



Waiver to Allow Participation in a Food and Drug Administration  
Advisory Committee

DATE: November 6, 2019

TO: Russell Fortney  
Director, Advisory Committee Oversight and Management Staff  
Office of the Chief Scientist

FROM: Laura E. Bailey, M.S.  
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Center for Devices and Radiological Health (CDRH)

Name of Advisory Committee Member: Joshua J. Jacobs, M.D.

Committee: Immunology Devices Panel of the Medical Devices Advisory Committee

Meeting Dates: November 13-14, 2019

Description of the Particular Matter to Which the Waiver Applies:

The Panel will discuss the topic of immunological responses to metal-containing products regulated as medical devices. The discussion will focus on metal-containing implants as well as dental amalgam. Implants are medical devices that are placed into a surgically or naturally-formed opening of the human body and are intended to remain there after the procedure for an extended period of time (typically, greater than 30 days). For decades, metal-containing implants have been used in a large number of medical specialties including cardiology, orthopedics, dentistry, gastroenterology, and neurology or neurosurgery. Recent postmarket issues with some metal-on-metal orthopedic implants and gynecological metal-containing implants have raised questions about the potential for some patients to develop unexpected or heightened biological responses to the implant. These may include local (peri-implant) adverse events and potentially systemic manifestations which may impact a patient's quality of life and necessitate medical or surgical intervention. While not considered an implant, dental amalgam is included in this discussion because of its potential for patient and user exposure to mercury compounds and some purported similarities in the adverse biological responses and clinical manifestations elicited by some dental amalgams to that of traditional metal implants.

FDA is convening this Panel to promote an open public discussion of, and seek expert opinion on, currently available scientific and clinical data pertaining to the biological responses to metal implants and dental amalgam and the potential associated clinical sequelae. The Panel will be asked to discuss and provide recommendations regarding:

- The extent immunological responses to certain metals may cause or contribute to device-related local and systemic adverse effects as well as the potential underlying mechanism(s) involved and corresponding clinical manifestations.
- Patient characteristics, metal types, and/or anatomical considerations which may put an individual at higher risk for a heightened immunological response to a metal-containing implant, and methods which may assist in their identification.
- Mitigations which may reduce the risk for unintended immunological responses, including changes to device composition and design.
- The evidentiary gaps in biomedical research and clinical/diagnostic management associated with immunological responses to metal implants.
- The adequacy, conclusions, and evidence gaps identified by a systemic literature review aimed to assess the recent epidemiologic and clinical evidence on adverse health effects reported in relation to occupational or non-occupational exposure to dental amalgam.

The meeting type is a particular matter of general applicability.

Type, Nature, and Magnitude of the Financial Interest(s):

Joshua J. Jacobs, M.D., serves as a temporary non-voting member of the Immunology Devices Panel, which reviews and evaluates data concerning the safety and effectiveness of marketed and investigational devices for use in clinical laboratory medicine including oncology, immunology, and allergy and makes appropriate recommendations to the Commissioner of Food and Drugs.

Dr. Jacobs' employer, Rush University Medical Center of Chicago, Illinois, has a research grant from (b) (4) a firm that manufactures an implantable metal device and will be affected by the particular matter before the Immunology Devices Panel. The title of the grant is: (b) (4)

(b) (4) The (b) (4) is indicated for degenerative disc disease of the cervical spine. The objective of the study is to perform serum metal analysis in patients implanted with these devices. This study is related to the general issues coming before the Panel: measurement of metal released from an implant that can be detected in the bloodstream. Dr. Jacobs' employer is being awarded between \$100,001 - \$300,000 total under the agreement. Dr. Jacobs, the Co-Principal Investigator for the study, does not receive salary support from this grant. The timeframe for this study is January 2017 to December 2020.

Dr. Jacobs' employer has also been awarded two research grants from the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH/NIAMS). The subject of the first grant is: *Corrosion Induced Hip Implant Failure: Synergistic Interactions of Patient, Material, Design, and Surgical Factors*. The purpose of this study is to identify modes

of corrosion that lead to adverse local tissue reactions and how they depend on material, implant design, surgical implantation and patient factors. The study is related to the meeting topic, but not to manufacturers of implants devices, as it focuses on understanding the factors that lead to excessive metal release and local tissue reactions that can lead to failure. Dr. Jacobs' employer is awarded between \$300,001 – \$1,000,000 total under the grant. As a Co-Investigator for the study, Dr. Jacobs does not receive salary support from this grant. The timeframe for this study is September 2016 to August 2021.

The subject of the second grant is: (b) (4). The major goal is to determine if biomarkers can be used for early detection of peri-implant osteolysis and to determine if bone anabolic agents can slow or reverse disease progression. This study is relevant to the topic of the Panel meeting, but not to manufacturers of implants devices, as osteolysis is a manifestation of the immune reaction to debris from orthopedic implants, including metal debris. Dr. Jacobs' employer is awarded between \$300,001 – \$1,500,000 total under the grant. As a Co-Investigator for the study, Dr. Jacobs does not receive salary support from this grant. The timeframe for this study is July 2015 to June 2020.

In addition to the above research grants, Dr. Jacobs serves as an expert witness in two lawsuits which address a matter that is relevant to the general issues coming before the Panel—adverse local tissue reaction and metal allergy. For defendant (b) (4), a firm affected by the particular matter before the Immunology Devices Panel, he provides expert testimony for a lawsuit involving adverse local tissue reaction to metal debris from the (b) (4). His current compensation for service in this case is \$0, but compensation is expected to be \$10,001 - \$25,000 in the next 12 months. The time period for this interest is March 2016 to present. For the law firm LaFollette, Johnson, DeHass, Fesler, and Ames, Dr. Jacobs provides medical malpractice defense as an expert witness in a case involving adverse local tissue reaction purported to be a metal allergy to a metal patellofemoral joint replacement device. The defendant in the case is a physician who is not regulated by, and does not have interests pending before, FDA. His current compensation for service in this case is \$0, but compensation is expected to be \$10,001 - \$25,000 in the next 12 months. The time period for this interest is February 2018 to present.

Dr. Jacobs is identified as a co-inventor of three products that are related to general issues coming before the Panel. Patent applications have been filed for these products. The patents are assigned to Rush University, but not licensed to any firms affected by the particular matter before the Immunology Devices Panel. Dr. Jacobs and his employer are entitled to revenue if the patents are approved and licensed, but they do not currently generate any revenue. They include: Metal Ion Biosensor that provides a method of determining metal ion levels in patents due to corrosion and wear processes of a metallic implant; Biomarkers of Implant Loosening; and a Biomarker for IL-17 for Metal Allergy identification.

#### Basis for Granting the Waiver:

Dr. Jacobs is serving as a temporary non-voting member of the Immunology Devices Panel. The Immunology Devices Panel reviews and evaluates data concerning the safety and effectiveness of marketed and investigational *in vitro* devices for use in clinical laboratory medicine including

oncology, immunology, and allergy and makes appropriate recommendations to the Commissioner of Food and Drugs.

***Dr. Jacobs has unique qualifications and specialized expertise needed for this particular matter.***

Dr. Jacobs is a pioneer in the study of immune reactivity to metals and metal implants. As such, he is nationally and internationally renowned for his research endeavors studying possible pathophysiological mechanisms of metal implant debris and immune system mediation of adverse responses to metal implants, particularly those with orthopaedic applications. His expertise is sought by those in industry as well as academia. He provides a unique combination of subclinical and clinical perspectives that is critical to the Panel's ability to have a productive discussion and successful meeting.

Dr. Jacobs holds several scholastic and research related appointments, including Vice Dean for Research and William A. Hark, M.D. - Susanne G. Swift Professor of Surgery in the Department of Orthopedic Surgery at Rush Medical College, Vice Provost for Research at Rush University, Vice President for Research at Rush University Medical Center, and Adjunct faculty in the Department of Materials Science and Engineering at McCormick Technological Institute.

Dr. Jacobs is a fellowship-trained Adult Reconstructive Orthopaedic Surgeon with an undergraduate degree in Materials Science and Engineering. He specializes in total knee and hip replacement and manages an active research program. Dr. Jacobs began his academic career at Rush University in 1987, and subsequently held a variety of positions including service as the associate Dean for Research Development from 2003 - 2008. Dr. Jacobs has authored nearly 300 scientific publications, more than 40 book chapters, has edited six orthopaedics-related textbooks, and holds a U.S. patent. Dr. Jacobs' major research interests include: total joint replacement, biocompatibility of medical device materials, metal toxicity, material science, and correlation of biocompatibility assessment to clinical outcomes, particularly with regard to metal implants with orthopedic applications. He has had multiple NIH grants studying various aspects of wear and corrosion of joint replacement components, including a very long-term grant entitled "Systemic Effects of Total Joint Replacement".

Dr. Jacobs has served as chair of the Council on Research, Quality Assessment and Technology of the American Academy of Orthopaedic Surgeons (AAOS), is a past president of the Orthopaedic Research Society (ORS) and is past president of the United States Bone and Joint Decade. He currently serves as a trustee of the Orthopaedic Research and Education Foundation, a trustee of the Journal of Bone and Joint Surgery, and the president of the Hip Society. In addition, Dr. Jacobs has chaired multiple National Institute of Health (NIH) study sections and served a four-year term on the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Advisory Council. He has also provided service to the larger medical device community through his standards work and service as a past chair of Committee F04 on Medical and Surgical Materials and Devices for the American Society for Testing and Materials International.

***There is limited expertise available and it is difficult to locate similarly qualified individuals without a disqualifying financial interest.***

Dr. Jacobs' highly regarded national and international reputation along with his decades of experience make him an expert of interest for both industrial and government entities interested in expanding their knowledge of the biocompatibility and post-operative assessment of metal implants. The Center is unable to identify another individual that approaches Dr. Jacobs' level and years of combined subclinical and clinical expertise with respect to metal implants. He will likely be the only requested Panelist that will be able to provide feedback across the full spectrum of areas to be covered such as the extent and mechanism by which certain metals and/or alloys may cause or contribute to immunologically-related events, identification of factors/scenarios that may increase likelihood of an unexpected or exaggerated immunological response to a metal-containing implant, understanding of what diagnostic modalities exist or need to be developed to detect the degree of ongoing changes or predict the course of a reaction, and awareness of other fundamental scientific questions or gaps related to metal implants that were not identified in the CDRH reviews that should be considered for further evaluation. Having a Panelist that understands these diverse areas of interest will be important for assisting with the synthesis of information shared during the Panel meeting and identification of common themes.

***The particular matter is sensitive.***

The particular matter to be addressed by the Panel may be considered sensitive because of public interest in immunological responses to implanted devices. Different people will react to metal implants in different ways. At this time, it is not possible to reliably predict who will experience a reaction, what type of reaction they might have, when the reaction will occur, or how severe the reaction will be. Soft tissue damage from a reaction may lead to pain, implant loosening, device failure, and the need for revision surgery. The interest in this matter reinforces the need to have the appropriate experts on this Panel to provide FDA with important insights and feedback.

***Dr. Jacobs' expertise in this particular matter is necessary in the interest of the public health.***

In the interest of public health, it is important for the Agency to receive relevant input that may improve understanding how certain individuals may react to metal implants in their bodies. Events reported to FDA for these devices have included local (peri-implant) and apparent systemic adverse reactions which have been stated to significantly impact a patient's quality of life and sometimes necessitate medical or surgical intervention. Currently, the lack of consistent definitions and a thorough understanding of the mechanism of reaction, coupled with the wide variety of reported symptoms and lack of adequate diagnostic tools, make it difficult to determine the cause of the reported events and whether or not they are device-related.

CDRH believes that the information discussed and gained from this meeting will improve the safe and effective design, testing, and use of metal implants in general. Dr. Jacobs' combined knowledge and experience of subclinical and clinical assessment of implant-host reactivity and orthopaedic metal implant performance will provide critical expertise for this important discussion. Dr. Jacobs is very familiar with many of the diagnostic/prognostic approaches

currently used to assess total joint replacement patients with metal implants and this should enable him to significantly contribute to the discussions on the limitations of current testing and possibly provide feedback regarding opportunities for augmented or expanded testing for patients with or considering metal containing medical devices.

***Any potential for a conflict of interest is greatly outweighed by the strong need for Dr. Jacobs' expertise in this matter.***

Current evidence, although limited, suggests that some individuals may be predisposed to develop an immune/inflammatory reaction when exposed to select materials such as metals. Both local (near implantation site) and systemic (throughout the body) symptoms have been reported. As an organization that makes regulatory decisions based on science, CDRH is seeking to engage stakeholders (public, scientists, industry, etc.) to gather information and help determine the current state of the science, critical gaps in the existing science that need to be addressed, what approaches should be considered to further our understanding of medical device materials and improve the safety of devices for patients.

Dr. Jacobs' professional expertise and experience are related to some of the general topics that will be discussed during the Panel such as metal implant biocompatibility, metal toxicity, and pre- and post-operative assessments for patients receiving metal implants. Dr. Jacobs' extensive knowledge and experience with immune reactivity to metal implants as a preclinical researcher and an orthopaedic surgeon are the reasons that he is sought out as an expert by various stakeholders within the medical device ecosystem. The meeting discussion should have limited impact on the financial interests reported by Dr. Jacobs. In addition, the meeting topic is one of general applicability and will not focus on any specific company, medical device, or application. Further, Dr. Jacobs is not involved in product development. His very specialized expertise should enable him to significantly contribute to discussions on a variety of topics of interest to the Panel such as possible pathophysiological mechanisms of metal implant debris, immune system mediation of adverse responses to metal implants, and limitations of current pre- and post-operative testing.

Accordingly, I recommend that you grant a waiver for Joshua J. Jacobs, M.D., a temporary non-voting member of the Immunology Devices Panel, from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

The individual may participate, pursuant to 18 U.S.C. § 208(b)(3) – The need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved.

Limitations on the Regular Government Employee's or Special Government Employee's Ability to Act:

