



24-Hour Summary

Immunology Devices Panel Advisory Committee Meeting

November 13th & 14th, 2019

Introduction:

On November 13th and 14th 2019, the Immunology Devices Panel of the Medical Device Advisory Committee met to discuss the topic of immunological responses to metal-containing products regulated as medical devices. The panel focused on metal-containing implants as well as dental amalgam. 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. Dental amalgam was also 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 implants.

General Issues Discussed:

The FDA and their invited presenters provided a summary of the state of currently known science in metal implant related biological responses. The topics covered included metal corrosion, toxicological and immunological mechanisms associated with adverse events, clinical manifestation of adverse events, the current FDA biocompatibility premarket review approach, biomarkers and diagnostic tests for screening patients and diagnosing adverse events, and finally a summary of the science, knowledge and tool gaps.

The panel also discussed device related factors that may increase or decrease an individual's risk of an adverse response to a metal implant. Factors include extent of wear, alloy composition, microstructure, and surface coating of an implant. Panelists all agreed it is important and beneficial for patient safety to have the device packaging labels updated to include a list of the elemental composition of the device.

The panel discussed several difficulties associated with the clinical utility of available diagnostic/prognostic tests for pre- and post-procedural assessment of implant host reactions. These reactions are likely multifactorial and evaluations that can provide more information on device status as well as the patient's biological and immune (innate and adaptive) responses are needed to achieve test results with higher correlation to clinical outcomes. The panel discussed the need for consistency in laboratory testing aimed at elucidating the cause of an individual's adverse, from way patient samples are collected to standardization of the components used. Further, the panel expressed a desire to collect prospective data to provide better information for regulatory and clinical decision-making.

The panel also discussed patient-related factors that could impact an individual's susceptibility to an adverse response to a metal implant. A person's age, medications, gender, and existing medical conditions (e.g. osteoporosis) are some of the characteristics that influence the type of response experienced. In addition, there was discussion on the biological plausibility of systemic immune responses arising from the presence of a metal implant and though some panelists agreed that it was possible, others expressed uncertainty.

The panel also discussed the adverse health impacts resulting from mercury exposure from dental amalgam. The panel recognized that mercury exposure from dental amalgam pose risks to the environment, patients, and health professionals, however felt the increase in the risk of adverse health effects is not clear. The panel recommended dental professionals move away from using mercury containing amalgams to other non-mercury dental implants.

The panel also discussed cross-transformation of mercury species in the human body. The panel discussed the conversion of methylated and non-methylated forms of mercury. One of the concerns is that standard testing does not clearly differentiate between the origin of different types of mercury which poses a knowledge gap.

The consensus recommendation from this advisory committee is that additional information regarding immunological responses to metal-containing medical devices, including dental amalgam, are needed. Though the panel agreed there was a need, it was unclear on the best approach to address it. Registries and/or longitudinal cohorts may be helpful; however the uncommon rates of such clinically meaningful reactions may pose issues related to the size of the cohorts needed. The panel recommended to consider the utility of developing an appropriate animal model, retrieval studies, as well as tissue and blood testing in patients who have had immunological responses. The panel, as well as the industry representative agree it is important that manufacturers disclose the composition of metal devices.

Open Public Hearing:

Patients, advocates, science and medical researchers and industry reps presented information and experiences covering the impact of adverse events to health and quality of life, and also highlighted the scientific challenges in connecting systemic adverse events to quantifiable evidence. They discussed the challenges in the medical provider community in addressing systemic, nonspecific adverse effects. Many patients expressed hardships following implantation of their metal implant and/or dental amalgam. Concerns were also raised about possible disparities in the use of amalgam in lower income and minority communities. Those in opposition to amalgam advocated for restrictions in its use to exclude potentially vulnerable populations such as children and pregnant and breastfeeding women. Industry highlighted the benefits that the majority of patients receive from existing metallic implants and the challenges of introducing new materials to replace some of the metals. Advocates of dental amalgam also highlighted the benefits of dental amalgam.

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