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

DATE: October 3, 2019

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

FROM: Laura E. Bailey, M.S.
Assistant Director, Committee Management and Planning
Division of Management Services, Office of Management
Center for Devices and Radiological Health (CDRH)

Name of Advisory Committee Member: Stephen F. Badylak, D.V.M., Ph.D., 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 to which 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 that 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 that 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):

Stephen F. Badylak, D.V.M., Ph.D., 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. Badylak's employer, the University of Pittsburgh, receives funding for a research contract 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 research funded by (b) (4) involves *in vitro* and preclinical *in vivo* studies that evaluate the host innate immune response to a metal heart valve. The study design was developed by (b) (4) and the University serves as a laboratory to conduct these studies. This study is related to a subtopic of the panel meeting; specifically, the evaluation of biological responses to implanted materials and understanding of normal versus exaggerated responses. Dr. Badylak's employer is awarded between $50,001 – $100,000 total under the agreement. As the Principal Investigator for the study, Dr. Badylak receives between $1,001 to $5,000 in salary support. The period for this study is March 2019 to March 2020.

Basis for Granting the Waiver:

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

Dr. Badylak is a national and international leader in studying host responses to implants and his expertise is sought by those in industry as well as academia. In addition, his expertise in the emerging area of macrophage and T-cell plasticity, and the role of these cells in normal tissue development, wound healing, and response to foreign materials is the type of fundamental science expertise that will be critical to the Agency's ability to have a successful panel meeting.

At the University of Pittsburgh, Dr. Badylak holds several appointments: Professor in the Department of Surgery of the School of Medicine and in the Department of Bioengineering in the Swanson School of Engineering, Deputy Director of the McGowan Institute for Regenerative Medicine, and Director of the McGowan Center for Preclinical Studies.

Dr. Badylak has practiced both veterinary and human medicine and is now fully engaged in research. Dr. Badylak began his academic career at Purdue University in 1983, and subsequently held a variety of positions including service as the Director of the Hillenbrand Biomedical Engineering Center from 1995 - 1998. Dr. Badylak holds over 70 U.S. patents, 300 patents worldwide, has authored more than 380 scientific publications and 50 book chapters, and has recently edited a textbook entitled "Host Response to Biomaterials." He has served as the Chair of several study sections at the National Institutes of Health (NIH), and is currently a member of the College of Scientific Reviewers for NIH. Dr. Badylak is a Fellow of the American Institute for Medical and Biological Engineering, a member of the Society for Biomaterials, a charter member of the Tissue Engineering Society International, past president of the Tissue Engineering Regenerative Medicine International Society (TERMIS) and a Founding International Fellow of TERMIS. Dr. Badylak's major research interests include: naturally occurring biomaterials, including extracellular matrix, and biomaterial/tissue interactions; developmental biology and its relationship to regenerative medicine; relationship of the innate immune response to tissue regeneration; clinical translation of regenerative medicine; and whole organ and tissue reconstruction and regeneration.

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

Dr. Badylak is well known nationally and internationally for his work in the area of implant-host response, and his decades of experience make him an expert of interest for both industrial and government entities. His extensive knowledge and experience in implant-host reactivity is the reason that Dr. Badylak is sought as an expert. This work indicates that Dr. Badylak is very familiar with many of the biocompatibility assessments used in preclinical stages and should enable him to significantly contribute to discussions regarding constraints of current testing and opportunities to address the identified gaps. The Center has not been able to identify another individual that approaches Dr. Badylak's years of experience in tissue engineering and regenerative medicine as well as his knowledge across different intended device applications (e.g., orthopedic, cardiac, gastrointestinal, etc.).

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 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. Badylak's 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 of 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. 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. Badylak's knowledge and experience in implant-host reactivity will provide the necessary expertise for this important discussion. Dr. Badylak is very familiar with many of the biocompatibility assessments used in preclinical stages and this should enable him to significantly contribute to the discussions on the limitations of current testing. In addition, he may be able to provide feedback regarding possible expansion and/or augmented testing associated with metal containing medical devices.

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

The meeting discussion should have little to no impact on the research funding Dr. Badylak's employer receives from (b) (4) . The meeting topic does not involve any premarket issue; rather, the topic is a post-market public health issue associated with metallic or metal containing implants. The questions to be addressed also do not focus on any specific product, device, manufacturer, or application area. Dr. Badylak's extensive knowledge and experience in implant-host reactivity is the reason that he is sought as an expert. It also indicates that Dr. Badylak is familiar with biocompatibility assessment used in preclinical medical device evaluations. His very specialized expertise should enable him to significantly contribute to discussions on the limitations of current testing and ways it may be possible to capitalize on the biological differences between a normal and exaggerated response to an implant for biocompatibility evaluation.

Accordingly, I recommend that you grant a waiver for Stephen F. Badylak, D.V.M., Ph.D., 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:

___**X**____ 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:

___**X**____ Non-voting

_____ Other (specify):

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_____ Denied – The individual may not participate.

/S/ **October 24, 2019**

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

Date