October 28, 2019

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-N-3767—Immunology Devices Panel of the Medical Devices Advisory Committee; Request for Comments

To Whom It May Concern:

On behalf of our 163,000 dentist members, we are pleased to respond to your request for information about the relative immunological safety of metal-containing implants, including amalgam restorations. We offer these comments in response to your Federal Register notice of October 1, 2019 (84 FR 52111).

Recent post-market issues with some metal-on-metal orthopedic implants and gynecological metal-containing implants have raised concerns regarding the potential for some patients to develop sensitivities and/or immunologic responses. In response, the Food and Drug Administration has convened the Immunological Devices Panel to obtain expert opinion on the immunological safety of these devices. Though not an implant, the panel is including dental amalgam in its discussions. The liquid metal alloy is used to fill cavities caused by tooth decay.

The scientific literature has repeatedly affirmed that dental amalgam is one of the safest and most affordable and durable materials available to restore damaged teeth. There are benefits and drawbacks to all dental materials, but dental amalgam is more affordable and offers longer lasting results than the alternatives.

Enclosed you will find our detailed comments about the safety of dental amalgam, including our findings about any immunological effects. Among other things, we found that:

- There is no evidence of amalgam being associated with systematic immunologic or other adverse effects beyond the approximately 1 percent of the population that may have local allergic responses.

- A series of comprehensive and systematic reviews of the literature have not found dental amalgam to pose serious health risks to the general public.

- Eliminating dental amalgam as a restorative treatment would exacerbate oral health disparities due to the limited selection of other restorative materials.

Thank you for providing us the opportunity to comment. We are confident that sound science will guide your deliberations about one of the safest and most affordable and durable dental materials available: dental amalgam.
If you have any questions, please contact Mr. Robert J. Burns at 202-789-5176 or burnsr@ada.org.

Sincerely,

/s/ Chad P. Gehani, D.D.S.  
President

/s/ Kathleen T. O’Loughlin, D.M.D., M.P.H.  
Executive Director

CPG:KTO:rjb
Enclosure
The American Dental Association is pleased to offer the following detailed comments regarding the relative immunological safety of metal-containing implants, including amalgam restorations.

**Histological Responses to Metals used in any type of implant**

**Dental Amalgam**

Dental implants, have been defined by the FDA classification panel as “a device that is surgically placed into, or in opposition to, the maxilla or mandible and which protrudes through the mucosa of the oral cavity” (45 FR 85964). Although dental restorative materials, including amalgam, fulfill the first caveat, they do not protrude through the mucosa of the oral cavity, and thus fail to meet the criteria of being a dental implant. Thus, rather than a dental implant, dental amalgam is considered an external communicating device (ISO 10993/7405) and is not defined as an implanted device by the FDA.¹

**Responses to the 5 topics listed in the Federal Register**

1. **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.**

   Allergy is the most common immunological response to dental amalgam and is experienced by less than 1 percent of people with amalgam restorations. This reaction is local, manifest as contact dermatitis, oral lichenoid lesions, gingivitis, and stomatitis.² However, in terms of more systemic adverse effects, while a systematic review of the literature finds evidence that mercury is an environmental factor affecting autoimmunity, they found no conclusive evidence linking mercury from dental amalgams in development, severity, or perpetuation of autoimmune disease.³

2. **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 that may assist in their identification.**

   There may be genetic factors affecting mercury kinetics and excretion, and a search of the National Library of Medicine’s online resource of human genes and genetic phenotypes for mercury returned six entries. Of these, four may have a role in an individual’s response or exposure to mercury. PARK7 binds various ions, including mercury, and has a role in control of intracellular oxidation; and three aquaporin genes (AQP1, AQP4 and AQP7) are involved in mercury sensitive fluid channels. Though none have been explicitly identified, it is possible that polymorphisms in these four genes exists which might affect mercury excretion and thus overall exposure. However, there is no actual data indicating the existence of genetic polymorphisms affecting immunologic responsiveness to amalgam.
3. **Mitigations that may reduce the risk for unintended immunological responses, including changes to device composition and design.**

Although rare, amalgam-related oral mucosa reactions occur in as many as 1% of people with amalgam restorations. It has been suggested that they derive from an antigen-mediated response. Although or not a true hypersensitivity to amalgam can be demonstrated, amalgam removal is commonly associated with partial or complete lesion resolution in these rare occurrences.

4. **The evidentiary gaps in biomedical research and clinical/diagnostic management associated with immunological responses to metal implants.**

Clinical data to define populations that may have enhanced risk from dental amalgam as well as clinical data on adverse health effects in identified sensitive populations is limited. However, it is critical to understand that well-designed studies, not just studies, are needed to evaluate those parameters. To best address this clinical dilemma, reported outcomes must focus on clinically relevant findings, not merely readily measurable parameters.

5. **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.**

Notwithstanding the individuals and citizen groups who have concluded, without scientific validity, that any number of adverse health outcomes derive from dental amalgam restorations, careful examination of the evidence of dental amalgam safety has yielded remarkably consistent findings. There have been a number of reports issued by a variety of agencies under U.S. Department of Health and Human Services (DHHS), from the early 1990s through 2019 that have reviewed and issued scientific assessments on the effects of mercury exposure from dental amalgam. Although conducted by different entities under DHHS, and approaching questions varying in scope and focus, the conclusions in all of the reports have been uniform, finding that there was not adequate data demonstrating direct harm from dental amalgam restorations.

Given that the most recent review of the literature examining the evidence for there being adverse health effects from dental amalgam was published by the FDA in September 2019 along with the consistency of findings from comprehensive examination of the literature over time, it is, in the opinion of the American Dental Association, redundant for the Immunology Devices Panel to conduct its own review of this same literature. A list of the previous reports prepared under the auspices of DHHS with a synopsis of their scope and findings is as follows:

1. The first of these, published in 1993, was managed by the DHHS Subcommittee on Risk Management/Committee to Coordinate Environmental Health and Related Programs (CCEHRP). While asserting that additional research was warranted, it concluded that mercury from dental amalgam did not pose a serious health risk to the general public.

2. The second was an update of the 1993 policy, published in 1997 which reviewed all the studies submitted in citizen petitions in response to the 1993 report. It concluded that the data was insufficient to support claims that individuals with dental amalgam restorations experience adverse health effects.
3. The third report funded by the National Institutes of Health (NIH) reviewed the available, high-quality, peer-reviewed studies published between 1996-2000 and again concluded that there was insufficient evidence to support a correlation or causal relationship between dental amalgam restorations and the various complaints attributed to this material.⁸

4. The fourth report was a 2009 white paper with an addendum prepared to include all of the Panel’s comments issued by the FDA Dental Products Panel and the Peripheral and Central Nervous System Drugs Advisory Committee.⁹,¹⁰ It evaluated the peer-reviewed literature since 1997 and found no information that would change the conclusions of earlier assessments. It acknowledged that clinical data were limited though positive that dental amalgams would not be associated with adverse health effects even in sensitive populations.

5. The fifth report was a systematic review, included as Appendix 1 of the September 2019 FDA Systematic Literature Review¹¹ examining the peer-reviewed epidemiologic literature published in 2008-2010 suggesting that while there were possible associations between exposure to dental amalgams and adverse health outcomes, none of the reviewed studies provided conclusive evidence on the causal associations with dental amalgam. It also acknowledged that the clinical data addressing sensitive populations was limited.

6. In 2010, the FDA convened an advisory committee meeting of the Dental Products Panel in response to citizen petitions received by FDA following publication of the draft and final rule (74 FR 38686) published in July 2009 which reclassified the components of dental amalgam (i.e., mercury and amalgam alloy) into a single classification to comply with an objective of the 1993 PHS report making dental amalgam a class II medical device.

After discussion of the uncertainties with the available assessments as well as the potential for there being certain populations with greater sensitivity to mercury exposure, the conclusions in the response letters from the FDA indicated that they did not find the available information sufficient to support the claim that the risks from mercury vapor release from dental amalgam justified a ban.

7. In 2012, FDA conducted a systematic assessment which is included as Appendix 2 of the September 2019 FDA Systematic Literature Review,¹¹ examining the peer reviewed literature on possible risks from exposure to mercury from dental amalgams among three sensitive groups. For pregnant women and their developing fetuses, they found inconsistent correlations between maternal dental amalgams and mercury levels in breast milk or biofluids from breastfed infants and young children. Other this inconsistent observation, none of three sensitive groups—pregnant women and the developing fetuses; children under six years of age; and nursing women and breast fed infants—showed any association between dental amalgams and adverse health outcomes. Given the limited number of appropriately designed studies, additional research was recommended.

8. In 2019, the FDA conducted a systematic literature review to update what was known about all health outcomes in all populations since the literature review conducted to inform the 2009 final rule, (74 FR 38686) (i.e., #6 above) and thus included studies published from 2010 -2019. It found no increased risks of adverse systematic effects
(e.g., neurologic, renal) have been clearly established. Further, they concluded that the existing evidence on candidate biomarkers was insufficient to support their use in clinical practice or regulatory considerations.\textsuperscript{11}

In addition to the multitude of reports developed by agencies under DHHS, a report comparing the safety and efficiency of composite resin and dental amalgam restorations was prepared in 2018 by the Canadian Agency for Drugs and Technology in Health (CADTH). While CADTH does not endorse specific treatments or products, they sought to answer the question of whether dental amalgam should continue to be used in Canada. They found that the “best available evidence indicates that compared with composite resin, amalgam restorations appear to be more clinically efficacious and as safe, while costing less”….and thus concluded “there is no clear reason to discontinue the use of dental amalgam in Canada.”\textsuperscript{12}

A commentary piece in the October issue of the Journal of the American Dental Association\textsuperscript{13} reminds readers that the United States is among the signatories to the Minamata Convention, an international environmental treaty which includes as a goal, a phase down in the use of the dental amalgam. While the preferred approach to reducing use of dental amalgam is elimination of tooth decay or dental caries, as long as dental caries one of the most prevalent disease in humans,\textsuperscript{14,15} there remains the need for it to be treated. Although there are current alternatives to dental amalgam, due to characteristics such as their cost, technique-sensitive use, and the length of time they are retained, there will be continued public demand for amalgam restorations.

References


