SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

IMMUNOLOGY DEVICES PANEL

November 13, 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
Amy McKee, Ph.D.
University of Colorado Anschutz Medical Campus
Aurora, CO

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 8:00 a.m. He noted the presence of a quorum and stated that the Panel members had received training in FDA device law and regulations. He announced that the Panel would be discussing the topic of immunological responses to metal-containing products regulated as medical devices and that the discussion would focus on metal-containing implants and dental amalgam.

PANEL INTRODUCTIONS

Chairperson Rao asked the Panel members and the FDA staff to introduce themselves.

CONFLICT OF INTEREST STATEMENT

Aden Asefa, M.P.H., Designated Federal Officer, read the Conflict of Interest Statement and reported that conflict of interest waivers were issued to Drs. Stephen Badylak and Joshua Jacobs. She introduced Dr. Whitney Christian as the Industry Representative.

DEPUTIZATION TO NON-VOTING MEMBER

Ms. Asefa read the Appointment to Temporary Non-Voting Member Status Statement appointing Dr. Rao as Temporary Chairperson and Drs. Michael Weisman and Mark Dykewicz as temporary non-voting members.

She then made general announcements to the public regarding transcripts and videos and introduced Michael Felberbaum and Angela Stark as the FDA press contacts.

WELCOME & INTRODUCTION

Aron Yustein, M.D., Assistant Director, Clinical and Scientific Policy Staff, welcomed and thanked the Panel members, the invited speakers, and the attendees. He provided background information on why the meeting was being held, summarized the objectives and scope, and outlined the agenda.

INTRODUCTION TO IMMUNOLOGY BASICS

Dori R. Germolec, Ph.D., National Institute for Environmental Health Sciences, discussed the role that the immune system plays in maintaining equilibrium within the body. She looked at factors that affect immunocompetence, such as age, sex, and genotype; discussed the differences in adaptive versus innate immunity; and identified different classes of inflammatory mediators. She then focused her discussion on adverse immune responses, challenges involved in assessing the effects of external determinants on the immune system, and host factors associated with autoimmunity.

CLARIFYING QUESTIONS FROM THE PANEL

Chairperson Rao asked what is known about the impact of age on the immune response. **Dr. Germolec** replied that it is believed that the immune system becomes less effective in protection and surveillance as an individual ages, and it varies with different cell populations and functions.

METAL IMPLANTS

FDA Guidance/Biocompatibility

Jennifer Goode, B.S., Biocompatibility Program Advisor, provided an overview of the types of evaluations that FDA performs to assess biological response to metal implants. She explained that a variety of assessments are conducted to understand whether materials used in medical devices can cause adverse biological responses and that they vary depending on the type of device and where it is used in the body. She noted that these assessments can include biocompatibility, corrosion and ion release, device-specific fatigue testing, and clinical studies.

Corrosion

David Saylor, Ph.D., Office of Science and Engineering Labs, gave a brief overview of the corrosion and metal ion release section of FDA's white paper. He stated that the section contains a synopsis of potential corrosion mechanisms and factors that influence susceptibility in metal implants as well as a description of in vitro test methods that are typically used to evaluate corrosion resistance in medical devices. He highlighted what is currently known about the corrosion of typical alloys, noting that there is limited information to suggest that in vitro test results roughly correspond to clinical observations. He then summarized current gaps in understanding and underscored the challenges involved in corrosion assessment.

Preclinical Issues

Nadim James Hallab, Ph.D., Rush University Medical Center, discussed innate immunity, adaptive immune responses to implant debris, and factors that contribute to reactivity. He looked at reasons for long-term implant failure, noting that the most prominent is aseptic osteolysis, which is mainly driven by a slow compromising of the implant/bone interface. He then looked at factors that may contribute to increased likelihood of adverse innate and/or adaptive responses. He stated that metal implant debris particles cause more inflammatory bone loss in females, that metal sensitivity is most likely to occur at less than 5 years, and that innate immune responses to implant debris mediate the majority of long-term problems and revisions. He noted that currently there are no diagnostic tests to determine who is more reactive to this kind of response.

Laura Santambrogio, M.D., Ph.D., Weill Cornell Medicine, described what is currently being learned about the immune response to polyethylene and metal implants. She

discussed biomaterial testing, noting that most of it is done on durability, fatigue, wear, performance, and clinical outcome. She noted that much less is done on the chemical composition of biomaterials in the body, on how they break down, on their toxicity, and on how quickly they are excreted from the body. She stated that more testing is needed to see if particulate debris can activate inflammasomes, if reactive oxygen species and metal ions can be produced, and if long-term in vivo testing can mimic how particulate debris would react in humans.

Clinical Non-Orthopedics

Stephen Weber, M.D., Office of Health Technology 6, FDA/CDRH, stated that recent issues with metal-on-metal hips and gynecological metal implants have heightened concerns about problems with these devices, noting that a broad spectrum of clinically manifested responses, both local and systemic, have been known to occur. He stressed the importance of having clearly defined terminology to explain these responses and to allow for valid comparisons between studies. He noted that adverse reaction to metal debris is not synonymous with true allergy, that metal allergy is rarely the mechanism for ARMD, and that patch testing has been shown to be largely ineffective for diagnosing and predicting implant failure. He also told the Panel that adverse reactions are being seen with dental devices and amalgams, which contain mercury, silver, tin, copper, and other metals, and that the most commonly implicated device has been temporomandibular implants.

Benjamin R. Fisher, Ph.D., Director, Office of Health Technology 3, Office of Product Evaluation and Quality, FDA/CDRH, focused his discussion on metal-containing implants that are not solid but are designed to conform to the shape of naturally formed cavities within the body. He noted that many of these devices contain Nitinol for its shape memory. He related that adverse reactions to metals in cardiovascular devices have centered on stents and pacemakers. Additionally, detrimental effects have also been reported with neurological and gastrointestinal stents. He pointed out that current diagnostic studies are inadequate to identify patients who are at risk for adverse responses to metals preoperatively or who may have an adverse response to an existing implant. He emphasized the need for a more nuanced evaluation of the entire spectrum of device/biomaterial specific ARMD.

Clinical Orthopedics

Young-Min Kwon, M.D., Ph.D., Harvard Medical School, gave an overview of clinically relevant biological reactions to orthopedic implants. He acknowledged that systemic adverse biological reactions to hip implants do occur, but current studies are limited by a small number of patients and short follow-up time. He stressed the need for further study in this area. He pointed out that there are no validated clinical tests to screen or diagnose metal hypersensitivity, that there is no clear dose-response relationship between metal corrosion load and metal levels with ALTR or ALVAL scores and that further research is needed in terms of identifying the role of individual patient reactivity. He further stated that revision surgery for adverse local tissue reaction is associated with a high complication rate, which correlates with the extensive amount of necrosis that is seen at the time of surgery. He explained that this suggests the need for systemic evaluation to optimize

revision outcomes.

Diagnostics

Elizabeth Stafford, Ph.D., Division of Immunology and Hematology, FDA/CDRH, discussed current tests and tools for measuring biological and clinical adverse responses. She related that patch testing and lymphocyte transformation tests are susceptible to analytical variability, technical challenges, and an unclear relationship between test results and implant status. She also looked at adverse responses from imaging as well as the pros and cons of histology and metal ion testing. She then identified current challenges and future goals, noting that the aim is to have tests that can provide clinically useful information on predicting responses before implantation, that can screen for device failure, and that can evaluate problematic implants.

Summary/Gap Analysis

Yelizaveta (Lisa) Torosyan, M.D., Ph.D., FDA/CDRH, discussed device versus patient factors in implant-related outcomes, clinical and terminological challenges in implant reactivity, and clinical implications of allergy-to-inflammation transition. She pointed out that there are more knowledge gaps surrounding patient characteristics, that diagnostic and therapeutic management of implant reactivity is affected by many clinical challenges such as uncertain diagnoses and treatment choices, and that the key to improving mechanistic understanding of implant reactivity starts with the acknowledged role of both adaptive and innate immunities. She concluded that lessons learned may benefit development of pathogenetically determined testing which would address the entire spectrum of ARMDs, would allow post-implantation detection of subclinical features, and would lead to biocompatibility testing for effectively predicting and modulating immune responses.

PANEL CLARIFICATIONS/DELIBERATION

John Zuniga, D.M.D., M.S., Ph.D., asked if any of the patch or LTT tests can discern between metal and non-metal responses. He also asked if reactive problems can be distinguished in situations with combined materials if this is so. **Dr. Hallab** replied that non-metal materials are being used for patch and LTT testing, primarily with bone cement products. He remarked that it would be difficult to envision how they could result in a flexible immune response since they are nonreactive and hard to chemically degrade.

Michael Pollard, Ph.D., asked if the severity of prior conditions has been considered in terms of subsequent responses to metal implants. **Dr. Kwon** replied that as far as he knows, it has not been identified as a potential risk factor associated with adverse local tissue reactions.

Chairperson Rao asked how metal devices get local corrosion, whether it is a hyperphysiologic response due to loss of the oxidative layer or if it is a manufacturing or device issue. **Dr. Saylor** explained that the test method for local corrosion puts an over-potential across the device which forces it to a breakdown condition, and the potential for decomposition can be significantly changed depending on how different alloys are manufactured.

Stephen Badylak, D.V.M., Ph.D., M.D., asked if there are any definitive studies that look at the results of these tests in patients who have no complications. **Dr. Kwon** replied that there are no diagnostic tests that can show which patients have adverse local tissue reactions, and none of the specialized tests have 100% sensitivity in picking these things up.

Dr. Hallab highlighted some of the advantages of LTT testing over patch testing in response to questions posed by Dr. Christian regarding how well the assays do in predicting the functional avidity of T cell binding.

Chairperson Rao asked if the issue with gynecological devices is an inflammatory response or a response to the local metal. **Dr. Fisher** suggested that the Essure device causes a macrophage-mediated inflammatory reaction that results in a foreign body response.

Dr. Torosyan stated that inflammatory response is not unique for metals and can be expected with other products.

Dr. Santambrogio pointed out that the immune system is not equipped to distinguish plastic from metal and that many of these responses are similar. She added that the mechanism of inflammasome activation is present in both metal and polyethylene.

Nicholas Giori, M.D., Ph.D., asked if there is a need to specifically define what an adverse reaction to metal is. **Dr. Kwon** observed that it would be difficult to develop a set of criteria. He acknowledged that standardization would be beneficial.

DENTAL AMALGAM

Background

Michael E. Adjodha, M.Ch.E., Acting Assistant Director, Restorative and Surgical Dental Devices Team, FDA/CDRH, provided background information on dental amalgam and gave an overview of previous assessments performed by FDA and other agencies. He explained that dental amalgam is a restorative material used for filling carious defects in teeth, that it has been on the U.S. market since the late 1800s, and that approximately 50 million amalgam restorations are done annually in the United States. He reviewed its characteristics and described how it reacts with mercury. He further explained that amalgam can release mercury vapor after setting, particularly under mechanical stress, abrasion, and elevated temperatures, and that the main route of exposure is by inhalation.

Clarifying Questions from the Panel

Michael Weisman, M.D., asked if there are alternatives to dental amalgam that would provide a proper risk-benefit ratio. **Mr. Adjodha** replied that composite resins and glass ionomer cements are the most widely used alternatives and that they have their own risk-benefit profile.

Yiming Li, D.D.S., Ph.D., asked if the data presented was primarily on mercury and not on other components of amalgam. **Mr. Adjodha** noted that the data is focused on mercury content because it presents the highest risk.

James Taylor, M.D., asked if NIOSH was involved with the 2009 panels. He also asked if the permissible occupational exposure levels have been changed. **Mr. Adjodha** replied that he does not believe NIOSH was involved or that there have been any revisions to the exposure levels.

Summary of FDA Scientific Review

Dr. Torosyan presented key findings from FDA's literature review of the risk of mercury exposure in dental amalgam. She discussed evidence relating to different amalgam-related outcomes, similarities between overall metal reactivity and amalgam-related responses, and limitations and challenges of the existing evidence on safety. She confirmed that no new evidence was identified on adverse outcomes in vulnerable populations and that no consistent evidence was found to support the causal relationship between amalgam-attributed mercury increases and various clinically manifested adverse outcomes.

Clarifying Questions from the Panel

Dr. Weisman recalled that mercury was once used as a diuretic. He asked if there are any other sources of organic or inorganic mercury in medications. **Dr. Torosyan** confirmed that it was used in certain medications in the past. She replied that she is not aware of any clinical studies that have addressed its use in other medications.

Dr. Zuniga asked what the conversation rate is of lichenoid lesions into malignancies. He also asked if there are any differences between amalgam-related lichenoid versus non-amalgam related lichenoid modifications. **Dr. Torosyan** replied that there have been some limited studies showing the link between malignancy and lichenoid lesions, and it is assumed to be possible. She replied that there is an overlap in the distinction between lichenoid lesions, but the relationship is not specifically known.

Biomarkers of Exposure

Alfred Franzblau, M.D., University of Michigan School of Public Health, addressed the question of what the appropriate biomarkers for elemental and methylmercury are. He discussed the sources of mercury emissions, the primary causes of exposure, and evidence of methylation and demethylation. He acknowledged that analysis of mercury-stable isotopes is an important research tool, but it is not practical for use in clinical settings or in epidemiological studies. He recommended assessment of elemental mercury in hair and urine as well as evaluation of exposure to fish and amalgam for biomarkers in population studies. He also advised that it would be helpful to have a larger study using direct measurement of mercury-stable isotopes to observe a wider range of subjects with regard to fish consumption and amalgam fillings.

Summary/Gap Analysis

Dr. Torosyan summarized the discussion on amalgam-related potential risks, existing knowledge gaps, and overall healthcare and environmental consequences. She acknowledged that no new evidence was found suggesting considerable risk increases, and the current considerations are based on the lack of strong evidence regarding negative outcomes associated with amalgam. She then identified the main gaps and possible next steps, emphasizing the need for addressing inconsistencies related to mercury measurements and for updated information on dental amalgam, including clarification of the full spectrum of

possible adverse outcomes as well as implementation of markers and predictors of enhanced susceptibility.

PANEL CLARIFICATIONS/DELIBERATION

Dr. Li asked if 24-hour urine specimens were used in Dr. Franzblau's studies. He suggested that they would be more representative of mercury exposure. **Dr. Franzblau** explained that 24-hour urine collection is not feasible for epidemiological studies and that spot specimens were used instead. He pointed out that the studies showed a strong correlation between the number of amalgams and mercury levels nonetheless.

John Suzuki, Ph.D., D.D.S., compared the advantages and disadvantages of composites and glass ionomers in response to a question posed by **Dr. Weisman** regarding alternatives to amalgam.

Richard Burton, D.D.S., pointed out that amalgam is an old material, that it has very good longevity and is stronger, whereas composites and glass ionomers are more aesthetic, they cost more, and they require additional remaining tooth structure for restorative purposes.

Dr. Torosyan related that recent studies from developed countries are showing decreasing trends in mercury levels. She suggested that the banning or decreasing use of amalgam could be part of the reason why.

Jason Connor, Ph.D., asked what fraction of new fillings in 2019 are mercury amalgam and if that number differs by socioeconomic class. **Dr. Burton** replied that amalgam fillings still represent a huge percentage of his Medicaid population and that he has not seen any radical decreases.

Jack Lemons, Ph.D., asked if there has been a decrease of mercury levels in the environment and in ground water. **Dr. Torosyan** noted that her references to reduced levels of mercury in developed countries were focused on humans. She explained that environmental assessment is not under FDA's authority and was beyond the scope of her review.

Dr. Franzblau provided more details on how data was collected in his studies with the Michigan and American Dental Associations at health fairs. He emphasized that resources were not available to do in-office studies or assessments of industrial conditions with air samplers.

Mark Dykewicz, M.D., asked if there is any reason to believe that the health effects of inorganic mercury would differ from those of organic mercury. **Dr. Franzblau** referred to examples from case studies and past environmental disasters that have shown some differences.

Joshua Jacobs, M.D., asked if there have been catastrophic adverse events with dental amalgam in individual patients. **Dr. Torosyan** replied that amalgam has been associated with events that could be termed systemic but not catastrophic.

Dr. Jacobs commented that case reports included in literature on cobalt intoxication seem to show some causal linkages and appear to be better validated. **Dr. Torosyan** concurred that the evidence on multi-system organ toxicity associated with cobalt is more valid than existing evidence regarding dental amalgam.

OPEN PUBLIC HEARING

Karin A. Pacheco, M.D., M.S.P.H., University of Colorado School of Medicine, presented data on immunological reactions to orthopedic implants. She looked at the scope of the problem, noting that sensitization to implant components is one of the three main causes of joint replacement failure, that 70% of patients with pre-operative history of metal reactivity are sensitized to a metal, and that 50% of patients with joint failure are sensitized to one or more components of their joint replacements. She recommended that patients with a history of skin reactions to jewelry, metals, gel nails, and skin glue should undergo preoperative testing, and allergy testing should be done at the first episode of joint failure that is not attributable to infection or mechanical issues.

Diana Zuckerman, Ph.D., President of the National Center for Health Research, stressed the need for more thorough premarket and human studies, bigger clinical trials, and a greater quantity of data. She recommended subgroup analyses, studies that are long enough to observe changes in immune responses, and looking for adverse events that are specifically related to immune reactions. She also expressed concern about extrapolating results from one device to another, and she identified the lack of comparative effectiveness research as one of the biggest issues.

Renu Virmani, M.D., President of the CVPath Institute, presented data from the CVPath/AFIP stent registry. She explained what restenosis is, looked at the relationship between inflammation and restenosis, and identified vessel injury, thrombus, and vascular smooth muscle cell as some of its mechanisms. She related that a recent study at the Mayo Clinic found no relationship between metal allergies and cardiac adverse events after stenting, that the prevalence of hypersensitivity reaction to bare-metal stents is less than 1%, and that no hypersensitivity reaction has been documented in peripheral stents.

Scott A. Schroeder, D.P.M., FACFAS, Foot & Ankle Center of Wenatchee, discussed systemic effects of metal implants. He stated that he has surgically removed over 1,000 metallic implants in over 400 patients over the past 10 years. He listed systemic effects that he has seen and treated; discussed sensitivity, galvanic, and allergic reactions; and presented case studies involving severe back pain, fibromyalgia, and episodic rigid quadriplegia.

He then made the following observations:

- A high index of clinical suspicion is required for diagnosing metal reactions.
- The Lymphocyte Transformation Test is beneficial and should be covered by insurance.
- The medical community needs to be trained in these issues and collaboration among all specialties is needed.

Stephen S. Tower, M.D., UAA/WWAMI, presented findings from a study that he has been conducting since having a hip replacement in 2006. He reviewed the symptoms of arthroprosthetic cobaltism, noting that it is not only a metal-on-metal problem but can present with any chrome-cobalt implant. He revealed that FDG/PET brain scanning is specific and sensitive to diagnosing arthroplasty cobalt encephalopathy, and reversibility has generally been seen in nearly 40 patients who were revised for a combination of systemic and local

periprosthetic issues. He stated that the commonality of his patients' symptoms to those seen with Essure patients is striking, and he related that in his own experience, his histopathology was total cell necrosis with a loss of tissue around the hip. He noted that industry was allowed to silently pull metal-on-metal hips off the market, and those patients who were not recalled are now coming to him with serious neurological illnesses and heart failure.

Linda Radach stated that she has endured five hip surgeries due to issues related to metals in the devices, and she described the pain and symptoms that she lives with on a daily basis. She asserted that this is not a small subset of people, that 7 million Americans are living with hip and knee replacements, and that 70 million are implanted with some type of medical device. She related that her toxicologist told her she would be better off with lead poisoning than with the cobalt that is in her body.

Madris Tomes, M.B.A., Device Events, showed samples of FDA adverse event reports on dental implants, noting that 1.6 million of the 2.2 million adverse events reported through August 2019 were serious injury reports. She stated that dental implants are the second most reported device in the history of adverse event reporting, and the vast majority of problems associated with them are due to loss of osseointegration. She further noted that the types of metal used in devices are not regularly included in the labeling, and she recommended updating the Unique Device Identifier to include metals and alloys contained in these products.

Amy Barnett spoke of the symptoms she experienced after Filshie clips were placed in her body during a tubal ligation and of the negative impact it has had on her life, even though they have been removed. She insisted that medical devices need life-long evaluation and tracking to learn of their true impact on the body, and even small devices such as staples and surgical clips can have devastating consequences.

Frances Scott described the debilitating symptoms, both physical and mental, that developed after having both of her hips replaced. She stated that this has devastated her family and put an end to her 20-year career as a news anchor. She called for the end of the 510(k) process for all implanted medical devices. She insisted that companies should not be allowed to sell devices that have not been tested on human beings in clinical trials, that they should be forced to disclose every material that is used in their products, and that they must be stopped from using neuro-toxic, cardio-toxic, and cytotoxic metals in implantable devices.

Susan Francis revealed that she scored 14.9 on the LTT test, which means that she is reacting to nickel, but the problem is no one can figure out exactly where it is in her hip. She stated that medical device labels are not comprehensive, and incomplete labeling poses a health and safety risk for patients with immune responses or allergic reactions to metals. She called for the enforcement of strict labeling and for accountability of the chemical composition of metals in all device components.

Tess Schulman, Ph.D., stated that she suffered for six years with a worsening array of symptoms from the Essure device, that she had major surgery to have it removed, and that there has been a significant improvement of the symptoms. She shared her pre- and post-op

allergy test results showing a decrease in IgE levels, reviewed adverse event results for Essure, and discussed the difficulties that physicians face with this issue, such as poor labeling and communication, limitations of tests, poor access to AE data, and disparate health systems.

Caren Beilin, Ph.D., discussed the side effects of copper intrauterine devices and of her own experience. She related that she had a copper IUD for only 6 days, and during that time, she felt overwhelmed with depression and thoughts of suicide and was experiencing heart palpitations, anxiety, and faintness. Shortly after the device was removed, she began having severe joint pain, could hardly walk, and was diagnosed with rheumatoid arthritis. She asked the FDA to apply more research to this issue and to caution the public.

Kathryn Shasha presented a comparison of the clinical manifestations of Wilson's disease to the adverse effects that women in social media forums are experiencing with copper IUDs. She remarked that the similarities are undeniable and that these women are demonstrating the symptoms of excess accumulation of copper in the liver, brain, and other organs. She called for thorough postmarketing studies to determine the incidence of heavy metal toxicity in these devices and for public awareness so that patients can recognize the source of their symptoms.

Natalie Heckendorn described the symptoms her husband has been experiencing since having triple bypass surgery, noting that they correlate with allergic reaction to gadolinium. She related that he is allergic to nickel and that she subsequently discovered that one of the contraindications listed on his stent card was known or suspected allergy to metal, cobalt, chromium, or nickel. She stated that ignorance is not the answer and physicians need to be informed.

Dawn Yuster described the numerous symptoms she suffers from since having spinal fusion surgery in 2018. She stated that these biological responses continue to expand in number and are worsening in intensity and frequency. She made the following recommendations:

- Patients should be provided oral and written notice of potential adverse reactions well in advance of and right before surgery.
- All doctors should receive training about potential biological responses to implants.
- Close attention should be given to patients with a history of immunological GI or other biological conditions.
- Information should be given about the exact composition of materials in implants.
- Doctors and hospitals should be required to submit adverse event reports for post-surgery patients who have unexpected outcomes.
- FDA should require enhanced and independent pre- and postmarket metal implant tests, and the results should be made available to consumers.

Urszula Tanouye, Citizens 4 Clean Air, discussed the impact that ethylene oxide has on communities that surround commercial sterilization facilities. She pointed out that EtO is

a recognized carcinogen, that it has been linked to lympho-hematopoietic and breast cancers, and that it significantly contributes to the development of several other cancers, including pediatric lymphoma. She asserted that FDA must help decrease the number of items that are permitted to be sterilized by ethylene oxide and that regulatory requirements can provide the impetus for change.

Linda Nelson, MELISA Diagnostics, Ltd., provided background information on the development of the MELISA test and explained how it works. She stated that it is used for research on inflammatory diseases, that it can pinpoint which metals patients react to, and that it has been used by tens of thousands of patients. She recognized that the main challenges are lack of awareness among medical professionals and manufacturers about the risk of hyper-sensitivity to metal implants, inability to find out what implants are made of, and little interest from industry in developing alternatives. She emphasized that all stakeholders can work together to achieve better outcomes for patients.

Curt Hamann, M.D., CEO of SmartPractice, stressed the need for standardized patch testing. He explained that test results using non-standardized allergens are difficult to interpret and that making comparisons is challenging if particle sizes are different. He noted that a successful diagnosis depends on a dose per unit area, and he pointed out that this discipline has not been taken seriously. He then outlined a plan for the development of standardized metal patch-test allergens, highlighted findings from two completed Phase II dose-response studies, and listed seven allergens that have been selected for further investigation in an upcoming Phase III safety and efficacy study.

Susan Alpert, M.D., Ph.D., spoke on behalf of the Advanced Medical Technology Association. She underscored the need for warnings about materials that are used in devices, for knowing which patients are at risk before they are implanted, and for collaborative work to develop tests that can improve patient evaluations. She cautioned against replacing established low-risk materials with ones that have unknown risk, and she advised that the development of advanced and more reliable tests will take time and effort.

Anthony Ragheb, Ph.D., M.B.A., and **William G. Van Alstine, D.V.M,, Ph.D.,** spoke on behalf of Cook Medical. They pointed out that the incidence of metal allergy appears to be very low with the types of metal implants that Cook supplies, citing low rates of adverse events from reports and from patient follow-up in clinical studies. They emphasized the need for increased clinician/patient awareness and discussion, for basic research to understand the biological mechanisms, for recognition of the practical limitations of collecting clinical study data on events that occur in small numbers of patients, and on maintaining patient access to the benefits of metal implants while this work continues.

Johann Wehrle spoke on behalf of Consumers for Dental Choice. He expressed doubt as to whether the valid scientific evidence that is needed for the proper regulation of amalgam will ever be obtained. He pointed out that it is well known that mercury vapor causes brain damage and that unborn and young children might be especially sensitive to the harm that it causes. He further noted that warnings have been issued for mercury in fish and skin creams, and a drug treatment for horses that contained mercury was recalled without

evidence that it caused harm to the horses. He presented a petition with almost 50,000 signatures from people who want children to be protected from dental mercury, and he called for better action.

ADJOURNMENT

Chairperson Rao gave an overview of the next day's agenda. He thanked the Panel, FDA, industry, the guest speakers, and those who spoke in the open public hearing for their contributions. He then adjourned the meeting at 5:49 p.m.

I certify that I attended this meeting on November 13, 2019 and that these minutes accurately reflect what transpired.

_____/S/_____
Aden Asefa, M.P.H.
Designated Federal Officer

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

_____/S/_____
Rajkumar Rao, M.D.
Chairperson

Summary Prepared by

Karen D. Martini
Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947
November 25, 2019