

**SUMMARY MINUTES**

**CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
IMMUNOLOGY DEVICES PANEL**

**November 14, 2019**

**DoubleTree by Hilton  
Washington DC North/Gaithersburg  
620 Perry Parkway  
Gaithersburg, MD 20877**

**Attendees:****Chair**

Rajkumar Rao, M.D.  
George Washington School of Medicine & Health Sciences  
Washington, DC

**Temporary Non-Voting Members**

Michael Pollard, Ph.D.  
Scripps Research Institute  
LaJolla, CA

Stephen Badylak, D.V.M., Ph.D., M.D.  
University of Pittsburgh  
Pittsburgh, PA

Scott Burchiel, Ph.D.  
University of New Mexico  
Albuquerque, NM

Yiming Li, D.D.S., Ph.D.  
Loma Linda University  
Loma Linda, CA

John Suzuki, Ph.D., D.D.S.  
Temple University  
Philadelphia, PA

John Zuniga, D.M.D., M.S., Ph.D.  
UT Southwestern Medical Center  
Dallas, TX

Richard Burton, D.D.S.  
The University of Iowa  
Iowa City, IA

Michael Weisman, M.D.  
Cedars-Sinai Medical Center  
West Hollywood, CA

Paul Jannetto, M.D.  
Mayo Clinic  
Rochester, MN

Mark Dykewicz, M.D.  
Saint Louis University School of Medicine  
St. Louis, MO

Christine Parks, M.D.  
National Institute of Environmental Health Sciences  
Research Triangle Park, NC

Dori Germolec, Ph.D.  
National Institute of Environmental Health Sciences  
Research Triangle Park, NC

James Taylor, M.D.  
Cleveland Clinic  
Cleveland, OH

Jack Lemons, Ph.D.  
The University of Alabama at Birmingham  
Birmingham, AL

Joshua Jacobs, M.D.  
Rush University Medical Center  
Chicago, IL

Melissa McDiarmid, M.D.  
University of Maryland School of Medicine  
College Park, MD

Jason Connor, Ph.D.  
ConfluenceStat, LLC  
Orlando, FL

Julia Babensee, Ph.D.  
Emory University  
Atlanta, GA

Nicholas Giori, M.D., Ph.D.  
Palo Alto Veterans Affairs Health Care System  
Palo Alto, CA

**Industry Representative**

Whitney Christian, Ph.D.  
Medtronic Restorative Therapies Group  
Jacksonville, FL

**Consumer Representative**

Wyatt A. Lison, Esq.  
Feinstein, Doyle, Payne & Kravec, LLC  
Pittsburgh, PA

**Patient Representative**

Joseph O'Brien, M.B.A.  
National Scoliosis Foundation  
Stoughton, MA

**Assistant Director, Clinical and Scientific Policy Staff  
Office of Product Evaluation and Quality**

Aron Yustein, M.D.

Food and Drug Administration  
Silver Spring, MD

**Director, Office of Health Technology 3  
Office of Product Evaluation and Quality**

Benjamin R. Fisher, M.D.  
Food and Drug Administration  
Silver Spring, MD

**Designated Federal Officer**

Aden Asefa, M.P.H.  
Food and Drug Administration  
Silver Spring, MD

## CALL TO ORDER

**Panel Chairperson Rajkumar Rao, M.D.**, called the meeting to order at 8:07 a.m. He noted the presence of a quorum and stated that Panel members had received training in FDA device law and regulations. He noted that Panelists would discuss the topic of immunological responses to metal-containing products regulated as medical devices, including both metal-containing implants and dental amalgam.

## PANEL INTRODUCTIONS

**Panelists** and FDA staff introduced themselves for the record.

## CONFLICT OF INTEREST STATEMENT

**Aden Asefa, M.P.H.**, Designated Federal Officer, read the Conflict of Interest statement into the record and noted conflict of interest waivers that were issued to Dr. Stephen Badylak and Dr. Joshua Jacobs. She described the day's agenda and stated that Dr. Whitney Christian of Medtronic would serve as Industry Representative. She made general announcements regarding transcripts, videos, and silencing of cell phones. She introduced Michael Felberbaum and Angela Stark as press contacts for the meeting.

## OPEN PUBLIC HEARING

**Eric Uram**, Consultant, Chicago Declaration, discussed his involvement with and work on the "Chicago Declaration to End Dental Industry Mercury Use." He stated his concerns about mercury. Impacts to neurological development, issues about in vivo methylation and demethylation by internal microbiomes of the mouth or digestive tract, and immunological impacts and damages to organ function were discussed. He noted that leadership demonstrated by other nations had moved beyond what FDA currently recognized as their obligation to protect U.S. citizens from mercury. He discussed currently available, physically equivalent, cost-competitive, and technically superior alternative materials to dental amalgam and urged FDA to move to restrict amalgam use in sensitive populations, such as children and pregnant or breastfeeding women.

**Mark J. McClure, D.D.S.**, practicing dentist in Washington, D.C., discussed the longevity of alternatives to dental amalgam. He noted that many recent studies verified that composites' longevity was comparable if not superior to amalgam, referencing the 2007 Opdam study. He stated that resin-based composites and glass ionomer restorations performed equally as well as amalgam, and the time it took to place an alternative was reduced significantly as dentists gained more experience in handling mercury-free materials. He noted that there was no current evidence of significant personal or environmental toxicity from non-metal alternatives. He referred to a 2004 Scottish study on mercury vapor levels in dental practices and body mercury levels of dentists. He urged the FDA to take action against using amalgam fillings in dentistry, assuring Panelists that the mercury-free materials available could meet the individual needs of all patients.

**Mark Mitchell, M.D., M.P.H., FACPM**, co-chair of the National Medical Association's Commission on Environmental Health, discussed the health and environmental effects of dental amalgam especially in children of color. He described Project TENDR and called on FDA to end the use of amalgam in pregnant women and children and to phase down all use of amalgam as required by the Minamata Convention. He noted that dental amalgam was bioaccumulative, toxic, and persisted in the environment indefinitely. He stated there was no organization that tracks the percentage of Americans that receive amalgam dental restorations. He discussed a 2016 analysis by Yen et al. that looked at blood levels of BPA, a toxicant in some composite dental fillings. He noted the study found no association between BPA and the number of dental fillings, given the low level of BPA in the fillings, its low bioavailability, and the fact that it was not persistent or bioaccumulative. He called on FDA to immediately phase out the use of amalgam in pregnant women and children and to advise against public funding of amalgam for any use.

**Kristie Trousdale, M.P.H.**, Deputy Director of Children's Environmental Health Network, discussed the Network's efforts to address the hazards of mercury. She noted recent science showing that mercury from dental amalgams could be transformed in the body to methylmercury. She stated that dental amalgam pollutes the environment's air, water, and soil through an estimated 28.5 metric tons of dental mercury released from cremation, sewage treatment, and other pathways. She stressed that children could be exposed to mercury through amalgam fillings and through maternal fillings prenatally. She reminded that the FDA itself admitted that there was no evidence that amalgam is safe for developing fetuses. She stated that individual genetic susceptibilities and individual mercury body burden levels from additional sources must be considered. She stated children and families from lower-income communities and communities of color are especially vulnerable, and she encouraged FDA to work toward ending all placement of new dental amalgam in the U.S. She noted that the Learning Disabilities Association of America and the Alliance of Nurses for Healthy Environments endorsed her comments.

**Rueben Warren, D.D.S., M.P.H., Dr.P.H., M.Div.**, Tuskegee University, discussed ethical and scientific concerns about mercury. He described the neurotoxicity of mercury, its absorption into the body from amalgam, and its conversion into methylmercury, which were all compounded by the preexisting disproportionate rates of neurodevelopmental disorders in children of color and the probable disproportionate use of amalgam in African American and Hispanic children. He stated it posed a public health challenge and a public health ethics dilemma. He discussed the 2000 U.S. Surgeon General's Report on Oral Health, which stated that children of color disproportionately suffered from dental cavities. He stated it was unethical to use dental amalgam in pregnant women and children until it scientifically demonstrated short and long-term efficacy and safety could be documented. He called on FDA to consider Medicaid guidelines to improve the oral health of children.

**Sharon Lewis**, Director of the Connecticut Coalition for Evidence Justice, discussed "environmental justice communities" that were composed of people living in close proximity to polluting facilities that contaminate air, water, and land. She stated these were primarily people of color but almost always poor. She urged Panelists to define terms such as

"marginalized," "disenfranchised," "disproportionately impacted," and "adversely impacted" because they did not adequately describe the true nature of what was happening in environmental justice communities. She discussed how such communities were powerless and did not have access to adequate food and healthcare. She discussed the high sugar consumption prevalent in these communities and pointed out that most people from EJ communities did not know mercury was toxic. She explained that, in 2015, a provider bulletin was issued in the state of Connecticut stating Medicaid would not pay for mercury-free restorations in the molar teeth regardless of whether the practice markets itself as amalgam-free. She urged FDA to reconsider their position on the toxicity of mercury and to follow the example of lead, where it was shown that there was no safe level.

**Charles G. Brown**, President of the World Alliance for Mercury-Free Dentistry, recommended the end of the use of mercury fillings. He stated that the Center for Devices had a much more tolerant acceptance of mercury than the other FDA centers. He discussed myths of why the U.S. needs mercury fillings, including myths about use in prisons, in the Army, for disabled children, in hospitals, for large employers, and in public programs. He discussed myths that amalgam lasts longer than composites and that composites are harder to place in patients. He stated amalgam was "tooth unfriendly" and dentists do not have to disclose to patients that amalgam was, in fact, mercury. He described how the push to keep amalgam was largely from the American Dental Association. He urged FDA to consider strict action against mercury use, as has already been done around the world.

**Karen E. Howard**, CEO of the Organic and Natural Health Association, expressed her concerns about amalgam use in dentistry. She discussed CFSAN concerns that low levels of heavy metals contained in multiple food sources could combine to result in higher levels of great concern. She stated that they must pay attention to vulnerable populations. She stated that mercury contaminated almost 50% of the tested samples of commercial high-fructose corn syrup used in the processed foods. She discussed that elemental mercury, like that in amalgam, could convert to methylmercury and was not stable. She discussed the effect of amalgam waste in the environment, citing dental offices as the number one source of mercury at sewage treatment facilities. She urged FDA to find mercury amalgams unsafe for vulnerable populations, such as children, as exposure was unnecessary given the alternative options.

**Silvia Dove**, Consumers for Dental Choice, discussed three major concerns with FDA's review of mercury amalgam. In their review, FDA was only considering the mercury that the studies attributed to dental amalgam, but many studies traditionally failed to attribute methylmercury to amalgam. She noted that if, according to FDA, amalgam can only be used safely in breastfeeding mothers under the condition that they do not have many other mercury exposures, then it could not be used safely in breastfeeding mothers, especially women of color and those from lower-income communities. Polling showed that patients do not know about amalgam's mercury content, and absent patient labeling or patient warnings, neither patients nor their dentists were in a position to assess whether mercury from amalgam was too much to add to their body's preexisting mercury burden. She asked FDA to revise its 2019 review to reflect that amalgam is not safe for all

breastfeeding infants, especially considering there were currently no patient warnings that would allow breastfeeding mothers to take steps to mitigate their mercury exposure.

**Alan Dumoff, J.D., M.S.N.**, stated that FDA statements have drastic impact on the way that dentists practice. He stated that dentists could get in trouble with the dental board if they provided informed consent to a patient about mercury toxicity and then replaced the restoration. He added that FDA concerns about the impacts of restricting amalgam interfere with the practice of dentistry, making it difficult for dentists to make valid clinical judgments about their patients.

**Rochelle Divers**, a representative of the International Indian Treaty Council, gave a statement read by **Mr. Uram**. In the statement, she stated that American Indians and Alaskan natives were already exposed to mercury in their environments and that indigenous peoples from traditional fishing communities disproportionately pay the high price of mercury contamination that impacts their health, environment, and subsistence rights. She added that dental amalgam was disproportionately used in racial minorities and indigenous peoples and that the cumulative effect of mercury exposure from the high fish diets of many indigenous peoples and mercury exposure from disproportionate amalgam use was not addressed in FDA's 2019 review. She described how high mercury levels in women's bodies caused an epidemic of pre-polluted babies in Minnesota, the most seriously impacted being unborn and nursing babies and young children.

**Carol Petersen, B.S.Pharm.**, gave a statement read by **Mr. Brown**. In her statement, she describes her role as a pharmacist on the Medical Advisory Board for the Center for Menstrual Cycle and Ovulation Research and her involvement in learning, researching, coaching, and writing about endocrine disorders. She described the use of dental amalgam as a "massive human experiment" and discussed evidence that mercury fillings leach and elemental mercury can be converted to organic mercury compounds. She discussed how mercury affects the hormone signalers in the brain, the hypothalamus and the pituitary, and the adverse effects of these organs being disrupted. She discussed how mercury produces problems with fertility in men and women, including the notion of estrogen dominance in both men and women. She discussed how humans have difficulty understanding implications of "slow and relentless toxicity."

**Jackie Hawthorne**, Commissioner, Los Angeles Housing and Community Investment Department, gave a statement by video. She discussed her concerns about devices containing amalgam and their negative impact in communities of color and low income. She expressed gladness that FDA included in their review a Canadian study recommending that amalgam fillings be avoided for use in the primary teeth of children, pregnant women, and individuals with kidney disease. She asked the Panel to support the Canadian recommendations for use of safer dental materials such as resin composite, glass ionomer, resin ionomer, porcelain, and gold alloys. She expressed concerns that FDA's literature review did not include studies adequately addressing the problem of amalgam in lower-income people and people of color. She discussed how continuing amalgam use would raise an equity issue, as lower-income people and people of color were more likely to



be affected by mercury pollution, more likely to receive amalgam, and less likely to be told that amalgam fillings were made with mercury.

**Sheldon Newman, D.D.S.**, described dental amalgam composition as a set of particles, including silver, tin, copper, and sometimes zinc, that are mixed with mercury. He stated that copper amalgam is not used in the U.S. He discussed the initial reactions of mercury in the mouth. He discussed gamma one and gamma two matrix phases, matrix one being Ag<sub>2</sub> to Hg<sub>3</sub> and matrix two being a crystalline silver mercury phase. He discussed mercury loss from dental amalgams grinding, presenting information from Mahler and Ferracane studies, and others. He discussed amalgam exposures to heat and presented photographs after 30 years as compared to 45 years, noting that "dental amalgam in the oral conditions could last forever." He concluded by revealing that the photographs were his own 50-year-old amalgams, which could not exist with some of the levels of continuous exposure that was expected from some of the studies discussed.

**Jack Kall, D.M.D., MIAOMT**, spoke on behalf of the International Academy of Oral Medicine and Toxicology. He explained that he discontinued using amalgam fillings when he learned that mercury escaped from them. He focused his comments on the effects of mercury vapor and its equal ability to cross the blood-brain barrier as readily as methylmercury does. He described that 80% of mercury vapor is absorbed through the lungs during inhalation and that mercury continuously off-gases from the amalgam surfaces. He presented a video from a study published in the journal *NeuroReport* in 2001, which summarized the methodology and results of the study. He stated that the "institutional inertia" surrounding mercury fillings, the alleged safety of which was perpetuated by the American Dental Association and in turn tolerated by FDA, was "reprehensible." He called for FDA to apply the precautionary principle and immediately restrict the use of amalgam in children, pregnant women, and those with kidney and neurodegenerative diseases.

**Mary Starrett**, County Commissioner, Yamhill County, Oregon, gave a recorded statement. In her statement, she stated that the failure to change away from amalgam had resulted in negative public health consequences for her community. She stated members of her community, especially those on Medicaid, were not receiving information about amalgam's mercury content from their dentists. She added that when Medicaid and insurance companies do not fully cover mercury-free fillings, often citing the FDA, it can limit access to dental care. She stated that providing limits and/or clear warnings on the use of amalgam to consumers and parents was a federal responsibility.

**Spiro Megremis, Ph.D.**, Science Institute of the American Dental Association, focused on biomaterials and their interactions with the surrounding environment. He described how amalgam was protected from its environment by the presence of a passive oxide layer that acts both as a physical and kinetic barrier to its surroundings. He discussed thermodynamics and how in vitro corrosion testing was designed to better understand the conditions under which electrochemical reaction kinetics resulted in accelerated corrosion rates. He discussed ISO 10-271 corrosion test methods for metallic material, three of which evaluated corrosion resistance of dental amalgam. He explained how amalgams have

improved corrosion resistance by almost completely eliminating the gamma two phase. He concluded that this information could be used to inform immunologists and toxicologists when assessing health effects to general and at-risk populations.

**Tom Hart, Ph.D.**, ADA Association Foundation's Volpe Research Center, had a statement summarized by **Dr. Megremis**. In the statement, he explained that reports reviewed by FDA that assessed literature did not find a causal link between release of mercury vapor and adverse health effects. He discussed FDA's recently completed comprehensive review of dental amalgam from 2010 to present and the FDA Dental Products Panel. He suggested that dental amalgam was still safe and that there was no urgency to take action. He added that there were challenges to accurately measure different forms of mercury, such as methylmercury in its ionic form; challenges in determining the source of mercury in diet or other environmental sources as well as from dental amalgam; and challenges in metrology methods to measure mercury in different forms that could be used in clinical environments. He stated that until the challenges are met, it was unlikely that clinical studies would provide more insights.

**Karen Palmer**, Certified Dental Assistant, noted that dental assistants were first to be exposed to mercury vapor during placement and removal and that they lack full-body protections needed during the procedures. She noted that tests show 10,000 times the level of mercury being exposed than the higher allowable safe limit. She expressed remorse for "poisoning" the patients she treated over the years. She showed a paper cone mask she wore as a dental assistant and then the mercury vapor mask that she actually should have been wearing. She described adverse health effects she personally experienced from exposure to mercury vapor, including heavy metal toxicity, full-body tremors, severe paresthesia, neuropathy, and fatigue. She noted she had estrogen-positive breast cancer and that mercury was a known estrogen disrupter. She stated that she was carrying 1,275% total mercury body burden above normal baseline and she had a 40% increased risk of developing Alzheimer's disease. She emphasized that FDA's refusal to test for safety was "beyond shameful," and she called for FDA to ban mercury amalgam.

**Brittany Seymour, D.D.S., M.P.H.**, Harvard School of Dental Medicine, noted that while ADA supported her travel, she was not being paid and her statement was her own. She discussed how misinformation online impacts health, decision making, and policy making. She stated that studies have indicated the placement and removal of amalgam leads to a temporary elevated blood plasma level of mercury, but there was no evidence it poses a health risk. She listed several groups who concluded that either there was insufficient evidence or no evidence at all that would indicate that dental amalgam poses a risk to health. She stated that according to the World Dental Federation, there was no universal substitute for dental amalgam. She added that less was known about alternative restorative options and that they were more costly than amalgam. She discussed how cavities were the most prevalent health problem worldwide. She concluded that dental amalgam remained an overall safe, long-lasting, and affordable treatment option for the majority of patients.

## PANEL DELIBERATIONS

**Dori Germolec, Ph.D.**, asked if any pre-implant screening was conducted prior to the placement of an orthopedic implant. **Joshua Jacobs, M.D.**, indicated that while they do an extensive process to identify risk factors, there was no standardized preoperative screening for identifying risks for chronic inflammatory response or a potential hypersensitivity response. He indicated patch tests and LTT tests were available but were not generally recommended for screening. **Nicholas Giori, M.D., Ph.D.**, stated that the extent of screening for metal reactions in general was an assessment of history of allergy. **James Taylor, M.D.**, added that preoperative testing was variable and device-dependent.

**Dr. Giori** addressed a question on the development of hip and knee replacement and gave a brief history on the evolution of revisions. He noted that with the reduction of metal-on-metal articulations, there was a rise in revisions. He stated that highly cross-linked polyethylene was a "clear winner" compared to metal-on-metal articulations. He noted that metal-on-metal implants were only rarely being used in service replacement arthroplasty. He stated that a positive that came out of the metal-on-metal experience was that it heightened awareness towards corrosion at the modular taper junctions of hip replacements, and given the trend towards elimination of cobalt and chrome from the hip replacement, there should be fewer problems.

**Dr. Jacobs** added that the results from metal-on-metal total hips were not uniform and were design-specific. He stated that the same type of local response to metal debris had been seen frequently in patients with metal-on-poly total hip replacements that had cobalt alloy heads and that the orthopedic community had responded by using fewer cobalt alloy heads to help obviate the problem. He discussed the different types of presentation from patients with hip replacement and knee replacement.

**Michael Weisman, M.D.**, asked if there was currently a movement to get away from alloy hip replacements and to instead use titanium and avoid metal-on-metal. **Dr. Jacobs** replied that the majority of hip implants currently did not have cobalt; there were some hip resurfacings that were still cobalt-on-cobalt, but it was a small number. He stated that for knee implants, cobalt-chrome alloy was the most common and would likely continue to be used because there was no capacity in the knee implant for it to have a metal-metal contact leading to advanced tribocorrosion. **Dr. Weisman** countered that for those with physical signs of erythema and hypersensitivity to the alloy, it would still be a concern. **Dr. Jacobs** noted that was very rare to see that in a postop total knee. He added that it was difficult to discern whether an individual with chronic pain after a total knee had an immune system response or an inflammatory response due to hyper-reactivity to metal. **Dr. Giori** agreed.

**Chairperson Rao** discussed how local wear debris from titanium base plates could be impressive and explained that replacing metals with titanium was not necessarily a solution because titanium had its own issues. He suggested that metal allergy was not a clinical issue in the spine world likely because the implants were often adjacent to soft tissue, muscle tissue, and vascular tissue.

**Mark Dykewicz, M.D.**, asked whether orthopedists would avoid nickel alloys in patients with histories of contact dermatitis to nickel in jewelry. **Dr. Jacobs** responded he would order a lymphocyte transformation test in that situation. He added that the challenge was when the LTT or patch test showed allergy to multiple metals and bone cement. He

noted that better predictive testing modalities were needed. **Dr. Taylor** agreed, adding that patch testing with nonmetal chemicals might help sort it out. **Dr. Jacobs** countered that patch testing would often test positive to multiple metals as well as to bone cement.

**Joseph O'Brien, M.B.A.**, Patient Representative, suggested that there might be more hypersensitivity and issues with spine surgery than what has been reported. He asked why metal allergy screening was not part of the regular routine. **Dr. Jacobs** replied that this was because of the lack of robust clinical validation that such tests would predict outcomes.

**Benjamin R. Fisher, M.D.**, Director, Office of Health Technology 3, Office of Product Evaluation and Quality, referred to metal-containing gynecological devices and asked if patients with expected immune response should be screened differently.

**Chairperson Rao** asked for comment on the cons surrounding immunological testing for metals. **Dr. Germolec** noted that the predictive nature of the LTT testing for post-implant failure was unknown and that true metal allergy was a small proportion of the inflammatory component that causes device failure. **Chairperson Rao** asked how a true metal allergy would be defined. **Dr. Germolec** and **Michael Pollard, Ph.D.**, both agreed that a true metal allergy would be a Type IV response. **Christine Parks, M.D.**, noted that a false sense of safety would be one of the cons relating to metal allergy testing. She added that in the case of systemic autoimmune diseases, where patch testing would not necessarily be useful, it would be better to take a more systemic approach to the individual's history of allergies and tendency to develop allergies as well as the family history of autoimmunity.

**Dr. Pollard** added that when looking at T-cell reactions to a metal exposure, they all have their own issues in terms of trying to figure out whether there was a specific response to a metal. He stated that the immune system was there to recognize something foreign and that immune response should be expected when anything foreign is put in the body. He added that they needed to understand what was happening as an innate immune response to metal components. He asked Panelists to comment on how common it would be to have an immune response. He asked if that would merely reflect the severity of the inflammatory response that was already occurring prior to device placement.

**Chairperson Rao** restated Dr. Pollard's question, asking Panelists how they would distinguish between the body's responses to wear debris versus the body's innate dislike for the metal in the body. **Dr. Germolec** indicated that she was not aware of anything other than patient history that could help identify who would be predisposed to have that type of inflammatory response. **Dr. Parks** agreed that more research was needed to answer the question. **Dr. Pollard** discussed how sensitivity to a metal would not occur without some involvement of the innate immune response system. He agreed that he did not know of a way to identify whether such involvement was a response to the leaching metal ions versus wear debris resulting from mechanical phenomena. **Chairperson Rao** and **Dr. Pollard** discussed whether the immune response to metal debris would be different from the response to polyethylene debris.

**Dr. Taylor** disagreed that true metal allergy would only include Type IV. He discussed how low-molecular-weight allergens could still produce Type I reactions. **Dr. Jacobs** agreed it was probably not all Type IV reactions. He brought up literature where there was antibody production to metal debris and he identified this as a "gap area" in understanding Type I through III reactions and how that may contribute to what they see.

**Stephen Badylak, D.V.M., Ph.D., M.D.**, pointed out that particulate debris would

cause a more aggressive inflammatory response than a single particle. He noted that mechanical properties and surgical technique were important in determining clinical outcome. He suggested that given that a mere surgical incision would cause an immune response, they should instead focus on defining what an acceptable immune response would be and then identify patients who were likely to have an unacceptable immune response. He discussed phenotypes of inflammatory cells, emphasizing that the mere presence of those cells within the tissue was not necessarily bad. He suggested that patients who present with problems might be ones who have an inability to transition from the M-1 to the M-2 macrophage type or a co-inflammatory stimulus that is present. He added that it would be helpful to be able to identify the patients who would likely have a Type IV response. He stated they needed to figure out how to identify the patients who are at risk for continuous inflammation or adverse responses.

**Scott Burchiel, Ph.D.**, discussed the confusion surrounding metals and what the metal peptidome was or what metals/peptides they were binding. He suggested that there was more going on than hypersensitivity. He discussed mechanisms of immunosuppression and immunostimulation that could be at play. He also discussed the role of adjuvant metals that nonspecifically stimulate versus other metals that bind to specific proteins.

**Julia Babensee, Ph.D.**, commented on terminology. She suggested it was clearer to say "innate immune response" or "inflammatory response" to a material versus "adaptive immune response" for where an antigen was present. She discussed how to distinguish the metal ion effect versus the particle generation effect.

**Dr. Jacobs** stated that it was difficult to distinguish between a particulate effect and an ionic effect on the local tissues. He explained that once wear debris gets in the tissues, it produces metal ions and corrodes. He asked for explanation about autoimmunity and the hypersensitivity/allergic response processes for metal implants. **Dr. Dykewicz** related the importance of and the challenges involved with studying innate immunity and suggested it should be a focus of their research.

**Dr. Weisman** discussed major clinical problems, such as pain following an implant and the question regarding whether or not implants trigger systemic rheumatic disease. He discussed the triggers of systemic rheumatic diseases such as ankylosing spondylitis and spondyloarthritis. He then asked for evidence that triggers of immune response due to metal implants were actually producing systemic rheumatic diseases.

**Jack Lemons, Ph.D.**, discussed commonalities between dentistry and medicine. He pointed out that there was relevant literature dealing with allergic response to metallic materials, including polymeric. He discussed how metal substance and debris was variable in terms of underlying chemistry, shape, size, amount, and location. He stated it was important to understand not only the biological reaction but the physical science aspects of what they were specifically analyzing.

**Dr. Babensee** stated it was important to identify how the material aspects were connected with the host response. She stated that it was important to understand what the intended application was. She discussed issues associated with adjuvants and noted that the initial innate immune response to implants could have an effect on the adaptive immune response to the antigen or the metal/antigen combination.

**Dr. Germolec** admitted that they understood little about the factors that regulate autoimmune disease. She explained that there were environmental triggers and that genetics

were also important. She stated that they needed to understand how the combination of those factors might contribute to autoimmune disease or systemic hypersensitivity.

**Melissa McDiarmid, M.D.**, stated that despite the shortcomings of the LTT test, it still would be prudent to bring it into the informed consent conversation.

**Dr. Parks** discussed issues of the natural history of the development of autoimmunity. She stated that one established environmental risk factor for systemic autoimmune disease was crystalline silica or quartz dust in the occupational setting at very high levels, which was associated with rheumatoid arthritis, lupus, or systemic sclerosis. She discussed the notion that a nonspecific immune adjuvant may contribute to the development of an autoimmune disease and that the phenotype may be driven by other genetic or environmental factors. She stated that they had a poor understanding of the natural history of autoimmune disease. She asked Panelists what happens to metal particulates in the body. **Dr. Jacobs** noted that the liver, spleen, and para-aortic lymph nodes were a common depository for metal debris.

**Chairperson Rao** asked for thoughts on the role of systemic toxicity to metal and how that might overlap the clinical manifestations. **Dr. Dykewicz** noted that the question points out a knowledge gap and indicates a need to study systemic hypersensitivity responses.

**Dr. Lemons** explained that what was seen at the tissue interface with implants was not metallic debris from the implant but rather metallic debris from the instrumentation or association of the procedure. He discussed the significance of this in terms of chronic exposure in some populations, such as those with piercings or tattoos.

**Mr. O'Brien** asked about the immunological response with regard to nonmetallic implants. Chairperson Rao agreed that nonmetallic implants had some of their own issues.

**Dr. Giori** suggested that it would be helpful to define a series of signs and symptoms or laboratory values that could then be used to define a particular syndrome.

## PANEL QUESTIONS

**Chairperson Rao** read Question 4: "Please discuss the status and clinical utility of available diagnostic/prognostic tests for pre- and post-procedural assessment or management of possible implant/insert-related host reactions. During your deliberations, please specify the existing knowledge gaps related to these tests and the next steps needed for innovation in methods to reliably predict an individual's potential for a heightened response or monitor potential post-procedural reactions."

**Paul Jannetto, M.D.**, discussed that much of the testing performed was not standardized and the result was inconsistent literature. He discussed pre-analytical issues with blood draw and collection processes, where contamination could occur and lead to erroneous results. He added that most of the reference ranges and information generated in laboratories were based in patients without implants. He added that the concentration of the elements in different matrices, such as blood, serum, urine, and synovial fluid, were highly variable. He explained how some matrices may be superior in terms of sensitivity and/or specificity.

**Dr. Weisman** pointed out that current tests only indicated an exposure to the metal

but did not indicate whether there would be a complication. He added that a prospective cohort of joint replacements where every patient receiving an implant would be followed with objective assessment criteria at intervals over time could help inform this. **Dr. Giori** suggested that a prospective study looking at the effects of joints in large numbers of people would have to be a registry. **Dr. Jacobs** agreed and discussed a UK cancer registry that could cross-reference cancer incidence with joint replacements. He stated that a prospective cohort study was needed once they could define what to look for. He suggested there was a role for NIH to put out RFAs that could help them understand the immune response to metal implants and develop better testing modalities.

**Dr. Weisman** questioned what immune measurements should be collected and whether or not there was enough information to know what to look for. **Dr. Pollard** replied that they needed evidence about adverse reactions that occur. **Dr. Hallab** provided some information, stating that there was a strong correlation between people that had well-performing implants and poorly performing implants in terms of adaptive immune responses. He added that while large-scale studies were always difficult, an animal model could be helpful in trying to reproduce a phenomenon. **Chairperson Rao** asked if the immune responses were a result of an intrinsic response to metal or to wear debris. **Dr. Hallab** replied that it was different in different people.

**Dr. Lemons** stated that consensus standards were needed for preclinical and clinical testing of overall device and debris quantification and biocompatibility.

**Dr. Badylak** stated that while a cohort study could advance their knowledge base and ability to predict adverse reactions, it would be flawed. He discussed how assays, such as the LTT, did not help identify patients at risk. He suggested they use assays that look at patients who have genetic signatures associated with tendencies towards certain diseases to help identify those that are or are not hyper-responders. **Aron Yustein, M.D.**, Assistant Director, Clinical and Scientific Policy Staff, Office of Product Evaluation and Quality, asked what areas should be studied to look for genetic variations that might predispose a response. **Dr. Badylak** suggested they start with known genetic markers.

**Dr. Babensee** again suggested they define what is happening in order to construct an explanation from a biomaterials point of view and an immunological point of view.

**Dr. McDiarmid** discussed metal measures and agreed with Dr. Jannetto that the upstream potential contamination was sometimes what was being measured. She discussed ways to standardize collection, noting that in the VA surveillance program, everything was measured in urine in order to avoid polyatomic interferences. She discussed how metal measures can be done in a reliable way and noted that the frustration was that metal measures did not reliably predict who would have a device failure. She assured colleagues that standardized collection was a manageable method to determine metal burden even though it may not predict failures. She discussed the value of patient questionnaires and added that serial measures could also be helpful. She recommended that FDA develop guidance on how to collect and measure metals of interest.

**Jason Connor, Ph.D.**, discussed the difficulty of estimating and predicting rare events. He stated that while a cohort would be a logical place to start, it was not ideal. He suggested they begin with an enrichment trial that studied patients who have had reactions/device failures and proposed that they approach it in a case control way.

**Dr. Parks** agreed that developing risk-enriched cohorts was ideal. **Dr. Connor** added that

they could start with patients with a family history of autoimmune disease.

**Whitney Christian, Ph.D.**, Industry Representative, indicated that they needed to understand the underlying science within the field of immunogenomics to get the benefit out of diagnostics and/or a cohort study. He stated they needed to know what variable to look for to gain benefit from a cohort study.

**Dr. Fisher** asked for comment on where to begin in terms of genetic risk factors.

**Dr. Parks** emphasized that despite not knowing what to measure, data should still be collected. She added that a retrospective study would not eliminate recall bias and other biases if they did not have data collected up front.

**Wyatt A. Lison, Esq.**, Consumer Representative, stated that it would be beneficial to consumers if they were informed about metal allergies and educated about the different types of testing available, such as patch testing and LTT tests.

**Chairperson Rao** summarized that there were several difficulties in providing the FDA with a clear response, which was primarily related to the need for different types of information regarding the metal component, the immune response component, and the histological response. He stated there was an issue regarding metal testing in terms of the collection process and how it could impact variations in the results and a need for consistency in pre-analytical processing. He discussed issues brought up regarding metal-level responses and the lack of a clear understanding of what a significant level was, particularly given the strong level of occupational exposure. He stated there was less agreement among Panelists regarding immune response testing and its validity pre-surgically or post-surgically. He described the Panel's desire to obtain prospective data on testing longitudinally in patients selected for joint replacements and implant placement. He noted that Panelists also felt the involvement of Federal institutions such as NIH would be helpful in the process of collecting longitudinal data. He added that it was unclear among Panelists whether the registries could provide those answers. He explained that there was little data available to address questions surrounding whether environmental triggers predisposed some patients to develop heightened responses to metal implants.

**Dr. Taylor** added that it was imperative to discuss patch testing and to determine who does the patch testing. He stated that they should encourage CDER to deal with CBER in terms of approving additional allergens.

**Panelists** discussed Question 1: "Please discuss the currently available scientific information with respect to the ability of a metal implant/insert to elicit a prolonged and/or heightened immunologically-mediated and clinically consequential inflammatory response."

**Dr. Burchiel** discussed acute and chronic local inflammatory reactions that could either be related to implant surgery or to the metal itself. He stated that while there were mostly Type IV metal allergies in patients, it may go beyond that. He suggested they consider the possibility that patients could get systemic immune activation with metals and central nervous system effects. He stated that metals were immunomodulators and not just hypersensitivity agents. He stated they could cause immunostimulation depending upon exposure. **Chairperson Rao** asked how much of the central nervous system activity would



be directly related to metal toxicity versus how much would be a specific immune response. **Dr. Burchiel** replied that it would be difficult to discern. **Dr. Jacobs** added that systemic effects from the metal materials or degradation products were documented and associated with extremely high levels. He added that he does not believe they are immune-mediated.

**Chairperson Rao** asked about the ability of implants/inserts to elicit a prolonged or heightened immunologically mediated response. **Dr. Jacobs** replied that it was "unequivocal" that the implants could do that at the local site. He added that the majority of the chronic inflammatory reactions were related to the degradation products from the implants. **Dr. Giori** added that corrosion is one of the major issues and that the corrosion bodies contribute to an immune-mediated local reaction.

**Dr. Yustein** asked what the data shows in terms of the likelihood that the local immune response could transform into a systemic response. **Dr. Burchiel** indicated that there will be central nervous system issues when there are elevated circulating cytokines. **Dr. Weisman** was not convinced they could connect the local response to longstanding systemic issues.

**Dr. Fisher** asked for discussion of a gynecologic device insert. **Dr. Weisman** stated that was difficult to answer given that the device was there to generate an inflammatory response. **Dr. Yustein** indicated they were in the process of studying this, but he wondered if the chronic ongoing local inflammatory response could lead to new systemic symptoms. **Dr. Weisman** noted the difficulty of relating such symptoms to the onset of a pain amplification syndrome.

**Chairperson Rao** asked whether there could be a potential immune response that could explain generalized systemic symptoms. **Dr. Parks** indicated that it was feasible but difficult to know. **Dr. Badylak** agreed it was biologically possible, but he stated that it would be hard to determine whether it was related to the metal itself or to the presence of something else causing chronic inflammation. He added that part of the problem was their lack of a good animal model. **Dr. Babensee** also agreed it was feasible, especially where there were elevated cytokine levels. She added that support for this lies in the fact that when patients had the device removed, the symptoms went away. She added that cytokine-level testing would be one way of exploring this. **Dr. Parks** stated that they could correlate the testing with symptoms pre- and post-removal of the device. **Dr. Weisman** stated that the fact that symptoms went away when removing the device was not "powerful evidence" that it caused a systemic reaction, but **Dr. Connor** indicated that they should not dismiss the idea and added that physicians might not be listening to patients enough. **Mr. O'Brien** reminded that while it might be anecdotal evidence, it was still the case that there existed patients who were ready to commit suicide because of the adverse reactions to metal implants.

**Chairperson Rao** summarized that a local inflammatory/immune response clearly occurred, but there were questions on whether a systemic immune response occurred. He stated that currently Panelists felt that there was neither the scientific weight of evidence nor a scientific process that would help them understand the mechanism better. He stated that given the clinical anecdotal evidence available and based on individual experiences, this would be an area for future study.

**Panelists** discussed Question 2: "Please discuss patient-related factors which, based

on available scientific information, you believe may increase or decrease a given individual's susceptibility to a heightened or prolonged response to a metal implant/insert. During your discussion, please consider potential factors including, but not limited to, the following:

Sex, age and/or reproductive status (e.g. women of childbearing age); medical comorbidities (e.g., allergy, connective tissue diseases, other inflammatory and autoimmune diseases); modifiable behaviors (e.g., tattooing, smoking, wearing metal jewelry); genetic markers and/or other biological or demographic variations; location of device implant (e.g., device-tissue interface); and duration of implantation."

**John Suzuki, Ph.D., D.D.S.**, agreed with the list of potential factors but added that there were also medication factors that contributed to the failure of dental implants. He added that it was not known if the association was immunological or mechanical.

**Dr. Lemons** stated that in terms of location of the device implant-tissue interface and duration of implantation, the influence of the functional conditions at the device-to-tissue interface would need to be assessed because it was very patient-specific.

**Dr. Jacobs** indicated that gender was the only patient-related factor that had convincing scientific evidence. He added there was metal-on-metal literature that females had a higher rate of failure, but other factors were less well supported.

**Dr. Christian** felt that the stochastic nature of the immune system could play into the effects in terms of patient variability. He discussed VDJ recombination and how receptors interact and play a role in Type IV hypersensitivity. He indicated there was bias in terms of the T-cell receptor repertoire and that some receptors could cross-react. He stated that one gap in knowledge was related to how the T-cell receptor DNA sequence played into antigen specificity.

**Dr. Yustein** asked whether the location of the implant could elicit different degrees of responses. **Dr. Weisman** replied that it did not matter where the foreign antigen was placed as long as there was access to the bloodstream. **Dr. Burchiel** countered that location could matter, such as in immunologically privileged sites like the eye, but he admitted that the science was imperfect. He discussed a recent trend in pharmaceutical and preclinical research to use humanized animals or to do studies on a chip with complex cells.

**Dr. Babensee** agreed and added in the case of the gynecological tract and the uterus, it depended on the purpose of those locations. She agreed that doing organoid studies or organ-on-a-chip studies could be helpful to try to understand what was happening in different sites.

**Dr. Taylor** stated that nickel sensitivity was frequent and that some patients having orthodontia prior to having piercings actually become tolerant to nickel. He discussed three variations of contact dermatitis: localized, regional, and disseminated. He suggested that looking at groups that have high volumes of patients with those specific implants that have registries would be beneficial.

**Dr. Fisher** asked for discussion about possibility of pseudo tumors forming in the knee if the same materials used in the hip were placed in the knee. **Dr. Giori** replied that it was not just the location but also the mechanics of the joint and the design of the implant.

**Dr. Jacobs** agreed. **Dr. Dykewicz** stated they should be cognizant of mucosal-associated lymphoid tissue and the difference that could make in terms of location.

**Chairperson Rao** summarized that there were some patient-related factors that could affect the local and/or systemic response to the implant. Some local factors were mechanical factors dealing with medications, age, and gender; there were some local factors that could play a role because of different biome contents. He stated that there were also systemic immune responses that could be patient-specific that Panelists were unclear about.

**Panelists** discussed Question 3: "Please discuss device (implant/insert)-related factors which, based on available scientific information, you believe may increase or decrease a given individual's risk for a heightened or prolonged response to a metal implant/insert. During your discussion, please consider potential factors including, but not limited to, the following: specific metal or metal alloy compositions, surface and coating characteristics, manufacturing processes, corrosion/degradation products, or other release of substances."

**Dr. Jacobs** discussed tribocorrosion of modular junctions in metal devices. He stated that the adverse local tissue reaction was primarily reported in association with cobalt-chrome devices and that the rationale for avoiding cobalt alloy heads in total hips was that there was more reactivity to cobalt-chrome than to titanium debris.

**Dr. Babensee** indicated that a device-related factor could be the composition of the device, the percent chemical composition, the microstructure of it, and the effect of the manufacturing process. She discussed how these impacted the response and suggested that there needed to be reporting of what the devices were made of. **Dr. Jacobs** stated that the amount and type of degradation debris from the implant would likely impact the response.

**Dr. Yustein** stated that it was not uncommon for labeling to describe a device as a stainless steel device but not that it was composed of multiple different individual elements. **Jennifer Goode**, Office of Product Evaluation and Quality, CDRH, described labeling and explained that some but not all metal devices included detailed ingredient information.

**Dr. Lemons** stated that they needed information on condition-dependent specific organometallic complexes that form as well as information on how the compounds transfer in terms of dose-response time reactions.

**Dr. Badylak** indicated that all of the composition should be listed on the labeling. He added that FDA needed to consider whether a biologic modulates the immune response for new devices coming on the market. He stated that for new device development, often years and millions of dollars go into product development before testing the immune response was even considered. He suggested that FDA should revisit what types of testing should be conducted and when.

**Richard Burton, D.D.S.**, asked why the various coatings, manufacturing processes, and/or composition of implants was not available to the doctor or the patient. **Dr. Taylor** agreed this should be available and suggested a contact list for information on product ingredients be easily accessible to physicians and/or patients.

**Dr. Burchiel** brought up the 1999 guidance on immunotoxicology and discussed the need for more information than simple yeses or noes that a certain device contained potentially immunotoxicological material.

**Chairperson Rao** summarized that device-related factors had an impact on patients'

responses to an implant or insert. He stated there could be multiple factors contributing to the device-related response, including the extent of wear debris generated by the alloy composition, the specific alloy composition, and its predisposition to wear debris. He added that there were other factors playing a role in mitigating a device-related response, such as changes in the microstructure of the implant and/or changes in potential coating of an implant with other substances. He emphasized that Panelists felt strongly that including a list of specific elemental composition of devices on the packaging would be beneficial.

**Dr. Yustein** indicated this was an adequate response for Question 3. He added that FDA had started to list ingredients in certain product areas, such as in labeling for breast implants.

**Panelists** discussed Question 6: "Based on discussions during the meeting, please discuss the strength and validity of currently available scientific information with respect to potential adverse health impacts resulting from mercury exposure from dental amalgam among: dental professionals, the general population, and subpopulations that may be more susceptible to adverse health effects, including children and pregnant women with their developing fetuses."

**Yiming Li, D.D.S., Ph.D.**, stated that the additional FDA literature review was extensive and largely confirmative to the previous knowledge and understanding of mercury and amalgam health risks. He stated there was still a concern about the risk to the professionals, but such concerns were largely due to the inadequacy in practicing mercury handling hygiene. He stated there was additional evidence that the allergic reaction to amalgam was not only to the dental professionals but also to the general population and to the environment.

**Dr. Weisman** indicated he was impressed with the new evidence regarding epidemiology of mercury levels in the United States. He added that the importance of the mercury in amalgam to the overall mercury burden was still high. He stated that there was compelling evidence that there was a disproportionate accumulation of mercury in the bodies of disadvantaged individuals in society, which continued to be a problem in health disparities in the U.S. He expressed his opinion that mercury-containing amalgam should be "on its way out," given the reasonable alternatives. **Mr. Lison** agreed.

**John Zuniga, D.M.D., M.S., Ph.D.**, agreed that the FDA review process was sequential and that the science was strong that mercury exposure was dose-dependent and frequency-dependent. He indicated that concerns about neurologic disorders in subpopulations was a question of informed consent and that dental professionals needed to have that discussion with patients.

**Dr. Li** added that while there was clear trend away from amalgam use due to safety concerns as well as the available of alternative materials, they needed to consider the purpose of amalgam for the general population. He cautioned that an immediate ban might lead to a portion of the population not having other options. **Dr. Connor** countered that the data showed that it was not the general population who tended to receive amalgam. He added that if a product that was 50% toxic came on the market currently and would only be used in disadvantaged populations, they would not be having a meeting about it at all.

**Dr. Burton** commented that in his experience, there was a drift towards getting rid of amalgam. He added that the move away from amalgam in Europe was primarily an environmental issue, and he felt that it would disappear in U.S. soon for the same reasons. He noted that how to handle those that had existing amalgam restorations would become the issue. He added that for the existing population, the retention of amalgam was shown by the data to be safe based upon the science, but it was likely time to move on to alternative materials.

**Dr. Suzuki** discussed the suitability of other alternatives to amalgam, such as glass ionomers, composites, porcelain, and gold. He explained that there were environmental concerns and concerns for selected populations of patients that may have a reaction to different components of amalgam fillings. He stressed a need for educating clinicians, professionals, and waste product removal services about these concerns.

**Chairperson Rao** summarized that the evidence presented confirmed what was previously known and tends to "move the needle further" in the direction that there was recognition and understanding of the environmental, patient risks, and risks to dental professionals associated with mercury-containing amalgams. He stated while the Panel did not have a clear understanding of a quantified increase in risk, the trend was to use alternatives when available, and the general direction should be to move away from using mercury-containing amalgams.

**Panelists** discussed Question 7: "Please discuss the evidence for in vivo cross-transformation (i.e., methylation/demethylation) of mercury species within the human body and how this may impact the extent to which we know the origin of mercury species (e.g., dental amalgam vs. seafood consumption) and adverse health effects attributable to inorganic mercury or methylmercury."

**Dr. Jannetto** stated that most testing for mercury measured total mercury rather than mercury speciation. He explained that the evidence showed that there was demethylation and methylation of mercury and cross-transformation of mercury species. He stated that the mercury measured in urine was always elemental or inorganic mercury whereas the mercury measured in hair and blot was the methylated mercury form; this indicated that it could have been methylated mercury that a patient was exposed to which then got demethylated. He then discussed how the speciation of all forms of mercury was toxic. **Dr. Li** agreed, adding that studies on this should be encouraged to further improve the quantitation of the different species of mercury.

**Dr. Weisman** asked whether cross-transformation could occur in the environment. **Peter Goering, Ph.D.**, Office of Science and Engineering Laboratories, CDRH, explained that mercury species cross-transformation does take place in the environment. He explained how inorganic mercury waste could settle into sediment and water where bacteria could then biotransform it into methylmercury and subsequently expose it to fish.

**Chairperson Rao** summarized that there was increased knowledge of the process of conversion between the methylated and non-methylated forms of mercury and that there was more transformation from one to the other in humans, in the environment, and in other

species. Panelists felt that one issue was that the current testing for mercury did not clearly speciate between the different types of mercury, which resulted in a knowledge gap. He indicated that there was not enough information to answer specific questions regarding the toxicity of one type of mercury versus the other or the relative contents of one versus the other within humans or in the environment.

**Panelists** discussed Question 8: "Please identify and discuss any other evidence gaps or challenges not addressed in FDA's report on dental amalgam and the approaches which should be considered to help narrow those gaps. Please also discuss whether there is any additional information FDA should convey to the public about what is known and not known about the risks of dental amalgam, in particular for susceptible populations."

**Dr. Dykewicz** discussed the uncertainty surrounding the additive effects of mercury neurotoxicity and other heavy metals such as lead. He stated that they needed more studies on this, but they should not wait to see if there were neurocognitive problems before they took action. He added that non-amalgam fillings should be used or at least considered in children.

**Dr. Weisman** stated that FDA should recognize the challenge of addressing the evidence and consider how to disseminate it to the public without creating a scare. He stated that he would support an implantation science research project to address the question of how to handle the issue of adding or removing amalgam.

**Dr. McDiarmid** suggested there be a risk message put out by FDA to stop implanting amalgam in vulnerable populations. She stated that the evidence of risk surrounding dental amalgam was enough to know the behavior of mercury in the developing brain of children. She cautioned against FDA "continuing to bless" amalgam use simply because the evidence "isn't quite there."

**Dr. Badylak** stated that resources should be devoted to understanding the pathophysiology of mercury in the body. He stated that there needed to be incentive to produce a device less expensive than amalgam, and he cautioned that if amalgam was taken off the market, there might not be incentive to develop more economically viable devices. He added that it was unclear how to take something off the market for one population and leave it for another. He felt these were issues that could be solved if they would focus on it.

**Mr. O'Brien** supported trending away from amalgam use. He added that it was important to carefully consider how this should be done.

**Chairperson Rao** summarized that there were gaps that existed with regards to dental amalgam primarily related to a lack of communication with the population about the potential risks of mercury-containing amalgams especially in vulnerable subgroups like children. Panelists felt that another significant gap was that the risk of removal of amalgams was unknown and deserved more study and research by the FDA or other federal bodies.

**Michael E. Adjodha, M.Ch.E.**, Acting Assistant Director, Restorative and Surgical Dental Devices Team, Division of Dental Devices, asked for recommendation on how FDA should convey information to the public. **Dr. Weisman** responded that the evidence gap was largely about the lifecycle of mercury, and he stated that FDA should put the power of

their voice behind getting the information out. **Chairperson Rao** suggested that the FDA look into revisiting announcements for mercury levels in fish in order to incorporate the overall potential effects of mercury exposure from fish, dental amalgam, and the environment. **Dr. Taylor** suggested that NIH, the National Institute of Child Health and Human Development, NIOSH, OSHA, and National Institute of Dental Health should be involved in getting information out to the public.

**Panelists** discussed Question 9: "Please discuss any other areas of scientific uncertainty and corresponding sources of new evidence or additional research/innovation which is needed to enhance our ability to understand and/or mitigate metal implant/insert-related adverse health outcomes."

**Dr. Christian** suggested that mitigation of adverse health outcomes was the key. He stated that industry supported the right to know what materials were in devices and that they were willing to work with the FDA in providing that information.

**Dr. Jacobs** suggested that national joint replacement registries and/or national implant retrieval registries would be powerful tools to enhance understanding in this area. He also proposed more robust preclinical testing modalities for tribocorrosion processes and dynamic corrosion testing. He added that there needed to be further understanding in terms of how inflammatory cells could be players in accelerating corrosion in certain circumstances. **Dr. Lemons** agreed and stated there needed to be more participation from different expertise areas. He pointed out that funding would be a limitation in achieving this type of participation.

**Dr. Weisman** questioned the feasibility of a registry and suggested instead a cohort of at-risk patients with specific data collections. **Dr. Jacobs** countered that both implant retrieval registry and such a cohort could both leverage a lot of information.

**Dr. Germolec** suggested they develop a better communication strategy overall from the outset of labeling to collecting information from patients pre- and post-marketing. She stated they needed to assess the "whole package" at multiple points in order to understand what the scientific evidence was underlying the factors that made implants either successful or unsuccessful.

**Dr. Connor** agreed that mitigation was important. He stated that from a public health perspective, understanding how to quickly identify adverse health outcomes and what to do in those patients should be the focus. He stated that it was likely too difficult to do a primary prevention strategy because of the large number of people and the small number of events.

**Dr. Badylak** stated that there was a need for better ways of informing patients who have potential risk, and he suggested that they revisit the way they determine safety and efficacy for these types of devices.

**Dr. Pollard** suggested they do more preclinical studies with animal models.

**Dr. Lemons** discussed issues surrounding innovation in the United States, including regulatory burden, recognition and respect to the discipline and the community at large, and litigation. He stated that information specific to litigation needed to be in the public domain in order to make progress and in order to conduct the appropriate scientific investigations to answer key questions.

**Chairperson Rao** summarized that additional information on metal-containing devices, implants, dental amalgam, and metal in the body was needed, but how to go about it was still unclear. He stated that some Panelists felt that registries and/or longitudinal cohorts may be helpful, but others suggested that the statistical rarity of those incidents created a situation where information might be better gathered by studying isolated incidents of adverse responses to metal implants. He stated that retrieval studies and/or tissue and blood testing in patients who have had failures or immune responses could be another area for focus and study. He stated the Panel and industry both supported the declaration of the composition of all metal devices in labeling. He stated that the Panel generally felt that improved preclinical testing of device implants was needed, and in terms of corrosion testing, they felt that FDA needed to move beyond just mechanical corrosion testing to electrochemical corrosion testing. There also needed to be studies on the role of biological tissues and how they contribute to corrosion. He stated that successful outcomes of procedures where devices were implanted in the body were multifactorial in their etiology; success depended upon the patient, the device, the surgeon, the technique used, and on a number of mechanical properties of the device in addition to immunological and/or other processes. He added that he was personally supportive of the work that the FDA continued to do to try and move forward on this topic.

## **SUMMARY**

**Dr. Yustein** thanked Panelists for their expertise, preparation, and participation in the meeting. He thanked members of the public for their comments and assured everybody that FDA was listening to their input. He thanked Chairperson Rao for his participation.

**Dr. Fisher** thanked the Panelists for their input and thanked the public for their participation and comments. He assured them their voices were heard. He thanked Chairperson Rao for serving as Panel Chair.

## **ADJOURN**

**Chairperson Rao** thanked Panelists for coming well prepared and for their participation in advancing patient care and patient safety. He adjourned the meeting at 3:56 p.m.



I certify that I attended this meeting on November 14, 2019 and that these minutes accurately reflect what transpired.

\_\_\_\_\_/S/\_\_\_\_\_  
Aden Asefa MPH  
Designated Federal Officer

I approve the minutes of this meeting as recorded in this summary.

\_\_\_\_\_/S/\_\_\_\_\_  
Rajkumar Rao, M.D.  
Chairperson

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