

Panel Discussion Items and Questions

Immunology Devices Panel of the Medical Devices Advisory Committee

November 13-14, 2019

GENERAL DISCUSSION QUESTIONS

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. During your deliberations, please discuss:
 - The local as well as systemic signs or symptoms which you believe are, or may be, biologically and clinically plausible as implant-related responses in a susceptible patient.
 - The major gaps in the scientific understanding of the interactions between components of the innate and adaptive immune systems, and metal implants/inserts or their corrosion products which need to be further elucidated to better understand the possible mechanisms and manifestations of a host's local *and* systemic response.

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)
 - Duration of implantation

At the conclusion of your discussion, please describe key areas of scientific research and innovation which are needed to better understand and/or mitigate the impact of such factors, and how they might be undertaken.

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

At the conclusion of your discussion, please describe key areas of scientific research and innovation which are needed to better understand and/or mitigate the impact of such factors, and how they might be undertaken.

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.

5. Please discuss any next steps that are needed regarding nonclinical biocompatibility assessments of metal implants/inserts with respect to the material's potential to evoke and modulate a host's immune and inflammatory responses.

QUESTIONS SPECIFIC TO DENTAL AMALGAM

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
 - Subpopulations that may be more susceptible to adverse health effects, including children and pregnant women with their developing fetuses
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.
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.

FINAL ITEM

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.