# Advisory Commission on Childhood Vaccines

## September 4, 2008

**Minutes**

## Members Present

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

**Executive Secretary**

Geoffrey Evans, M.D., Director, DVIC

**Staff Liaison**

Michelle Herzog, Principal Staff Liaison

**Introduction and Approval of Minutes**

Mr. Sconyers convened the 70th quarterly meeting of the Advisory Commission on Childhood Vaccines (ACCV) at 1:00 p.m. and welcomed all participants. He invited a motion to approve the minutes of the June 5-6, 2008 meeting. On motion duly made and seconded, the minutes of the June 5-6, 2008 meeting were unanimously approved.

Mr. Sconyers welcomed new members Sarah Hoiberg, the mother of a vaccine-injured child, Sherry Drew, a petitioner's attorney, and Tom Herr, a pediatrician.

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

Dr. Evans welcomed members and guests in attendance, noting that the National Vaccine Injury Compensation Program (VICP) was established 20 years earlier, on October 1, 1988. He reviewed the agenda for the two-day meeting. Noting that Kay Cook had joined the DVIC as branch Chief of Policy, he added that her experience at the HRSA Office of Financial Management would be a particularly welcome staff asset. Dr. Evans also welcomed three new members. Ms. Sherry Drew comes to the Commission having represented petitioners before the U.S. Court of Federal Claims and having participated in the attorney assessment of the VICP. Dr. Tom Herr, a pediatrician in private practice in Illinois, has been active in the American Academy of Pediatrics and has testified on issues related to childhood immunization. Finally, Ms. Sarah Hoiberg is the mother of a child who experienced encephalopathy after administration of a DTaP vaccine and was subsequently awarded compensation under the VICP.

***Financial and Statistical Report***

Dr. Evans reminded the Commission that there was a surge in non-autism case filings in July 2007 related to the deadline for filing influenza vaccine claims, when more than 200 influenza claims were filed altogether. The rate of non-autism filings is back to the previous level of an average of 12 claims per month. Autism claims filings were in a slight downtrend until 2006, turning upward in 2007 because of the publicity surrounding the Omnibus Autism Proceeding. So far this year, 221 claims have been filed. Dr. Evans noted that the final test case for the thimerosal-only theory (Theory 2) in the Omnibus Autism Proceeding was completed in July, and the parties will be filing briefs later this year.

Regarding awards, the average total compensation awarded has averaged about $65 million annually for the past eight years, with attorney's fees at about $4 million. The total awards since the program's inception in 1988 has been $901 million. An additional $902 million was awarded for claims adjudicated before the program began in 1988. Hence, the program has paid out $1.8 billion in total.

The trust fund currently stands at $2.6 billion. This year, gross income will be about $320 million, a significant contribution coming from the tax on about 130 million doses of influenza vaccine that will be distributed in 2008.

***Legislative Update***

On the legislative front, Representative Dan Burton has introduced the National Vaccine Compensation Program Improvement Act of 2008 (an amendment to the Public Health Services Act), which is identical to his bill introduced in 2005. The bill contains a number of the recommendations sent to the Secretary in March 2007. Senator Lisa Murkowski also introduced legislation: the Infant Immunization Improvement Act of 2008. There has been no activity since the last Commission meeting.

**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 Civil Division, Torts Branch, vaccine section at the Department of Justice (DOJ) while Mr. Rogers remains deployed to Iraq.

**Personnel**

There was no staffing changes since the last meeting. Currently, DOJ is sufficiently staffed to meet the demands of the Office of Special Masters, however, there remains a backload of cases that largely comprise the autism claims.

**Statistics**

Mr. Matanoski reported that since June 5, 2008, there were 90 cases filed. Of those, 60 were autism and 30 were non-autism petitions. Of the pending cases, 33 were resolved by the court. In the prior four-month period, 177 cases were filed and 101 cases were resolved, which indicates that the backlog of cases continues to increase. Of the 33 cases, however, 20 cases were compensated, 13 were dismissed. Of the 20 compensated cases, 16 cases were resolved by settlement and 4 were resolved by the Office of Special Masters by a decision favoring petitioner. Regarding the 13 dismissed cases, 11 were dismissed by the Office of Special Masters finding no entitlement to compensation and 2 were voluntary dismissals on the part of the petitioners. To compare with the last quarter ending in June, 2008, 60 cases were

compensated. Of those, 53 were settled and 7 were resolved by the Office of Special Masters with a decision favoring petitioner. Percentage wise, the number of cases being compensated remains roughly equivalent to the number being dismissed. Mr. Matanoski remarked that less cases tend to be adjudicated in late summer, August, as the special masters take vacation leave.

Asked about how cases are compensated, Mr. Matanoski explained that one way occurs when a petition is filed and on review within HHS the Secretary may find that compensation is appropriate under the Act's requirements for compensation i.e., it meets the Table conditions or meets the standard for actual causation. Another method of compensation occurs by settlement. There are different kinds of settlements. A case can be settled after the special master determines that the petitioner meets the requirements for compensation under the Act. Rather than have the special master convene a damages hearing, the parties work together and decide jointly upon a reasonable settlement. A stipulation setting out the terms of the settlement is filed with the Court, which enters a decision consistent with the Stipulation, and judgment follows. The majority of cases, however, are compensated by settlement. By settlement, Mr. Matanoski means "litigative risk" settlements. That is where the petitioners maintain that they are entitled to compensation and the Government maintains that they are not. However, the parties agree that the case should be settled without resorting to a decision through litigation. "Litigative risk" settlements resolve the case without a resolution of whether or not under the Act a petition is entitled to compensation. In contrast, cases that are settled after a special master awards entitlement to compensation but before convening a damages hearing are not considered 'litigative risk' settlements. If, after a hearing, the special master determines that petitioner is entitled to compensation, and the parties cannot settle the damages, then the special master can convene a second hearing to resolve the amount of reasonable compensation, or decide the matter based on the information in the record.

Mr. Matanoski noted that settlements have varied across the years from a low of 67% of the compensated cases versus 33% conceded by the Secretary, to a high in 2008 where 82% of the cases were compensated and 18% conceded. Adjudication has increased over the past five years to a peak in 2004 when 296 cases were adjudicated (21% received compensation). Mr. Matanoski believed that in 2004 some of the cases were dismissed because they were time-barred autism claims. In 2008, thus far, 253 cases have been adjudicated (49% compensated to some extent- most likely litigative risk as opposed to concession or settlement following a decision on entitlement). Mr. Matanoski's impression was that the increased percentage of compensated cases was probably due more to changes in the special master's decision process following Althen v. HHS, rather than any changes in vaccine safety. He emphasized that these statistics do not reflect upon vaccine safety. More likely, compensation statistics reflect changing patterns of what the law requires in terms of proving entitlement to compensation under the Vaccine Act.

When asked if there was tracking information to show a history of conceded settlements, litigative risk settlements, and entitlement decisions, Mr. Matanoski explained that such data could only be derived by undertaking an individual review of each case to determine what type of settlement it was. Without reviewing each case to determine its settlement status, DOJ endeavored to provide a general breakdown of settlements. Regarding terminology, there was a brief discussion about the meaning of the terms used when discussing these statistics, such as settled, conceded, litigative risk, and compensation. For future meetings, Mr. Matanoski offered to provide a glossary of terms to be distributed with his statistics presentation.

In response to another question concerning the increase in the number of claims being filed, Mr. Matanoski attributed the increase in part to recent publicity surrounding vaccines generally. He emphasized that whether the cases reflect actual vaccine injuries is for the court's determination. Moreover, Mr. Matanoski cautioned that one should not necessarily equate compensation in the Program as an indication that vaccines cause certain injuries because compensation can be determined by legal standards and settlements, which are agreements between the parties to resolve a case notwithstanding the parties views of entitlement to compensation. In response to

a question on conceded cases, Mr. Matanoski noted that of the 16 cases settled, those were not reflective of conceded cases. Mr. Matanoski acknowledged the confusion surrounding the terminology, and emphasized that a glossary would be helpful and available at the next meeting, to aid in distinguishing between settlements and conceded cases that are later settled, if that statistic can be provided.

In response to a question about whether there was a formula that guides decisions about conceding claims, Mr. Matanoski explained that each case must be evaluated individually in light of the Vaccine Act requirements, the parameters of the Injury Table and the evidence submitted with the particular case. Developing a formula is not feasible. Dr. Evans added that when a claim is filed, the medical records attached are reviewed by HHS to ascertain if there is sufficient evidence of a table injury, or evidence of another cause. If, for instance, it is a straightforward table injury, then the determination would be to concede the claim. Another basis for concession, would be where petitioner supplies sufficient evidence of actual causation, but that basis would occur much less frequently. Equally less frequent is sufficient evidence that a child's preexisting condition was significantly aggravated. Seeking clarification, Dr. Salmon commented that the Secretary, in the initial decision, does not concede that a vaccine caused a specific adverse event; only that the claim meets the statutory requirements of the Act. In other words, it does not reflect a biomedical determination. Dr. Evans responded that when a case is conceded based on proof of causation, it is a medical and legal determination, depending upon the particular vaccine and particular injury. Mr. Sconyers emphasized that the word "cause" has several different meanings. Acknowledging the comment, Mr. Matanoski emphasized that the program operates under a law and that legal standard applies to the term actual causation, which is a legal determination influenced by evidence. He further explained that under the Act, the law influences, in actual causation cases, whether there would be a concession of actual causation because the program operates under the law.

**Autism**

Mr. Matanoski reiterated that the hearing in the second theory of causation was completed and, because all parties agreed that the evidence for the third theory of causation (MMR vaccine alone as a cause) would be identical to the second theory, there would be no hearings on the third theory. He noted that the hearing transcripts had been reviewed by the DOJ and forwarded to the Petitioner's Steering Committee (PSC) for final review. After that review the court will establish a post-hearing briefing schedule. Mr. Matanoski indicated that the PSC identified a third case, which was tried in July. Also, the PSC decided against pursuing evidence from the MMR trial in the United Kingdom.

Mr. Matanoski discussed the pending 5,000 filed claims, and the status of activation by the Chief Special Master for records and review to determine jurisdiction. The intent of the court is to activate all 5,000 claims. So far, 1,400 claims have been activated. The review by DOJ only determines whether or not the claim meets the jurisdictional requirements. If it does not meet jurisdictional requirements, DOJ recommends dismissal. If insufficient information is available to determine jurisdiction, that is conveyed to the court. Currently, DOJ has kept up with the Chief Special Master's original demand of reviewing the activated cases, though the resource demands have been heavy. It appears, however, that the petitioner's attorneys may be running into logistical challenges in making at least 200 cases available each month for review. Scheduling deadlines has become more complicated because individual cases are delayed and rescheduled for additional record submissions. As the review process continues, there are instances arising where petitioners and the Government disagree on whether there is sufficient evidence to establish jurisdiction. In those instances, the court is starting to schedule conferences and hearings to determine whether a particular petitioner has established jurisdiction. Depending upon the circumstances of a given case, factual evidence, as well as testimony from expert and/or treating physicians may be required to determine what constitutes the first symptom or manifestation of the onset of autism and jurisdiction.

After explaining the requirement to file a claim within three years of the first symptom or manifestation of onset of symptoms of autism, there was a brief discussion about the ambiguity of autism symptoms and the temporal characteristics of vaccination(s) and the onset of autism symptoms. Mr. Matanoski explained that the claims must be reviewed in light of scientific evidence and the requirements of the program. He noted that onset of autism is often at age 12-18 months which coincides with the infant vaccine schedule. In the DOJ's view, causation has not been scientifically established.

**Appeals**

Mr. Matanoski commented on a previously discussed case, (Avera v. HHS), issued by the U.S. Court of Appeals for the Federal Circuit (Federal Circuit). The Court held that an award of interim fees and costs is available in certain circumstances. At the last meeting, there had been only one fee petition seeking an award of interim fees and costs. Since then, however, there are fifteen pending interim fee applications. In response to a question, Mr. Matanoski explained that the Government was endeavoring to work with a group of petitioners' counsel who together handle a significant number of vaccine cases to identify mutually acceptable "break points" in a case to seek an award of interim fees and costs. However, several of the fifteen interim fee applications received so far were inconsistent with those breakpoints. The concern is that resources will be spent on resolving interim fee applications instead of resolving the merits of a particular claim. Mr. Matanoski remains optimistic and will continue to working with the petitioner's bar to develop a solution to the problem. He anticipates that the court will probably be helpful in that effort.

Mr. Matanoski noted that there are three cases pending before the Federal Circuit. The first, (Kay v. HHS), involves a denial of attorneys' fees where the underlying claim was time-barred and dismissed for lack of jurisdiction. Petitioners have appealed the denial of fees to the Federal Circuit. The second pending case, Mojica v. HHS, also involves a time-barred claim. In Mojica, the petition was filed late because of an error solely attributed to the commercial delivery service that delivered the petition one day late. One week after oral argument, the Federal Circuit panel issued its decision upholding the dismissal of the petition as untimely. The decision was per curiam, meaning the panel was unanimous, and that the issue, by implication, did not present a difficult legal question. The petitioners requested a re-hearing by the Federal Circuit en banc, meaning reconsideration by the entire circuit. The request has not been acted on by the Court yet. The third pending circuit appeal involves the dismissal of a claim because the alleged onset of petitioner's alleged injuries (demyelinating injuries) occurred too soon (eleven hours) after the administration of the vaccine. That case, which was discussed at the last meeting, is Bazan v. HHS. In response to a question, Mr. Matanoski recalled that 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 U.S. Court of Federal Claims (CFC) 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 Federal Circuit agreed and reversed the CFC judge. The Federal Circuit found that the petitioner bears the burden of establishing that petitioner's demyelinating condition within eleven hours of vaccination was attributable to the vaccination. Since petitioner could not establish that early timing of onset was consistent with a vaccine-related injury, petitioner could not prevail. There was a brief discussion about whether the vaccine could have aggravated a condition established by a previous vaccination. Mr. Matanoski indicated that there wasn't preexisting condition at issue in those proceedings.

In response to a question regarding the activated autism cases, Mr. Matanoski explained that three special masters are assigned to the Omnibus Autism Proceeding, however, the activated cases that require jurisdictional determinations and/or hearings appear to be assigned to remaining special masters. Responding to a question, Mr. Matanoski reiterated that the record in the Omnibus cases was closed but he could not predict when a decision would be issued in Cedillo et al.

***Report on Autism Hearing from Petitioner's Attorney***
***Tom Powers, J.D.***

Mr. Powers commented that, of the Omnibus Autism Proceedings cases, two have been closed (Cedillo and Hazlehurst) and one has been concluded but the special master has allowed additional time for parties to submit replies (post-hearing briefs). The second round of hearings on the second theory of causation have been concluded and the transcripts are in review by the government and petitioners. The process is lengthy because the hearing generate a large volume of transcript pages, which may include highly technical medical/scientific testimony. First the government carefully reviews the verbatim transcript against the sound recording of the proceedings, making corrections as appropriate. Then the petitioner's attorney does the same. Then the final transcript is filed with the Court.

In clarifying the process during the Omnibus Proceedings, each special master will prepare a decision. In every hearing one special master was in charge of the hearing, but two other special masters attended and listened to all the testimony. There will be one opinion and order in each of the six test cases, written by the special master to whom the claim was assigned and who presided over the hearing of that case. There were six cases under the two theories of causation, which will result in 6 decisions, which may be accepted by the government and/or petitioners or moved into the appeals process. Mr. Powers noted that it is a lengthy process.

Mr. Powers explained that the first theory of causation (that the MMR vaccine in combination with shots containing thimerosal was a substantial contributing cause of autism in some children) relied evidence that the live measles virus was the triggering agent. Therefore, the evidence that would be presented in the third originally-scheduled hearings on causation (MMR alone) would be substantially similar to the evidence in the first test cases and there would be no purpose in holding those hearings. All parties agreed to eliminate them from the schedule.

Mr. Powers turned to the review of the current claims. He noted that until the merits of the causation issues are resolved by decisions in the test cases, the DOJ and petitioners are complying with orders from the special masters requiring petitioners to file medical records in each case so that DOJ can review the records in order to determine whether cases were filed within three years from onset or manifestation of first symptoms as required by statute. In some cases the government and the petitioner agree that a particular claim was filed on time. In other cases the parties agree that a case was not filed on time and should be dismissed. He added that there was some objection by petitioner's attorneys with the three-year limit, which is much shorter than the liability limit for most injury claims that are not related to vaccines.

The sticking point is the large number of cases for which there is dispute as to when the first symptoms appeared. Those cases require substantial time and expense in the process of providing medical and other evidence on the timeliness of the claim. That expense must be borne by the petitioner and, if the claim is ultimately rejected there is no reimbursement for legal fees and other case-related expenses. There is a case now on appeal relating to the jurisdictional issue of whether costs and fees are recoverable in a claim dismissed on statute of limi9tations grounds.

Mr. Powers noted that the Federal Circuit has ruled that interim fees and costs are recoverable in compensation cases in the NVICP. The PSC is planning to file an interim fee and cost petition in the Omnibus Autism Proceeding relating to the general causation and discovery work performed by the petitioners' attorneys beginning in late 2001 and through the last round of test cases. The PSC and DOJ are negotiating the particulars of the interim fee and cost petition, and hope to settle as many issues as possible by agreement before asking the Special Master to resolve disputes in the petition.

**Vaccine Safety Agenda: Update on Vaccine Safety Workgroup**

**Public Engagement and ACCV Role**
**Dan Salmon, Ph.D**
**National Vaccine Safety Office, DHHS**

Dr. Salmon explained that the National Vaccine Program Office (NVPO) was established under the authority of the same legislation that established the VICP and ACCV. Its basic responsibility is to coordinate federal vaccine activities.

The National Vaccine Advisory Committee (NVAC) provides advice and counsel to NVPO. NVAC has a working group specifically concerned with vaccine safety (the Vaccine Safety Working Group) that is composed of a diverse group of experts in vaccine related fields. He noted that Ms. Buck represented parents (consumers) on the NVAC Vaccine Safety Working Group. The Working Group's first charge is to review the CDC's Immunization Safety Office's (ISO) Scientific Agenda in terms of content and priorities. The Scientific Agenda was developed, and the NVAC review process was initiated, in response to an Institute of Medicine (IOM) recommendation. During development of the ISO Scientific Agenda, meetings were held with scientists and vaccine manufacturers to solicit recommendations. ISO then developed a draft Scientific Research Agenda and presented it to the NVAC Vaccine Safety Working Group for review and comment. The Working Group will develop a set of recommendations that will be reviewed, revised, and endorsed by NVAC, after which NVAC will forward the recommendations to the Assistant Secretary for Health. The Working Group hopes to have a draft proposal to submit to the full NVAC in the spring of 2009 and the NVAC will work to finalize a report by the fall of 2009.

Following completion of the ISO Scientific Agenda review, the Vaccine Safety Working Group will review the federal vaccine safety system and write a white paper describing an optimal vaccine safety system to prevent adverse events related to vaccines and enhance public confidence in the vaccine program.

Engaging the public on the ISO Scientific Agenda is very important to the Working Group. The NVAC Vaccine Safety Working Group meeting in April 2008 was open to the public and drew over a hundred public audience members who had an extended opportunity to comment. These individuals were mainly those involved in vaccine-related occupations and organizations and also expressed interest in providing input on the ISO Scientific Agenda through public engagement.

HHS is leading the public engagement activities on the ISO Scientific Agenda. The Association of State and Territorial Health Officials (ASTHO) is assisting and has subcontracted to the Keystone Center. Currently, Keystone plans to hold at least two open meetings in other parts of the country, plus at least one meeting with identified stakeholders (groups that have a primary interest in vaccine safety), to gather information. The agenda for those meetings will be developed by a small subcommittee of individuals from the NVPO staff and NVAC Vaccine Safety Working Group, including the ACCV's Tawny Buck. Although anyone may attend the public meetings, there will be an effort to involve parents of children in the general public.

In response to a question about including diverse groups in the stakeholder's meeting, Dr. Salmon agreed that groups representing minorities, subpopulations and special populations who are also involved in the vaccine safety process in one way or another should be included. The first of these meetings is planned take place in November. When asked about participation by vaccine manufacturers, Dr. Salmon reminded the Commission of the NVPO-sponsored meeting with manufactures previously mentioned, and the fact that, by statute, the NVAC must have industry representatives in it membership, including both vaccine manufacturers and agents who purchase vaccines, mainly insurance companies (the Association of Health Insurance Plans has a member on the NVAC). These representatives will have an opportunity to weigh in when the full NVAC reviews the recommendations of the Vaccine Safety Working Group.

**Thimerosal and Vaccines**
**Marion Gruber, Ph.D.**

**CBER, FDA**

Dr. Gruber described the history of thimerosal in U.S. vaccines, noting that the organic mercury compound, ethyl mercury, was initially added to vaccines in the 1930's as a preservative to prevent the growth of microorganisms, particularly bacteria and fungi. It has no therapeutic effect. Thimerosal has also been used during the manufacturing process for the same products. The U.S. Code of Federal Regulations requires the presence of thimerosal whenever multiple-dose containers are manufactured (21 CFR 610.15).

Thimerosal contains about 50% mercury. In childhood vaccine doses the concentration is between 12.5 and 25 micrograms mercury per dose. The ethyl mercury compound is different from the more common environmental toxicant, methyl mercury, which is a known neurotoxin. As methyl mercury leaches into the air it can be re-deposited on surface waters and becomes part of the aquatic food chain. Several studies have shown that high exposure to methyl mercury due to daily consumption of methyl mercury contaminated bread or fish by pregnant mothers can result in neurologically injury of their offspring.

In 1997 the FDA Modernization Act required the FDA to compile a list of all foods and drugs containing intentionally introduced mercury compounds, children's vaccines included. As part of the FDAMA review, the FDA evaluated the amount of mercury an infant might receive in the form o**f** eth**yl**mercury from vaccines under the U.S. recommended childhood immunization schedule and compared these levels with existing guidelines for exposure to methy**lm**ercury, as there are no existing guidelines for ethylmercury, the metabolite of thimerosal. 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.

As a precautionary measure, the Public Health Service (including the FDA, National Institutes of Health (NIH), Center for Disease Control and Prevention (CDC) and Health Resources and Services Administration (HRSA) and the American Academy of Pediatrics issued two Joint Statements, urging vaccine manufacturers to reduce or eliminate thimerosal in vaccines as soon as possible (CDC 1999) and (CDC 2000). In 1999 and 2000 CBER wrote the manufacturers urging them to eliminate thimerosal from pediatric vaccine formulations. Manufacturers immediately began to comply, developing new single-dose formations without the preservative.

In its report of October 1, 2001, the IOM's Immunization Safety Review Committee concluded that the evidence was inadequate to either accept or reject a causal relationship between thimerosal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder (ADHD), and speech or language delay. Additional studies were needed to establish or reject a causal relationship. The Committee did conclude that the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders was biologically plausible. The Committee believed that the effort to remove thimerosal from vaccines was "a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible." In 2004, the IOM's Immunization Safety Review Committee issued its final report, examining the hypothesis that vaccines, specifically the MMR vaccines and 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 2000, much progress has been made in removing or reducing thimerosal preservative from childhood vaccines. As a result of these efforts, the maximum cumulative exposure to ethyl mercury for a six-month-old child is now about 3 micrograms rather than the 187 micrograms of a decade ago. Dr. Gruber noted that the exception is the presence of thimerosal in some influenza vaccines which may, because of a recent Public Health Service recommendation to immunize children against flu, be administered to a child. However, available pediatric flu vaccines are manufactured in both a preservative-containing and preservative-free formulations. The live attenuated influenza vaccine, FluMist, is manufactured as thimerosal-preservative free formulation only.

Dr. Gruber noted that the term "preservative-free" indicates that no preservative (thimerosal or otherwise) is used in the vaccine; however, traces used during the manufacturing process may be present in the final formulation. For example, some vaccines may be preservative-free but may contain traces of thimerosal (1 micrograms mercury or less per dose); in such settings, this information is noted in the package insert. In summary, Dr. Gruber stated that all pediatric vaccines are now available in preservative-free formulations and that manufacturers are working to increase the supply of thimerosal- preservative free influenza vaccine formulations.

**Report from the Workshop: Mitochondrial Encephalopathies: Potential Relationship to Autism**
**Walter Koroshetz, M.D.**
**NINDS, NIH**

Dr. Koroshetz discussed a conference held in June 2008 that brought together two groups of physician-scientists, one which focused on treatment of mitochondrial diseases and the other on the autism and Autism Spectrum Disorder. Although the meeting was primarily about mitochondrial encephalopathies (ME), the two groups discussed the possible relationship between the two disorders, including the need to develop a research agenda, including an element on triggering events that exacerbate ME that may or may not induce ASD.

There have been a number of reports that show a link between children with ASD and subsequent identification of a gene mutation in those children that affects mitochondrial function. In addition it has shown that some children with mitochondrial disorders have siblings who are autistic. There have also been genetic studies in both autistic children and children with ME that indicate there may be a genetic factor involved in both disorders. Dr. Koroshetz noted that ME symptom are sometime very similar to those of autism -- hypotonia, seizures, developmental delays, behavior problems

Dr. Koroshetz described the mitochondria as a component of all cells, inherited maternally, that is implicit in the regulation of heat and energy, and is involved in the timing of apoptosis. Since the brain is an organ that requires a high level of energy to properly function, the importance of normal mitochondrial function is clear. Muscle also requires a high level of energy. Both muscle and brain are involved in the symptomatology of autism and mitochondrial disorders.

Most mitochondrial disorders are detected before the age of five. Diagnosis of mitochondrial disease is complex, involving a variable combination of clinical observations, and biochemical, pathological and molecular studies. Lab results vary because of procedures, timing of bio samples, and stage of the disorder. The final diagnosis is usually qualified based on the strength of evidence (definite, probable, possible, unlikely). One challenge is that, even if a child has a mutant gene, that gene may not occur in all mitochondria, which makes definitive genetic diagnosis very difficult. In addition, some abnormalities can only be detected at certain times, such as when a child has an infection. One possible marker of mitochondrial dysfunction is the level of lactate in the blood. Lactate is produced when cells switch from mitochondria to glycolysis to produce energy.

A number of things can adversely affect mitochondria and produce negative outcomes. Mercury, for example, is believed to affect mitochondria, as will some infections and certain drugs. For example, children with high fevers might take aspirin, and the combination of the aspirin and the infection causing the fever would damage liver mitochondria, resulting in renal failure.

Concerning research approaches to develop knowledge about the connection with autism, the first involves a targeted approach looking at children who have ASD and an overlapping mitochondrial disorder. That involves focusing on lab results, analysis of bio samples requiring a number of invasive procedures -- muscle biopsies, spinal taps, MRIs usually requiring sedation in very young children. And there would have to be a control group, and such procedures are rarely approved in healthy pediatric subjects. An alternative approach is to develop a survey that might include some minimal risk sampling techniques (buccal swabs, simple blood draws).

Dr. Koroshetz concluded by noting that there is clearly a small group of children who are diagnosed as autistic who also have an underlying mitochondrial disorder. The first step is to try to identify that population as a basis for further research.

**Update on the NIAID Vaccine Activities**
**Jessica Bernstein, NIAID, NIH**

Ms. Bernstein reported that NIH and CDC recently released a program announcement inviting grant applications for studies in vaccine safety (http://www.niaid.nih.gov/topics/vaccines/). NIAID also launched a web portal that includes information on vaccines and vaccine research (at www.niaid.nih.gov). Finally, Ms. Bernstein commented that NIMH had published requests for public comment on behalf of the Interagency Autism Coordinating Committee (IACC) concerning the Committee's Draft Strategic Plan for Autism Spectrum Disorder Research, and for comments about priorities for the IACC's Services Subcommittee for Autism Spectrum Disorder.

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## September 5, 2008

**Minutes**

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**Update on Center for Biologics and Evaluation Research (CBER), FDA Vaccine Activities**
**Marion Gruber, Ph.D.**

Dr. Gruber reported that FDA, pursuant to CBER review, had approved two new vaccine products in June 2008. On June 6, a pediatric combination vaccine, Pentacel, was approved for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease caused by Haemophilus influenzae type b. The vaccine may be administered to children 6 weeks to 4 years of age. On June 24, a GlaxoKlineSmith combination vaccine was approved (Kinrix) a diphtheria, tetanus toxoids, acellular adsorbed pertussis and inactivated poliovirus vaccine. It may be administered as a fifth dose for children who have received DTaP in four previous administrations, or as a fourth dose in an inactivated poliovirus vaccine series. It may be administered to children 4 through 6 years of age. Neither vaccine contains thimerosal.

Dr. Gruber added that FDA has begun to release influenza virus lots that allow manufacturers to distribute the vaccines for the 2008-2009 influenza season.

There was a brief discussion about the efficacy of vaccines to the majority of vaccine recipients and the unfortunate adverse events that occur in a small segment of the vaccinated pediatric population. Concern was expressed that the combination vaccines may present risks not fully understood.

**Update from the National Vaccine Program Office (NVPO)**
**Dan Salmon, Ph.D., NVPO**

Dr. Salmon discussed the upcoming NVAC meeting on September 16-17 in Washington, D.C. Of interest to the ACCV will be an agenda item that addresses vaccine financing and supply, and another agenda item that will address the issue of vaccine hesitancy (the prevalence of parental vaccine delay, focus groups and in-depth interviews being done by CDC to learn more about the issue, and comments from outside organization also involved in vaccine issues). There will also be a session at the meeting to update on the newly organized Federal Immunization Safety Task Force, which is chaired by the Assistant Secretary for Health. The Task Force has four working groups -- research, data coordination, risk communication and public engagement. The Task Force is concerned with both vaccine efficacy and vaccine safety (minimizing adverse events) in its charge.

**Updating the National Vaccine Plan**
**Ray Strikas, M.D., NVPO**

Dr. Strikas reiterated that the NVPO was established 20 years ago under the legislation that established the VICP. It is a small office under the Assistant Secretary for Health charged with reviewing federal activities in vaccine research, development, production, procurement and distribution, and with developing a plan for carrying out the charge, including establishing priorities and provisions for the best use of federal resources. That plan was published in 1994 and it specified four goals -- development of new, improved vaccines; assurance of optimal safety and efficacy of vaccines; a program for public education and communications; and a plan for optimum use of existing vaccine products to prevent disease, disability and death. It included a strategy for support of the VICP through adequate funding and periodic updates of the vaccine injury table.

In 1994 there were a number of important issues, including a recent measles outbreak that stimulated interest in the immunization process, a focus on vaccines that might impact HIV/AIDS and emerging diseases, and interest in planning for a pandemic. The 1994 plan has not been revised since its inception. In 2007, the Assistant Secretary for Health mandated a revision to reflect current scientific knowledge, priorities and issues. These include disease incidence changes, new vaccines and immunizations schedules, the communications infrastructure that includes surveillance, registries, and public information programs, and the more urgent biodefense and pandemic issues.

Dr. Strikas demonstrated that vaccines have been effective with significant decreases in all diseases covered by the immunization program, with the exception of pertussis which has diminished, but is still a significant public health issue. Immunization coverage among children has improved since 1994, currently at about 77% to 90%, depending on the specific vaccines and combinations involved. Coverage for other groups -- adolescents, adults, subgroups (racial, ethnic, elderly, etc.) is lower. Coverage among adolescents is affected by the venue, school regulations and requirements, and the issue of informed consent by parents.

Biodefense and the threat of pandemic are clearly more important than they were in 1994. Project Bioshield has $5 billion over the next five years for threats including biological attacks (anthrax, botulism, smallpox) and an additional $5 billion for pandemic preparedness. Finally, there are general concerns about safety, financing, reimbursement, international collaborations, and the supply chain.

The new plan must address basic and applied research, development of specific vaccines (HIV, tuberculosis and malaria), maintaining high pediatric coverage, increasing adolescent coverage to 90%, establishing coverage goals for adults, reducing/eliminating financial obstacles, enhancing security of vaccine supplies, and developing a stronger vaccine safety infrastructure. In addition, the plan must address the assurance that the VICP will continue to provide support for vaccine-

injured children, that surveillance continues to work and is improved, and that communication and education of the public is effective.

An interagency task force has been established to guide development of the plan. It includes agencies within the HHS, and periodic participation by DoD, VA and USAID. The Institute of Medicine has agreed to review the 1994 plan as a tool for developing the new plan, and the NVAC will actively participate in reviewing the IOM report when released. An interim letter report from the IOM committee highlighted several recommendations -- identify priorities, goals (short-term to long-term), potential innovations that might apply, ways to involve stakeholders in the plan process, and a focus on vaccine supply.

A series of public fact-gathering forums will be held in 2009. The Assistant Secretary for Health expects a draft plan report by November 2009. During discussion, Dr. Fisher commented that an important part of the plan would be the development of a process to measure results, and some mechanism to enhance coordination between the many agencies and other entities that will be involved in executing the plan. Dr. Strikas agreed, adding that there were a number of separate parts to the process that would dictate that the final plan would be an evolving document as more information becomes available over time. For example, Healthy People 2020, which includes coverage targets, will not be issued until March 2009. Setting specific targets for research is a challenge because the research community is averse to committing to distant goals (like an HIV vaccine by 2015). The plan will evolve through the various review steps that will be provided by the IOM, NVAC and others.

**CDC Web Site Demonstration**
**Michelle Batch and PerStephanie Thompson**

In an interactive demonstration of the CDC web site, Ms. Batch explained to the Commission how to locate information about vaccines, vaccine safety and vaccine-preventable diseases. She noted that the ISO has responsibility for maintaining up-to-date information about vaccines on the site. Among many areas of information on the site, Ms. Batch demonstrated several important pages -- health and safety topics, vaccines and immunization, the Top Ten section on the main page that contains links to the latest information on various public health topics, including vaccines, and the separate home page for Vaccines and Immunizations (on the icon located in the Top Ten section of the CDC home page or at www.cdc.gov/vaccines).

Ms. PerStephanie Thompson briefly described the newly launched vaccine safety home page (www.cdc.gov/vaccinesafety), which includes a left navigation section on “Vaccine Safety Basics” that is designed for the general public. Information such as how vaccine safety is monitored, commonly asked questions and vaccine safety concerns are found in the basics section. The second section titled “Public Health Activities” highlight programmatic activities such as scientific studies, information for clinicians, scientific publications, etc. The center of the home page contains features with links to specific information about vaccine safety that visitors may review. This section is also used for releasing new data, news flashes and servers as a traffic cop directing ISO’s Web visitors. The right navigation section is dedicated to linking visitors to related health topics, federal agencies, partners and helpful links. Additionally, on the right top of the home page is a text box with one click link to the VAERS site for more information and to report a vaccine-related adverse event. Ms. Thompson reported that the site has been very successful in the short time it has been available to the public. A webmaster has been assigned and in the future the technology to monitor site activity will be added. She added that a Google search of “vaccine safety” results in the site being in the number one position in the search.

**Issues and Process for ACCV Input into the National Vaccine Plan**
**Jeffrey Sconyers, J.D., Chair, ACCV**

Mr. Sconyers introduced the discussion by noting that, for Commission review, Michelle Herzog had compiled all of the ACCV letters to the Secretary and any responses received from the

Secretary's Office since the Commission was established. A number of issues were answered in a positive manner -- some issues concerning legislation, coverage of counseling and guardianship expenses, interim payments of costs and fees, and modifications in Commission membership parameters. The Commission has been involved in the process to stabilize the funding for the program and in the development of mechanisms to add vaccines to the vaccine injury table and to coverage under VICP. As the Commission knows, the purpose of the VICP is to insure fair and adequate compensation for individuals who can show that a vaccine induced an adverse event, and to ensure a stable supply of vaccines by controlling and limiting liability for manufacturers and administrators.

Mr. Sconyers reminded the Commission of the provisions of the charter: to advise the Secretary on the implementation of the VICP; to recommend changes to the vaccine injury table; to advise the Secretary concerning vaccine products that result in fewer adverse side effects; to gather information about various immunization programs; to recommend to the NVP research related to vaccine injuries; and to provide review and recommendations regarding the composition of vaccine safety information publications. Although there are federal agencies that are directly responsible for a number of the Charter issues, the Commission has been able to contribute comments and recommendations that have provided positive input to those agencies.

The Commission has addressed sources for funding vaccine safety research with little success, but there has been consensus on the Commission that the funding should not come from the VICP trust fund.

Mr. Sconyers invited Commission discussion. Ms. Buck commented that, to correct the record, the Commission had apparently had no input with regard to the Burton bill (Representative Burton's office did not reply to the Commission's recommendations letter). She added that the original 2004 bill had been the basis of some of the recommendations in that letter. Mr. Sconyers agreed, noting that even with letters to the Secretary, the response is often appreciative but noncommittal. He added that he sensed some concern about the Commission's role, inviting comment about whether the Commission members felt it was appropriate to make recommendations about any changes in the VICP as part of the work Commission's work on the National Vaccine Plan. He added that Dr. Strikas had suggested the Commission could review the draft National Vaccine Plan, provide comments to the NVPO and participate in some way in the IOM review process.

Ms. Buck commented on the white paper being prepared by the NVAC, an important part of which is consideration of methods for improving public trust and confidence in the federal vaccine program. There is also concern that the National Vaccine Plan addresses the reduction of adverse events, taking advantage of advances in scientific and medical knowledge, and the opportunities in genetics to identify infants at risk before they are vaccinated. She expressed concern that, although the Commission had made recommendations about amendments to the vaccine injury table, it seems to take an inordinate amount of time before the recommendations are implemented. Ms. Gallagher agreed, commenting that the Commission might consider working on recommendations to improve the efficiency of amending the injury table. Dr. Fisher suggested developing a brief history of the vaccine injury table, the changes over the years, and how those changes came about.

Ms. Castro-Lewis commented that the report by the Department of Justice has been very difficult to understand and some method to present the information in a more organized and simpler way would be appropriate, perhaps even including some graphic presentations and a complete glossary of terms. A representative of the DOJ commented that there would be an effort to provide information in graphic form (perhaps a PowerPoint presentation) and to include more statistics about claims filed.

Ms. Buck suggested that a presentation by the petitioner's bar or the PSC would be a helpful addition to the next meeting agenda, and it was noted that the petitioner's bar is trying to work out

a meeting at the time of the next Judicial Conference. There was a comment that the "petitioner's bar" is not a formal organization, but an informal association of several of the more active petitioner's attorneys who maintain a continuing communication among themselves. Ms. Buck added that she had contacted one of the individuals involved in the formulation of the program, Barbara Loe Fisher, who indicated a willingness to visit the Commission and present her perspective of the Commission's history and mission.

Dr. Evans commented on the process that evokes change in the injury table. The first step is a thorough evaluation of the current literature and the Institute of Medicine must complete an independent study of adverse events following vaccines before proposals to modify the Vaccine Injury Table are developed. That proposed revisions then through the standard rulemaking process with a Notice of Proposed Rulemaking, a 6-month public comment period, including a public hearing, and publication of a final rule. The ACCV has opportunities to provide input at various times in that process, which is a lengthy one. The last extensive IOM review of vaccine adverse events was published in 1994, and the IOM committee, which took almost three years to complete.

Dr. Evans added that, although the number of vaccines in the table has nearly doubled, the injuries related to those vaccines have not, mainly because it requires a relatively long post-marketing experience to confidently identify such injuries. Therefore, most of the claims being filed are for off-table injuries. An exception was rotavirus, when there was compelling and evidence of the relationship between the vaccine and intussusception in the year following vaccine licensure.

There was a brief discussion about whether it is appropriate to place vaccines on the market and retrospectively monitor adverse events such that children are injured during that process. There was opinion that the system should be designed to identify adverse events before they occur. Noting that this would probably delay release of the vaccine, there was concern expressed about how many individuals would be affected by the disease during that delay. There was also an observation that there may be more vaccine-related adverse events because many parents are probably unaware of the VICP and other related vaccine safety programs.

Mr. Sconyers noted that, although the comments were valid, they were not within the purview of the Commission's concern, which is advising the Secretary about the VICP. He added that it was appropriate to be concerned about insuring that parents and practitioners know about the program, and that the Vaccine Information Statements that parent receive when a child is vaccinated are clear and accurate. He also suggested that an FDA presentation on the rationale to create combination vaccine products and the process to clear these combinations might be an appropriate agenda item. Finally, he noted that the Commission's interest suggests that the injury table process would be an appropriate agenda item for the next meeting. Concerning the agenda, Ms. Buck suggested an update on the petitioner's satisfaction survey

**Public Comment**

Mr. Sconyers stated that no requests for public comment had been received.

**Future Agenda Items**

Mr. Sconyers noted that several future agenda items had been mentioned during the meeting, including a clearer presentation by the DOJ, and an update on the petitioner's survey. Other suggestions included a briefing on the IOM advisory committee progress, a discussion about public awareness (what has worked, what hasn't worked).

**Adjournment**

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

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| Jeffrey Sconyers, J.D. | Tawny Buck. |
| ACCV Chair | ACCV Vice-Chair |
| _____ | _____ |
| Geoffrey Evans, M.D. | Date |
| Executive Secretary, ACCV | |