as the two-year deadline for filing claims approached had failed to materialize. Rather than the 500 to 1,000 claims expected, less than 200 had been filed by the July 2007 deadline. Autism claims had been in a downtrend from 1,088 claims filed in 2004 to 167 in FY 2007. However, as a result of the 2007 autism hearings and the publicity related to the Hannah Poling case, claims have been increasing since the latter half of 2007. Autism claims filed after June 2007 are required to undergo jurisdictional screening and DVIC medical staff review if medical records are present, as is done routinely for non-autism claims.

Awards have averaged \$62 million for the past six years, with about \$4 million more in legal fees (which are paid whether or not the ruling is favorable to the petitioner). The awards in 2007 were considerably higher, \$97 million, and a similar amount will probably be awarded in 2008. It should be noted that one reason for this is that the Court became fully staffed with special masters and more cases were processed.

Dr. Evans reported that the Trust Fund was now over \$2.8 billion, and considering expenditures, the fund is netting about \$300 million a year. Interest contributes about 27% of that amount. The inclusion of the flu vaccines has contributed significantly to the increase (about 130 million doses have been distributed).

Director's Activities

Turning to activities since the last meeting, Dr. Evans reported that he had provided program briefings to the American Academy of Allergy, Asthma and Immunology on March 18th, and the annual meeting of Vaccine Safety Datalink project on April 2-3. He also briefed the Committee on Medical Liability of the American Academy of Pediatrics, which is especially interested in appeals decisions of the Federal Circuit. Dr. Evans noted that he and Ms. Buck are involved with NVAC Vaccine Safety Working Group, which is working on a safety plan for the CDC's Immunization Safety Office. Dr. Evans said that he attended the National Vaccine Advisory Committee meeting on June 3-4. Finally, the Omnibus Autism Proceeding began on May 12 and continued through the end of the month.

Legislative Update

Concerning legislation, two relevant bills are under consideration on the Hill. The Federal Advisory Committee Act (FACA) may be amended to enhance transparency and accountability (requiring membership criteria and membership lists to be published, as well as transcripts of meeting, if prepared). The Infant Immunization Improvement Act of 2008 was introduced, which would support a vaccination program through the Women, Infants and Children's program.

Discussion

In response to a question, Dr. Evans confirmed that the program has compensated cases of "autism" in the program's 20-year history. Compensation was based on a finding of a Table injury, either encephalopathy or seizures, with the final outcome either through a concession by HHS, or a special master decision. Autism was not alleged in these cases, and all of the cases were adjudicated prior to creation of the Omnibus Autism proceeding.

Asked about the backlog of claims waiting to be adjudicated and the trend over time, Dr. Evans explained the delays were primarily related to the hepatitis B claims. Over 400 were received in the late 1990's when the 2-year deadline for filing retroactive claims for the newly added vaccine expired. It's only within the past 1-2 years that the Court has been adjudicating these claims. Dr. Evans thought the trend will be downward unless a new vaccine safety issue arises.

Report from the Department of Justice Vince Matanoski, J.D, Acting Deputy Director Torts Branch, Civil Division, Department of Justice

Mr. Matanoski reported that he is serving as Acting Deputy Director for the Torts Branch, vaccine section while Mr. Rogers remains deployed to Iraq.

Personnel

Since the last ACCV meeting, the Department of Justice (DOJ) has hired one more attorney, with another attorney joining the office in the few weeks. The office is still in the process of trying to expand its staff in light of the activated autism cases.

Statistics

Mr. Matanoski reported that since February 1, 2008, there were 177 cases filed, almost double the filings from his report at the last meeting. Of those, 52 were non-autism and 125 autism claims (a bump in autism claims could have been attributed to the publicity surrounding autism lately). Of the pending cases, 101 were resolved since February 1, 2008, which represented fewer cases than were filed. Referencing the 6,000 cases, this presents a challenge to DOJ to reduce that differential by processing more cases than are filed. Of those resolved, 7 claims represented entitlement decisions by a special master. During this time period, 53 claims were resolved through settlement, which means that the Government and the petitioner cooperate to reach what is called a litigative risk settlement, and avoid the unknown outcome of a trial. Regarding the settled cases, Mr. Matanoski explained that the claims are not identified as a Table injury or off-Table injury settlement as each claim evolves throughout the entitlement phase of litigation. However, if the Department of Health and Human Services (HHS) concedes a case, that statistic is available. There were 41 cases dismissed. Of those, 28 claims were entitlement decisions for the Government and no compensation was awarded petitioner. Twelve claims were voluntary dismissals by the petitioners. Finally, one claim was withdrawn pursuant to Section 21(b) of the Vaccine Act, which allows a petitioner to withdraw his case after the expiration of 240 days B the result here. If a petitioner withdraws under that provision, he still has the option to file a civil action outside of the Program. Mr. Matanoski was not familiar with the number of petitioners, if any, who pursue civil actions after withdrawing from the Program. He recalled a number of the earlier autism cases that withdrew pursuant to Section 21(b) of the Vaccine Act, but most petitioners remained in the Program as part of the Omnibus Autism Proceeding. Ms. Buck questioned whether DOJ could provide a breakdown of conceded settlements, litigative risk settlements, and entitlement decisions over the years to evaluate any patterns. Mr. Matanoski offered to look into providing that information.

Autism

Of the more than 5,000 autism cases pending, most were filed without any supporting records. As mentioned at the prior meeting, the Court has deemed it appropriate to begin to process those cases. Mr. Matanoski recalled that the Chief Special Master has ordered 200 cases per month to be processed. In those cases, petitioners are required to provide sufficient documentation for the Government to review whether the Court has jurisdiction to proceed with the case -- was it filed in a timely manner. So far, the cases are falling into three categories: 1) cases that were clearly filed too late; 2) cases that were clearly filed in a timely manner; and 3) cases for which either determination is not clear. In the third category, the gray area, petitioners are being asked to provide additional information. In some instances, the Court is issuing show cause orders seeking more information.

Over the course of the last five months, a thousand of the cases have been activated. Illustrating the procedure, Mr. Matanoski explained that for each grouping of 200 cases, petitioners have been provided 90 days to compile their records. However, of the 200 cases roughly 140 need additional time to compile records. As a result, while the cases are being activated in an orderly fashion, the evaluation times vary depending upon the time it takes for petitioners to complete their documentation. Thus, petitioners are seeking extensions, resulting in a wide variety of deadlines.

Discussing the resolution of the gray area cases for timely filing, Mr. Matanoski predicted that many of the cases involving autism present a subtlety with which the first symptoms manifest themselves. That is, the nature of the onset of autism symptoms can create a question of whether or not a case is filed in a timely manner, which in turn may require expert testimony to

sort out the answer. The Government is considering ways to efficiently address the issues of timeliness with the Court and petitioner=s counsel.

Mr. Matanoski turned to the autism litigation, and the three cases representing petitioners first theory of causation: Cedillo v. HHS, Hazelhurst v. HHS and Snyder v. HHS. He stated that briefing in all three cases is complete, noting that Petitioners= Steering Committee (PSC) in the Snyder case have decided against seeking information from the United Kingdom. The first theory is whether the measles-mumps-rubella (MMR) vaccine combined with Thimerosal act to modulate the immune system leading to live measles virus persisting in the body, particularly the brain, to cause damage and autism. The second theory is whether Thimerosal alone causes autism. That theory was recently tried in May, 2008, with the following test cases: Mead v. HHS and King v. HHS. Notably, one of the three test cases dropped out so the PSC is seeking a replacement test case to provide to the special master. Four experts appeared for petitioners and twelve experts appeared for respondent. On the issue of general causation for the second theory, additional testimony from two toxicologists for the Government is scheduled for July, along with the third test case. The third theory is whether the MMR vaccine alone causes autism. The PSC has indicated that the mechanism for the third theory is the same as the first theory, i.e., whether live measles virus persists in the body and in the brain to cause autism. Thus, no further evidence on general causation is expected. It appears that the special masters will apply the general causation evidence from the test cases of the first theory to the yet-to-be-chosen test cases of the third theory.

Appeals

Mr. Matanoski reviewed the decision of Avera v. HHS, issued by the U.S. Court of Appeals for the Federal Circuit (Federal Circuit) on attorneys= fees and costs. While he discussed this at the last meeting, it was relatively new and there has been some development on the implications of Avera. Avera raised new issues for the Program:

1) whether the hourly rate for attorneys= fees was governed by the forum of Washington, DC and, 2) whether an award of interim fees is available to petitioners. The forum rates for Washington, DC are higher than most forum rates where the attorneys maintain offices. The petitioners sought compensation for their attorneys consistent with their view of Washington, DC rates instead of rates that their attorneys received in Cheyenne, Wyoming, where petitioners= attorneys were located and practiced law. The Federal Circuit decided that the forum-rule applied to the Program, however, the Court applied an exception to the forum-rule, which looks to where the bulk of the work was performed. Under the facts of this case, petitioners= attorneys were not entitled to the hourly rates of the forum, which it deemed to be Washington, DC. Petitioners= attorneys were entitled to hourly rates consistent with Cheyenne, Wyoming, where they performed all of the work in that case. Mr. Matanoski predicted that most, if not all, of the cases brought in the Program would fall into an exception to the forum-rule. In vaccine cases, unlike traditional tort cases, the hearings are typically conducted outside of Washington, DC, and if conducted in Washington, DC, last approximately six hours (or one day) so that bulk of time spent by a petitioners= attorney would be performed outside of Washington, DC at his/her office. In addition, many hearings are conducted by telephone, or the special masters and counsel travel to the most convenient location for the petitioner. So far, the Government has not seen a lot of litigation on the issue of hourly rates following Avera.

Regarding the second issue in Avera, the Federal Circuit decided that under certain circumstances, not defined in the decision, an award of interim attorneys fees and costs is appropriate. However, the Court denied petitioners= request for attorneys= fees and costs in Avera even though the case was on appeal. Because the Court offered little guidance on when an award of interim fees would be appropriate, Mr. Matanoski contacted several members of the petitioners= bar to discuss some possible parameters for seeking payment of interim fees. There was a meeting with some of those attorneys regarding broad parameters within which they would seek interim fees. Some ideas included: seeking fees after a decision issues from the special

master as that presents a natural break in a case before the damages phase or appeal and in amounts of at least \$25,000.00, as well as limiting the number of fee requests. So far, only one case has been filed seeking interim fees, although Mr. Matanoski predicted more filings as the parameters of Avera are tested. Mr. Matanoski reiterated the Government=s commitment to move the cases toward resolution without being sidetracked by interim fee requests. Also still pending before the Federal Circuit but not yet decided is Mojica v. HHS, which was brought by petitioner. In Mojica, the petition was filed one day late because of an error entirely attributed to Federal Express delivery. There, the judge, Court of Federal Claims, held that the special master correctly dismissed petitioner=s case for lack of jurisdiction. Even under those circumstances, the Court of Federal Claims found that equitable tolling did not apply afford jurisdiction.

Mr. Matanoski also discussed a case argued today before the Federal Circuit, DeBazan v. HHS. Petitioner sought compensation for a demyelinating condition that manifested itself eleven hours after vaccination. Based upon the medical evidence, the special master denied entitlement to compensation because the onset of petitioner=s injury occurred too soon after vaccination. On appeal, the Court of Federal Claims judge reversed finding that the onset of petitioner=s demyelinating condition within eleven hours made vaccine causation more likely. The Government appealed to the Federal Circuit maintaining that petitioner had not met her burden of proof in demonstrating that the vaccine was the most likely cause of injury. The medical evidence demonstrated that the onset of petitioner=s demyelinating condition within eleven hours of vaccination was not attributable to the vaccination. Early timing of onset is insufficient to establish causation particularly here, where the medical evidence contradicted petitioner=s claim.

There are ten cases pending in the Court of Federal Claims, the first appellate tier of vaccine cases. The cases were all appealed by petitioners and involve either a claim for attorneys= fees or error by a special master erred in denying entitlement.

Ms. Buck asked about Zatuchni/Snyder v. HHS, which was a claim decided by the Federal Circuit. The Court decided that if, during the pendency of a vaccine claim, a petitioner died, petitioner would be entitled to seek the \$250,000.00 death benefit, as well as additional damages to include lost wages, pain and suffering and past unreimbursed expenses up until the time of death. Mr. Matanoski was unaware of any pending cases following Zatuchni/Snyder. The Government did not seek further review of that decision.

Responding to earlier comments about how cases were filed, Mr. Matanoski explained that cases are rarely filed on the basis of a vaccine Table injury. The pleadings typically do not provide much information about the details of a particular injury other than to aver that a vaccine was administered and an injury occurred. The specifics of each case usually emerge as the facts and case develop and after petitioner files supporting records and documentation. Regarding activation of the autism cases, Mr. Matanoski explained that typically, the claims are reviewed by a paralegal for the narrow issue whether the claim is time-barred and lacks jurisdiction. Attorneys review the case and, as necessary, move to dismiss time-barred claims. There are a lot of cases that fall into the aforesaid gray area and need further information (factual and/or expert development) and documentation to evaluate further for dismissal.

***Report on Omnibus Autism Proceeding from Petitioner=s Attorney
Tom Powers, J.D.***

With regard to the statute of limitations for filing petitions, there are some cases that are clearly within the time requirements and some cases that were clearly filed too late. But the majority of cases fall into a gray zone and a lot of effort will be required to resolve the issues. About 180 attorneys are involved in responding to issues raised by the Department of Justice, a significant effort to facilitate the process of activating what will eventually be nearly 5,000 cases.

A key issue is when there is agreement that a medical diagnosis starts the clock on the 36-month time period during which a petition may be effectively filed. Autism has been difficult to diagnose based on early symptoms. Therefore, some time may elapse between the first symptoms identified and the actual confirmed diagnosis of autism. The assumption that the first symptom starts the clock, rather than the firm diagnosis, is an issue that will apply to many of these cases where the timing of onset is not clear. The Office of the Special Masters is seeking a rational and resource-responsible way to resolve these issues with petitioners' attorneys.

Aside from this challenging situation, the three test cases based on the second theory (thimerosal alone) are under way, and hearings in two of these cases have taken place. The third test case scheduled dropped out and a search is going on for a replacement. Hopefully the search will be successful and the hearing on the third test case will take place in late July. The process to identify a viable case involves reviewing existing cases for timeliness of filing and determining whether a table injury could be deemed appropriate (which would make the case eligible for a concession). Of the five cases under review, Mr. Powers felt confident that one would qualify as the third test case.

In terms of the first theory presented in 2007 (MMR and thimerosal combined resulting in autism or Autism Spectrum Disorder), Mr. Powers noted that the hearings have been completed, as has the briefing phase, with the special masters now ready to render a decision. There was an anticipated request by petitioners' attorneys for an opportunity to obtain information from sources in Great Britain, but that request failed to materialize and the request was withdrawn.

Finally, petitioners' attorneys do not anticipate a general causation hearing in the third theory (MMR vaccine alone) because the evidence would be essentially the same as for the first (combined) theory tried in June 2007. The Petitioner's Steering Committee (PSC) is following a number of possible test cases that could be heard in the fall, but there have been no decisions related to that process.

Mr. Powers raised another issue of importance to petitioner's attorneys, that of interim payment of fees. Some attorneys have worked a number of years on the various cases, expending significant time and financial resources pursuing their clients' interests. Based on the recent Federal Circuit decision in *Avera*, those attorneys may prepare petitions for significant financial recompense and reimbursement. The PSC has adopted the position that conclusion of the prima facie case on general causation in the autism proceeding is an appropriate breaking point at which attorneys should be able to file such a petition. There are other such breaking points as the case continues to final disposition.

As the Omnibus Autism Proceeding advances, petitioner's attorneys continue to expect access the research data and other information generated by the Vaccine Safety Datalink. It will be important to update case information as new science is published with regard to autism and vaccine safety.

Vaccine Safety: Overview of Current Vaccine Safety Activities
Dan Salmon, Ph.D.
National Vaccine Safety Office, HHS

Dr. Salmon described the process by which a newly developed vaccine becomes approved for use in humans, which requires specific approval by the Food and Drug Administration before it can be routinely recommended in the U.S. population. Preclinical development of a new vaccine involves characterization of its chemical, biological and physical characteristics. The process usually involves animal models and includes assessment of safety. Once the developer of the vaccine is satisfied that there is a potential benefit in humans and indication of the safety of the vaccine, an Investigational New Drug application (IND) is submitted to FDA. If the FDA approves the IND application, a series of clinical trials in humans follow, beginning with a Phase I trial, which primarily looks at safety and possible adverse events related to the vaccine. Phase I trials are small, with 10

to 30 study participants per dose level. If no concerns are raised in the Phase I trial, the developer may initiate Phase II trials, which are larger (50 to 500 subjects) and evaluate efficacy as well as safety. There may be several Phase II trials. When the safety and efficacy of the candidate vaccine are promising in Phase II trials, a Phase III trial is undertaken involving thousands of subjects. Both safety and efficacy are evaluated in these trials.

Phase II and Phase III clinical trials are usually randomized, double-blind, placebo controlled studies, meaning that the subjects are randomly divided into two or more cohorts (e.g., those who will be given the study vaccine and those who will be given a placebo), and neither the study investigators nor the participants know into which group each subject has been placed. This is done to reduce the potential for bias and confounding. Studies will have inclusion and exclusion criteria to reduce confounding effects and to minimize risk in susceptible populations. For example, an underlying disorder (such as diabetes or hypertension) might have an effect on the study outcome, and bias or confound the results. Also, pregnant women are usually excluded from initial clinical trials because of theoretical risks to the fetus.

An important objective of clinical trials is to identify possible adverse reactions to the study vaccine -- from rash or fever to serious adverse effects like anaphylactic shock. Common reactions may be evident in the Phase I and II clinical trials, but rarer reactions require much larger study populations. The rarer an event, the larger the study population of a clinical trial must be. Therefore, clinical trials are very useful to identify common adverse events, but have some limitations in detecting rare adverse events.

Clinical trials with hundreds of thousands of participants are costly and not feasible. Therefore, to identify rare potential adverse events, the safety of a vaccine must continually be evaluated after the vaccine has been licensed. To obtain a license, the pharmaceutical manufacturer will submit a Biologic License Application (BLA) to the FDA, which includes detailed description of the vaccine's manufacturing process and the safety and efficacy data obtained from the prior clinical trials. FDA sometimes requires the manufacturer to conduct a Phase IV surveillance study that will identify adverse reactions to the vaccine as it is distributed into the marketplace for general use. Safety data is continually gathered by the Vaccine Adverse Event Reporting System (VAERS). VAERS is a passive system that collects reports from anyone, including health care providers, manufacturers, researchers, patients and any others who choose to report such events (although such reports are mandatory for manufacturers). People are encouraged to report to VAERS any potential adverse event caused by a vaccine, although a report to VAERS does not mean the vaccine caused the adverse event. VAERS is important to generate signals of potential vaccine adverse events that can be followed up through rigorous scientifically studies. One limitation of VAERS is that adverse events are both under-reported, especially the less serious adverse events, and over-reported, when reports are made which are not actually the result of a vaccine. Nor is VAERS able to specify a denominator since the total number of people receiving a vaccine is not known and therefore rates of adverse health outcomes among vaccinated and unvaccinated persons can not be compared using VAERS.

However, there is a system that is useful for following up signals generated by VAERS. The Vaccine Safety Datalink (VSD) relies on cooperative studies involving 8 major managed care organizations representing 1.8% of the entire US populations and 1.5 % of that population under 18. Funded by CDC, the VSD can develop hypothesis-driven studies and obtain patient medical records on the study population, a full range of adverse medical outcomes, and other relevant conditions. The strengths of the VSD include the ability to analyze emerging vaccine safety issues, and the ability to assess data in a near real-time manner. However, even the VSD population is too small to study cases of very rare adverse events. Also, the managed care populations do not perfectly mirror the entire U.S. population.

When studies are conducted relying on different definitions and standards they are difficult to compare and combine for analysis. The Brighton Collaboration is an international cooperative organization supported by the World Health Organization, the CDC and the European version of

the CDC. Its primary objective is to develop a set of standards and a common language so that various studies can be compared. The Clinical Immunization Safety Assessment (CISA) is a CDC-sponsored collaboration involving six major US medical centers and America's Health Insurance Plans, to conduct vaccine-related research on adverse events. CISA also provides case management support to individual physicians who may encounter an adverse event both on clinical care and subsequent immunization.

Since 1988, on a periodic basis, the government has asked the Institute of Medicine of the National Academy of Sciences to conduct independent reviews that assess potential causal relationship between a vaccine(s) and adverse event. Relying on a multidisciplinary panel of distinguished experts, in 2004 the IOM looked at thimerosal in vaccines and the MMR vaccine as causal factors in autism, and concluded that the evidence favored rejection of a causal relationship in both cases.

Finally, CDC undertakes a number of activities designed to identify patterns of vaccine usage, demographics, parental attitudes and beliefs about vaccines, and levels of understanding about vaccine programs. CDC also provides a wide variety of educational and informational resources to parents, the medical community, and health care providers. The National Vaccine Program Office (NVPO) coordinates vaccine safety activities across all HHS agencies.

Outside HHS and CDC there are a large number of entities also involved in vaccine related programs and activities -- the Department of Defense, academic researchers, parent and advocacy groups, philanthropic organizations, and professional organizations, such as the American Academy of Pediatrics.

In closing, Dr. Salmon presented a case study of rotavirus vaccines. Historically, rotavirus affects most children in the US by age five, causing gastroenteritis. While rotavirus is rarely fatal in the U.S., in the developing world rotavirus illness is a significant cause of death among children. In the 1990s, clinical trials of RotaShield, an effective vaccine against rotavirus, demonstrated a possible slight increased risk of intussusception, a compression of the bowel which can be a serious medical emergency, although it was not statistically significant. After RotaShield was licensed in 1998, VAERS detected a signal of intussusception following vaccination. This prompted carefully designed studies that demonstrated a link between the vaccine and intussusception about 3 to 14 days after vaccination. RotaShield was pulled from the market by the manufacturer in 1999. In 2006 a new rotavirus vaccine was licensed. Because of the previous experience with RotaShield, clinical trials for the new vaccine were expanded such that the same risk, if present, would be identified prior to licensure. Studies showed that this new vaccine did not cause an increased risk of intussusception. This example serves to illustrate how different components of the federal vaccine safety system work together to maximize vaccine safety.

During discussion, there was a comment that the risk-benefit consideration continues to be an important aspect of vaccine safety. Asked how the federal agencies affect the selection of diseases to target for vaccine development, Dr. Salmon explained that epidemiological studies often point to candidates, but that various aspects of the candidate disease (etiology, mechanisms of action of the disease vector, etc.) may make it very difficult to launch a vaccine development program. It was also observed that defining the appropriate target population for the vaccine may influence a decision to pursue development.

Concerning improvements in the surveillance system, Dr. Salmon noted that the VSD is a relatively new improvement that has greatly increased the effectiveness of immunization safety research. In addition, technological advances have made possible more rapid improvement of vaccines, such as the acellular pertussis vaccine. In addition, there are now genomic studies being undertaken that will expand knowledge in the vaccine arena. Finally, there was a brief discussion about the importance of, and difficulty related to defining the needs of subpopulations, which include issues of health disparities and the needs of special populations. There are also

issues related to the costs of conducting additional pre-licensure trials in subpopulations and the delays involved in getting an effective vaccine into widespread use when such clinical trials delay the licensing process. What vaccines are selected for development not only depends on the various federal groups concerned with funding research, but whether or not the pharmaceutical companies can justify the costly development process. This is especially true when relatively small subpopulations are involved.

Industry Role in Vaccine Safety
Bob Sharrar, M.D.

Dr. Sharrar explained that he had spent the first half of his career, 17 years, as a public health officer for the City of Philadelphia, and the second half of his career monitoring vaccine safety for a major pharmaceutical company, Merck and Company. He stated that responsible pharmaceutical companies develop and manufacture safe and effective drugs, and continuously monitor that safety and effectiveness by maintaining a safety profile for each product.

As an example of the care taken in developing safe vaccines, Dr. Sharrar described the manufacturing of measles virus vaccine, which is derived from chicken embryo tissue cultures. At the outset, Merck located a flock of chickens that were free of avian flu or other disease, continuously maintained that flock in a tightly controlled environment to insure that the original purity of the strain would be maintained. In another example, Dr. Sharrar noted that the original hepatitis B vaccine was made from plasma collected from homosexual men who had high titers of hepatitis B surface antigen. But there was a serious resistance to using that vaccine because of a perceived risk, even though multiple purification steps in the manufacturing process assured an absolutely safe product. So Merck developed a recombinant process that eliminated the need for the plasma. A similar process was developed for MMR vaccine that eliminated the need to use human serum albumin

The removal of thimerosal as a preservative in multi-dose units of vaccine was prompted by a public demand for thimerosal-free vaccine (accomplished by packaging vaccine in single dose units). But the companies had to conduct extensive tests to show that the efficacy and safety profiles had not changed by the removal of thimerosal.

Dr. Sharrar noted that pharmaceutical companies were getting better at recruiting more diverse populations, and they are conducting clinical trials in other parts of the world. The drawback is that for various reasons, when more subpopulation clinical trials are conducted, the sample size is reduced, which makes it more difficult to identify rare adverse reactions to new drugs. The quality control process is also very stringent -- Merck conducts more than 200 tests at different stages in the MMR manufacturing process. And if any of those tests fail, the entire lot is discarded.

To really get at the true safety profile, including identifying rare adverse effects, the post-marketing surveillance process is important. That involves gathering information on all reported events from whatever source, and providing that information to the appropriate Federal offices. Although the process works well, there are weaknesses - the process does not make judgments on causation, but simply develops an adverse reaction database. In addition, it has to rely on the diagnoses provided by the individual reporting the incident, which may or may not be correct. That process has been improved by adding a proactive testing program (the VSD) to the traditional passive VAERS-type surveillance program. That means highly specific studies are conducted in cooperation with major health care providers, like Kaiser Permanente. That allows a much more accurate analysis of more data, including knowledge of the entire number of individuals receiving the vaccines.

In some cases laboratory tests can clearly determine if a particular vaccine was involved in an adverse reaction. In many instances that is not possible because definitive tests are just not available. For disorders like autism, multiple sclerosis, and SIDS, there are no markers currently

available that establish a causal link between the condition and a particular vaccine. That has to be developed and perhaps the VSD will be one of the mechanisms to do that.

During discussion, in response to a question about how the federal agencies would enhance the safety profile process in the manufacturing setting, Dr. Sharrar stated that regulatory requirements have become burdensome, that new regulations are piled on top of older regulations, and the process of conforming becomes time consuming and expensive. Streamlining those regulatory requirements would be a positive step.

Concerning mandatory reporting requirements, Dr. Sharrar felt that, although pharmaceutical companies can provide clinical trial data on adverse events relatively easily, it is a much different issue with regard to the huge number of health care providers. Strict enforcement of such mandatory reporting requirements might be impractical in that arena. For instance, there is a federal mandate that physicians report adverse events through VAERS, but there is no practical way to enforce the mandate. He added that the growing electronic health record system will make it easier to obtain adverse event information without going directly to the physician.

FDA's Role in Vaccine Safety **Marion Gruber, Ph.D.**

Dr. Gruber explained the clinical development process of an investigational vaccine by which a manufacturer (sponsor) obtains FDA approval to market and distribute the product. One important aspect of the pre-licensure program is the non-clinical evaluation of the vaccine which includes the development of a manufacturing process that ensures that the vaccine can be made reproducibly and consistently and conforms to the established release specifications.

Step one is submission of an investigational new drug application that describes the vaccine and contains a proposal for the first clinical trial, the so-called Phase I study. The IND includes a description of the candidate vaccine, its anticipated use, as well as a description of its manufacturing process, data on the proof of concept work, toxicological studies and any other animal model data available. If FDA does not identify any safety issues upon review of the IND submission, the vaccine proceeds to phase 1 clinical trial which involves relatively few healthy adult subjects (usually around 20). This first trial involves adults even if the ultimate intended use is for pediatric populations, e.g. infants. If the adult trial proves successful, additional Phase I trials may be conducted in children of younger age groups and ultimately in the target population, e.g. infants. The study's primary purpose is an initial assessment of safety of the vaccine in human subjects. Immune responses may also be assessed.

If the Phase I trial is successful, the clinical development proceeds to Phase II clinical trials, which will involve a larger number of subjects. Phase II trials are to optimize the dose, dose schedule and sometimes route of administration. Immunogenicity of the vaccines is assessed in these Phase II studies as well as safety outcomes. During these trials there is regular communication between the sponsor and the FDA.

Phase 3 trials typically enroll thousands of individuals and provide the critical documentation of effectiveness and important additional safety data required for licensing. The primary endpoint is typically prevention of disease. Effectiveness may also be inferred through an immune endpoint. The Phase III trial provides an expanded assessment of vaccine safety and its potential side effects. In special cases when it is not practical or ethical to conduct a trial in humans (e.g., for anthrax vaccine), the FDA may approve a vaccine product based on a demonstration of effectiveness of the vaccine in animal models. In these situations, safety studies in humans would still be required.

CBER has no published guidelines on the size of vaccine safety studies. The size of the trial depends on the product under investigation, the subject population, the outcomes measured, the disease incidence, etc. The "rule of three" is frequently invoked -- that the trial should be able to

detect an adverse reaction with an incidence rate of one in a thousand, this would require a sample size of approximately 3,000 subjects.

If successful, the completion of all three phases of clinical development can be followed by the submission of a Biologics License Application (BLA). These applications contain the complete results of the trials and all relevant information and aspects related to manufacturing of the vaccine. They also include a pharmacovigilance plan to identify and evaluate potential safety signals post-licensure. Pre-licensure safety studies are typically not large enough to detect rare adverse events or adverse events occurring in certain subpopulations. These are more likely detected as part of post-marketing surveillance.

The Food, Drug and Cosmetics Act and the Food and Drug Administration Amendment Act (FDAAA 2007) provide the FDA with authority for monitoring the progress of postmarketing studies and, if certain prerequisites are met, to require holders of approved products to conduct postmarketing studies and clinical trials at time of approval or after approval. CBER has established various product safety teams (blood products, cellular and gene therapy products, vaccines) to improve the acquisition, analysis and communication of safety information.

During discussion, Dr. Gruber explained that the FDA works closely with sponsors during the clinical development process for a vaccine. Phase I and Phase II studies are more concerned with detecting adverse events. However, Phase III studies are designed to meet the primary endpoint to establish efficacy and are often large enough to also establish the safety of the vaccine in the pre-licensure setting.

Thimerosal and Vaccines: Vaccine Content Marion Gruber, Ph.D.

Dr. Gruber stated that, except for some influenza vaccines, thimerosal-preservative has been removed from pediatric U.S.-licensed vaccines and from most vaccines indicated for the adolescent and adult population.

Thimerosal contains organic ethyl mercury. The mercury compound that has been most publicized as a human risk in seafood, breast milk, some cosmetics and dental amalgams, is methyl mercury, which is a known neurotoxin to which the fetal brain is especially receptive and which can cause severe developmental disabilities.

The Food and Drug Administrative Modernization Act of 1997 required FDA to identify products containing organic mercury and to assess the effects of mercury compound on humans, especially infants. As part of that review, the FDA evaluated the amount of mercury an infant might receive in the form of ethylmercury from vaccines under the U.S. recommended childhood immunization schedule and compared these levels with existing guidelines for exposure to methylmercury, as there are no existing guidelines for ethylmercury. At the time of this review in 1999, the maximum cumulative exposure to mercury from vaccines in the recommended childhood immunization schedule was within acceptable limits for the methylmercury exposure guidelines set by FDA, ATSDR, and WHO. However, depending on the vaccine formulations used and the weight of the infant, some infants could have been exposed to cumulative levels of mercury during the first six months of life that exceeded EPA recommended guidelines for safe intake of methylmercury. There was no evidence of any adverse reaction related to those levels of mercury in infants. However, it seemed reasonable to remove thimerosal from vaccines intended for pediatric use and in July 1999, the Public Health Service published a recommendation to eliminate thimerosal from vaccines as soon as practicable. At the same time, the FDA sent a letter to manufacturers urging the same action.

In 2004, the IOM's Immunization Safety Review Committee examined the hypothesis that thimerosal containing vaccines are causally associated with autism. In this report, the committee incorporated new epidemiological evidence from the U.S., Denmark, Sweden, and the United Kingdom, and studies of biologic mechanisms related to vaccines and autism since its report in

2001. The committee concluded that this body of evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.

Since 2001, all vaccines intended for pediatric use contain no thimerosal or only trace amounts that remain when thimerosal is used in the manufacturing process. Prior to the initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury via routine childhood vaccinations during the first six months of life was 187.5 micrograms. With the introduction of thimerosal-preserved-free formulations of pediatric vaccines, the maximum cumulative exposure from the routinely recommended childhood vaccines decreased to less than three micrograms of mercury in the first 6 months of life. With the addition in 2004 of influenza vaccine to the recommended vaccines, an infant could receive a thimerosal-containing influenza vaccine at 6 and 7 months of age. This would result in a maximum exposure of 28 micrograms via routine childhood vaccinations. There are thimerosal-free flu vaccines available but not in sufficient amounts to supply the whole pediatric population for which influenza vaccine is recommended. Also, manufacturers have stated that a large amount of thimerosal-free vaccines had to be discarded.

Vaccine Distribution and Utilization

Jeanne Santoli, M.D., M.P.H.

Immunization Services Division, National Center for Immunization and Respiratory Diseases, CDC

Dr. Santoli explained that CDC is involved in making recommendations for vaccine development and the vaccine program through the Advisory Committee on Immunization Practices (ACIP). ACIP collaborates with the American Academy of Pediatrics, the American Academy of Family Physicians and the American College of Physicians to develop recommendations. Secondly, CDC plays a major role in tracking the flu strains that emerge that appear to be specific threats for the upcoming flu season. Then a combination (trivalent) vaccine can be developed to address the flu strains that most likely will infect vulnerable populations. CDC supports the process of purchasing flu vaccines, especially for children, through 64 immunization grantees around the country. Distribution of vaccines is mainly a private sector function, although CDC does provide some informational support in coordinating distribution. CDC also provides education resources for the administration of the vaccine program.

In 2004, the first recommendation was published for the immunization of children 6 to 23 months of age, followed in 2006 by a recommendation to expand coverage to children 24 to 59 months of age. Then in 2008, a recommendation was published to immunize all children 6 months to 18 years of age. Dr. Santoli noted that the increase in the size of the entire population who should receive flu shots went from about 80 million in 1964 to almost 260 million in 2008. CDC contract purchases of pediatric vaccine accounts for about half of that market, but only about 10 % of the adult vaccine market.

The actual production of vaccine doses is smaller -- in 2007, 141 million doses were produced, 113 million were distributed (purchased), and therefore 28 million doses were discarded unused at the end of the flu season. That unused category does not include doses purchased by health care providers but not dispensed and ultimately discarded. Supply and demand is clearly not in sync.

Since 2001, thimerosal has not been added to vaccines except for a few influenza vaccines distributed in multi-dose vials. In those it may be added as a preservative or used in the manufacturing process and then removed, leaving only trace amounts in the distributed vaccines. There are currently 11 influenza vaccines, four of which contain thimerosal (all sold in multi-dose vials). Manufacturers have the capacity to produce 50 million doses for the next flu season, only 20 million of which are licensed for children. Although those numbers would be insufficient for the two-dose regimen for children, because of uneven distribution, some of the pediatric doses will not be used and will be discarded.

During discussion, in response to an inquiry about the economics of single-dose versus multi-dose packaging, Dr. Santoli stated that one problem is storage of single-dose vials. Concerning the costs, the federal contract for multi-dose vials is about \$10 per dose, for single-dose vials about \$13 per dose, and for the intranasal application about \$18 per dose. The costs on the public market are about one or two dollars more per dose.

Public Comment

Dr. Sconyers announced that Council Member Dr. Meg Fisher was receiving the Oksana Korzeniowski Patient Care Award from Drexel University for her outstanding skills and commitment in the clinical care of patients and through her teaching which has contributed to the skills and knowledge of residents, students and medical colleagues.

He then invited public participation in the meeting. There were no requests by members of the public to comment.

(Whereupon the meeting recessed at 5:10 p.m. to reconvene the following day at 9:00 a.m.)

Advisory Commission on Childhood Vaccines Meeting Conference Call

June 6, 2008

Minutes

Members Present

Jeffrey M. Sconyers, J.D., Chair
Tawny Buck
William P. Glass, Jr., J.D. (via teleconference)
Tamara Tempfer, RN-C, MSN, PNP (via teleconference)
Charlene Gallagher, J.D.
Magdalena Castro Lewis
Jaime G. Deville, M.D.

Executive Secretary

Geoffrey Evans, M.D., Director, DVIC

Staff Liaison

Michelle Herzog

Review of Vaccine Information Statement Skip Wolfe National Immunization Program, CDC

The Commission considered the vaccine information statement for MMR, and there was a brief discussion about the use of the term “provider” or “health care provider” for “doctor and/or nurse” and the Commission agreed that either was appropriate. There was concern that in referring to response to adverse events, the term “doctor” should be used because of the specific medical implications of such an event. There was agreement that the term “doctor” implies a provider and that for consistency throughout the text, the word “provider” should be acceptable. There was a suggestion to consider adding a glossary to the information sheets if space was available.

Ms. Buck commented that the warning on the MMR information sheet concerning very rare, very serious adverse events that might be attributed to the vaccine, although not proven, should be explained (especially whether there is current research to verify the events). Mentioning events like permanent brain damage, seizures, and coma could be frightening to a patient.

Mr. Wolfe noted that Dr. Fisher had submitted a list of suggestions that included mentioning acute fulminant hepatitis B as a condition against which the vaccine was appropriate, and removing the phrase “chicken pox is common” since that is no longer true. On the tetanus, pertussis, diphtheria information sheet, there was agreement that the phrase “coughing episode often lasting weeks to months” should be added under the pertussis discussion.

Ms. Castro-Lewis noted that the information sheets contain a statement that there is a Spanish version available. She suggested adding that phrase in Spanish. She also recommended having an independent reviewer check the translations provided by the several translation contractors who create the Spanish language information sheets.

Mr. Wolfe explained the process by which an information sheet is created -- CDC creates a draft which is reviewed by an internal panel, the new VIS goes to the ACCV and the FDA for review and comment, the original draft is published in the Federal Register for public comment, it goes to one or more provider and/or parent consultants for comment, it is re-drafted and re-reviewed by the internal CDC panel, and an announcement that the VIS is being published is placed in the Federal Register, after which it becomes official and is released. The process can take up to six months. There was a brief discussion about dating the documents and Mr. Wolfe said that one proposal was to date the VIS to reflect each full revision, but to then add a second date indicating the latest review.

Update on the Immunization Safety Office

Karen Broder, M.D.

Immunization Safety Office, CDC

Dr. Broder explained that the ISO, which reports to the Director of CDC, is responsible for assessing the safety of vaccines administered to children, adolescents and adults. In collaboration with other agencies, the ISO supports four major vaccine safety programs -- the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), the Clinical Immunization Safety Assessment Network (CISA) and the Brighton Collaboration.

In 2005, the Institute of Medicine issued a report that, among other recommendations, called for a subcommittee of the NVAC to develop recommendations for a VSD research plan. Out of that, the ISO took on the responsibility of developing a proposed five-year scientific agenda, an important part of which would be the integration of the four major activities described above and not a focus only on the VSD. The scope of the agenda would include vaccine safety research, selected surveillance and selected clinical guidance activities that are a part of the ISO mission. The focus is on scientific activity and not on aspects such as education or communications.

The process includes three steps -- the development of the draft agenda by the ISO, a review of the agenda by the NVAC, and ISO response to NVAC's review comments and recommendations. The final agenda will be approved by CDC within the context of the ISO mission, feasibility and harmonization with the priorities of the CDC. The draft agenda contains three recommendations -
- to respond to emerging issues and conduct required scientific activities in response to those issues; to enhance vaccine safety public health and clinical guidance capacity in seven areas; and to address five-year research needs.

To accomplish the first objective, ISO will monitor the safety of new vaccines, ACIP-recommended vaccines, and established vaccines that acquire new recommended practices, and to respond to unanticipated safety concerns that may occur. ISO will provide technical support to CDC and others involved in collaborative and multidisciplinary scientific activities. ISO will be prepared to monitor vaccine safety with regard to a mass vaccination campaign or vaccine safety emergency.

The second major agenda area is enhancement of vaccine safety public health and clinical guidance capacity in seven areas: Infrastructure for VAERS and VSD; epidemiologic and statistical methodology for vaccine safety; laboratory methods and genomics of vaccine safety; vaccine clinical practice guidance; case definitions, data collection and presentation for adverse events following immunization; and vaccine safety clinical practice guidance.

The third major objective addresses a five-year research plan and includes 30 areas of interest involving specific safety questions (7 items), and three thematic areas -- vaccines and vaccination practices (8 items), special populations (7 items), and clinical outcomes (8 items). The study designs for these various areas of interest were not considered in developing the agenda. That process will occur when the agenda is finally approved.

The specific vaccine safety questions include whether vaccines are associated with increased risk for Guillain-Barre syndrome, whether live attenuated influenza vaccine increases risk of asthma in vulnerable populations (children and persons with a history of wheezing); if thimerosal is a risk factor for tics and Tourette syndrome; whether acellular pertussis vaccine are associated with a risk of neurological events; whether immunization contributes to neurological deterioration in children with mitochondrial disorders; whether MMRV contributes to febrile seizure; and whether varicella vaccines increase risk of adverse events related to varicella vaccine virus reactivation.

In the vaccine and vaccination practices research area, topics include bivalent HPV; zoster vaccine; annual influenza vaccination of children and adolescents; non-antigen components of vaccines; simultaneous/multiple vaccination; safety of different products in the same vaccine category; off-label use of vaccines; and vaccine-drug interactions.

In the special populations research area, topics include preterm delivery and low birth weight infants; pregnant women; adults over 64 years of age; persons with primary and secondary immunodeficiency and with autoimmune disorders; and children with inborn errors of metabolism.

In the clinical outcomes thematic area topics include autoimmune disease; CNS demyelinating disorders; encephalitis/encephalopathy; neurodevelopmental disorders (including autism spectrum disorder); vasculitis syndrome; myopericarditis not associated with smallpox vaccine; adverse events related to post-immunization fever; and post-vaccination syncope and its sequela.

Concerning the NVAC review with regard to prioritization, ISO suggested that the first agenda item required no specific prioritization, although an assessment of the relative importance of the various specific issues would be helpful. Prioritization of the seven capacity areas and the five-year research needs would be appropriate. The ISO did provide some guidance on the prioritization criteria for the three major agenda areas.

Update from the National Vaccine Safety Program Office Dan Salmon, Ph.D.

Dr. Salmon reviewed the activities of the NVAC Vaccine Safety Working Group, which is charged with reviewing the ISO Scientific Agenda, and developing a white paper that assesses the Federal vaccine safety system. In developing the working group, the appropriate disciplines were identified first, after which individuals were recruited. There are 18 non-federal members and 11 ex officio members representing federal agencies. There was considerable pressure from various constituencies to expand the membership to include a wider variety of stakeholders. In the interest of an efficient committee process and fairness, the Working Group discussed the matter and unanimously agreed to maintain the membership at the current members. At the same time there was agreement that the public engagement in the Working Group process should be encouraged, and that there should be a mechanism to facilitate that.

The first Working Group meeting was held on April 11, 2008. Although not required by the Federal Advisory Committee Act to be open, the first meeting was advertised in the Federal Register and open to the public. Over a hundred members of the public and a number of media representatives attended. The agenda included a presentation of the ISO Scientific Agenda and a panel discussion on engaging the public, which included presentations by two advocacy groups, Autism Speaks and Voices for Vaccines. The Keystone Center, a group that facilitates public engagement presented a basic course in how to accomplish effective public engagement. There was lively discussion and almost an hour set aside for comments by members of the public in attendance.

The Working Group is currently addressing its first task, to review the ISO Scientific Agenda. To that end there was a decision to create four subgroups to work on specific areas of the agenda. There will be monthly conference calls to share progress and to develop recommendations.

**Update on the National Institute on Allergy and Infectious Diseases, NIH
Barbara Mulach, Ph.D.
Division of Microbiology and Infectious Diseases**

Dr. Mulach briefly commented on NIH activities, noting that Deputy Secretary Tevi Troy met with NIH staff to discuss NIH programs related to vaccine safety. There are a number of activities looking at the basic science of issues like autism, human immune response, the increasing incidence of allergies in humans and similar issues. Dr. Mulach noted that NIH researchers are involved in some of the early stages of work that ultimately lead to advances in vaccines -- cell culture, small animal models, special populations and so on. She added that NIH also conducts Phase I and Phase II trials of new and improved vaccines that focus mainly on safety.

Public Comment

Mr. Sconyers acknowledged with appreciation the dedicated service of departing Commission members Dr. Jaime Deville and Mr. William Glass. He also noted that Dr. Indira Jevaji was leaving to take a position at NIH.

He invited members of the public to contribute during the public comment period.

Mr. James Moody, Director of Safe Minds, brought two studies to the attention of the Commission. The first was a study by Young that indicates a statistically significant association between thimerosal-containing vaccines and autism. The study relied on data from the VSD which was not readily available to the public. He urged that the Commission consider this issue at the next meeting.

The second study was presented at the International Meeting for Autism Research in London and related to Bell's disease in non-human primates and the issue of the vaccine schedule. He urged the Commission to consider the vaccine schedule as a whole, rather than focusing on specific vaccines in isolation.

Future Agenda Items

Mr. Sconyers announced that there would be an e-mail invitation for proposed agenda items for the next meeting. Ms. Buck suggested an expanded version of Dr. Gruber's thimerosal presentation, and an update on the omnibus proceedings.

Adjournment

On motion duly made and seconded, there was unanimous agreement to adjourn. The meeting adjourned at 10:55 a.m.

Jeffrey Sconyers, J.D.
ACCV Chair

Tawny Buck
ACCV Vice-Chair

Geoffrey Evans, M.D.
Executive Secretary, ACCV

Date

