U.S. FOOD & DRUG ADMINISTRATION

May 26, 2022

Charles G. Brown
Consumers for Dental Choice
316 F Street, N.E., Suite 210
Washington, DC 20002

Re: Citizen Petitions, Final Response
Docket Nos.: FDA-2015-P-3876, FDA-2016-P-1303,
FDA-2016-P-3674, and FDA-2017-P-2233

Dear Mr. Brown:

This letter responds to your citizen petitions[1] filed on October 20, 2015,[2] May 17, 2016,[3] November 1, 2016,[4] and April 7, 2017,[5] concerning the need for additional warning and labeling requirements for amalgam use in dentistry.

*Decision Summary*

Having reviewed the Petitions, the supplemental information you submitted, and the public comments included in the public dockets established for the Petitions, under 21 CFR 10.30(e)(3) FDA grants the Petitions in part; otherwise, the Agency is denying your requests for the reasons described below.

[1] In this letter, the petitions are referred to individually as CP-1, CP-2, CP-3, or CP-4, respectively, or as "the Petition" generically depending on the context, and as "the Petitions" collectively when referring to all or more than one of the petitions.

[2] See https://www.regulations.gov (search for document FDA-2015-P-3876-0001) (CP-1)).

[3] See *id.* (search for document FDA-2016-P-1303-0001) (CP-2)).

[4] See *id.* (search for document FDA-2016-P-3674-0001) (CP-3)).

[5] See *id.* (search for document FDA-2017-P-2233-0001) (CP-4)).

## A. Actions Requested

CP-3 and CP-4 request the Food and Drug Administration (FDA, we, or the Agency) "to warn against [dental] amalgam use in children, pregnant women, and other sensitive populations"[6] and "to stop amalgam use in children under age 15, pregnant women, and breastfeeding mothers,"[7] respectively, by taking the following three actions: (i) issue a safety communication to dentists, parents, and dental consumers; (ii) require manufacturers to distribute patient labeling that includes the warnings; and (iii) develop and implement a "public relations campaign…against amalgam use" in these vulnerable populations. CP-1 also requests that FDA implement a media and education campaign to promote mercury-free dental filling materials;[8] and CP-2 requests that FDA amend our regulations to require manufacturers to distribute patient labeling that specifies amalgam's mercury content, risks, damage to tooth structure, damage to the environment, and the benefits of mercury-free filings.[9] CP-1 also requests FDA to amend the dental amalgam regulation[10] and to revoke "the sections of the mercury amalgam rule promoting amalgam use … [or] opposing the phase down of amalgam use."[11]

As reasons for FDA to take these requested actions, the Petitions cite U.S. Government acceptance of the U.N. Minamata Convention on Mercury (referred to in this document as the Minamata Convention or simply the Convention),[12] the actions of the European Union (EU) and other countries, European Commission and World Health Organization findings, FDA's 2006 and 2010 advisory committee panel meetings, and various scientific studies, among other sources.

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[6] CP-3, at 1.

[7] CP-4 at 1.

[8] CP-1 at 1.

[9] CP-2 at 1.

[10] 21 CFR 872.3070.

[11] CP-1 at 1.

[12] U.S. Department of State, Treaties in Force, Jan. 1, 2020, TIAS 17-816, at 527, signed by the U.S. on Nov. 6, 2013 and available at https://www.state.gov/wp-content/uploads/2020/08/TIF-2020-Full-website-view.pdf; ____ U.N.T.S.____, entered into force on August 16, 2017 and available at https://treaties.un.org/doc/Treaties/2013/10/20131010%2011-16%20AM/CTC-XXVII-17.pdf. The Convention and the U.S. Government commitments under it are discussed in Section D.4 of this document.

## B. Legal and Regulatory Background

The Federal Food, Drug, and Cosmetic Act, as amended (the FD&C Act),[13] authorizes the Agency to regulate medical devices, including by classifying and establishing controls for them to "provide reasonable assurance of the safety and effectiveness of the device."[14] In determining the safety and effectiveness of a device for purposes of classification, the Agency is required to, among other relevant factors, "weigh[…] any probable benefit to health from the use of the device against any probable risk of injury or illness from such use."[15]

FDA only considers valid scientific evidence in assessing safety and effectiveness,[16] which includes evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, among others.[17] Such evidence does not include isolated case reports, random experiences, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions.[18] There is a reasonable assurance that a device is safe "when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks."[19]

The Agency also has specific authority to restrict the sale, distribution, or use of a device by regulation if "there cannot otherwise be reasonable assurance of its safety and effectiveness."[20]

As a medical device, dental amalgam is subject to the general controls of the FD&C Act, including prohibitions against misbranding, such as false and misleading labeling of a device.[21]

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[13] 21 U.S.C. 301, et seq.

[14] Section 513(a)(1) of the FD&C Act.

[15] Section 513(a)(2)(C) of the FD&C Act; see also 21 CFR 860.7(b).

[16] 21 CFR 860.7(c)(1).

[17] 21 CFR 860.7(c)(2).

[18] *Id*.

[19] 21 CFR 860.7(d)(1).

[20] Section 520(e) of the FD&C Act.

[21] See section 513(a)(1)(A) of the FD&C Act. General controls are the device controls authorized by or under the following provisions of the FD&C Act: Sections 501(adulteration), 502 (misbranding), 510 (registration), 516 (banned devices), 518 (FDA notification), 519 (records and reporting), or 520 (general device requirements, including good manufacturing

As a class II device, dental amalgam is also subject to special controls, including certain labeling for dental professionals on the properties and proper use of the device, as described in 21 CFR 872.3070(b).[22]

The U.S. Government is committed to comply with the Minamata Convention, which, among other things, identifies dental amalgam as a mercury-added product contributing to global pollution. When taking regulatory actions intended to have the force of law, however, FDA must act in accordance with the rulemaking procedures of the Administrative Procedure Act[23] and within the scope of the legal authorities granted to the Agency under the FD&C Act, among other authorities. The FD&C Act could be amended through an international agreement, such as the Minamata Convention, if the agreement were ratified or approved by Congress.[24] However, the U.S. Department of State did not submit the Convention to Congress for ratification as a treaty;[25] and Congress did not thereafter enact special legislation to implement any of the U.S. Government's undertakings identified in the Convention. There is no Federal statutory restriction or prohibition pertaining to the mercury content of dental amalgam in the U.S.

### C. Factual Background

#### 1. Our September 2020 Safety Communication, the Recommended Informational Brochure for Patients, and FDA Website Updates Concerning Dental Amalgam Use in Certain Vulnerable Populations

FDA may issue safety communications when there are emerging signals about a device.[26] A signal represents a new potentially causal association, or a new aspect of a known association, between a medical device and an adverse event or set of adverse events.

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practice (GMP) requirements and restrictions on sale, distribution or use). Section 513(a)(1)(A)(i) of the FD&C Act.

[22] See Class II Special Controls Guidance Document: Dental Amalgam, Mercury, and Amalgam Alloy – Guidance for Industry and FDA Staff (July 2009), available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073311.htm.

[23] 5 U.S.C. 701 *et seq*., see 21 CFR 10.40.

[24] See Medellin v. Texas, 552 U.S. 491, 526-27 (2008).

[25] U.S. Dept. of State, "United States Joins Minamata Convention on Mercury" (press release), Nov. 6, 2013, available (archived content) at https://2009-2017.state.gov/e/oes/eqt/mercury/index.htm, and Discussion section below.

[26] See FDA guidance document entitled "Public Notification of Emerging Postmarket Medical Device Signals ('Emerging Signals'); Guidance for Industry and FDA Staff" (December 2016),

In September 2020, the Agency issued a Safety Communication[27] concerning dental amalgam use in certain vulnerable populations, introduced an Informational Brochure for patients about dental amalgam,[28] and updated the FDA webpages concerning dental amalgam[29] and dental caries treatment options.[30] We reiterated our previous finding that there remains scientific uncertainty about the potential for adverse health effects from dental amalgam when used in certain high-risk populations.[31] We also clarified that, unless medically necessary, FDA does not recommend removal or replacement of existing amalgam fillings in good condition. In these communications, we recommend that non-mercury restorations be used, when possible and appropriate, in certain vulnerable subpopulations that may be at greater risk from the potential adverse health effects of mercury exposure associated with dental amalgam use. The Safety Communication and our updated webpages identify the following vulnerable populations with respect to dental amalgam:

- Pregnant women and their developing fetuses;
- Women who are planning to become pregnant;
- Nursing women and their newborns and infants;
- Children, especially those younger than six years of age;
- People with pre-existing neurological disease;
- People with impaired kidney function; and

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available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm479248.pdf.

[27] "Recommendations About the Use of Dental Amalgam in Certain High-Risk Populations," September 24, 2020, available at https://www.fda.gov/medical-devices/safety-communications/recommendations-about-use-dental-amalgam-certain-high-risk-populations-fda-safety-communication.

[28] "Information for Patients About Dental Amalgam Fillings," revised September 2020, available at https://www.fda.gov/media/142415/download.

[29] "Dental Amalgam Fillings," revised September 2020, available at https://www.fda.gov/medical-devices/dental-devices/dental-amalgam-fillings.

[30] "Treatment Options for Dental Caries," revised September 2020, available at https://www.fda.gov/medical-devices/dental-amalgam-fillings/treatment-options-dental-caries.

[31] In November 2019, the Agency convened an Immunology Devices Panel to discuss the potential adverse biological responses and clinical manifestations attributable to trace materials released from embedded, metal-containing medical devices, such as dental amalgam. See the meeting information and event materials available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-13-14-2019-immunology-devices-panel-medical-devices-advisory-committee-meeting-announcement.

- People with known heightened sensitivity (allergy) to mercury or other components of dental amalgam.

## 2. Other Factual Background

Determining the safety and effectiveness of a device for classification purposes involves a complex assessment of risk and benefit in accordance with the FD&C Act.[32] Dental amalgam has several advantages as a restorative material. It has a broad range of applicability in clinical situations, is easy to use, and is relatively insensitive to variations in handling technique and oral conditions. It also provides high strength, durability, and marginal integrity – features that may help prevent recurrent decay.[33] However, dental amalgam contains elemental mercury and releases mercury vapor. At high enough levels, mercury vapor is a neurotoxicant and can have adverse health effects. A central question in assessing the risk of dental amalgam is whether the levels of mercury vapor released from dental amalgam are associated with adverse health effects and, if so, which population groups might be at greater risk for experiencing potential adverse health effects from this exposure.

Prior to issuing the September 2020 Safety Communication and over the past 20 years, FDA has taken other actions to ensure a reasonable assurance of safety and effectiveness for dental amalgam. In 2002, FDA issued a proposed rule that proposed reclassification of dental amalgam and its components from class I into class II, subject to special controls.[34] Following the proposed rule, FDA published a White Paper in 2006 that reviewed the literature on the safety of mercury vapor exposure from dental amalgam and found that exposure to mercury vapor from dental amalgam is not associated with adverse health effects in the general population.[35] Later in 2006, FDA sought the advice of external experts at a joint meeting of the Dental Products Panel

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[32] See section 513(a)(2)(C) of the FD&C Act and 21 CFR 860.7(b)(3); see also FDA guidance document entitled "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications" (Aug 2019), available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm517504.pdf.

[33] Dental Amalgam: A Scientific Review and Recommended Public Health Service Strategy for Research, Education and Regulation; Public Health Service, U.S. Department of Health and Human Services, January 1993 (PHS Scientific Review).

[34] 67 FR 7620 (Feb 20, 2002).

[35] FDA, White Paper (presented August 2006 in Draft Form and finalized July 2009), available at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/ucm171117.htm.

and the Peripheral and Central Nervous System Drugs Advisory Committee.[36] Responding to the recommendations of the 2006 panel and a review of over 1,800 public comments regarding dental amalgam,[37] in 2009, FDA updated its White Paper with an Addendum to the White Paper.[38] In the Addendum, we found no new information that would change the conclusions of earlier FDA assessments. In August 2009, FDA finalized the proposed rule by reclassifying dental amalgam from class I into class II based on the findings detailed in the finalization of our most recent rulemaking proceeding on the matter (the Final Rule).[39]

Regarding amalgam use in vulnerable populations, FDA acknowledged in the Final Rule that there is very limited to no clinical information available regarding long-term health outcomes in pregnant women and their developing fetuses, and children under the age of six, including infants who are breastfed[40] and that certain individuals with a pre-existing hypersensitivity or allergy to mercury may be at greater risk from the potential adverse health effects from mercury vapor released from dental amalgam.[41] In conjunction with the Final Rule, FDA published special controls for dental amalgam in the form of a guidance document (the Dental Amalgam Special Controls Guidance).[42] In the Final Rule, FDA concluded that, in combination with the general controls of the FD&C Act, the special controls sufficiently mitigate the risks of dental amalgam to provide a reasonable assurance of the safety and effectiveness of the device.

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[36] The transcript and meeting minutes for this panel meeting are available at https://wayback.archive-it.org/7993/20170404141646/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/ucm428701.htm.

[37] FDA Docket FDA-2006-N-0352.

[38] FDA, Addendum to FDA Draft White Paper, Addendum Review in Response to Advisory Panel Comments and Recommendations, July 2009, available at http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/UCM173908.pdf.

[39] Final Rule for Dental Amalgam, 74 FR 38686 (Aug 4, 2009), available at https://www.gpo.gov/fdsys/pkg/FR-2009-08-04/pdf/E9-18447.pdf.

[40] 74 FR at 38692.

[41] 74 FR at 38694.

[42] Class II Special Controls Guidance Document: Dental Amalgam, Mercury, and Amalgam Alloy – Guidance for Industry and FDA Staff (July 2009), available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073311.htm.

Shortly before and following issuance of the Final Rule in 2009, FDA received several petitions that requested the Agency to, among other things, contraindicate dental amalgam use in vulnerable populations.[43] After receiving these petitions, FDA engaged experts in toxicology and risk assessment to review the information provided in the petitions and in the available scientific literature on amalgam and mercury allergy. In December 2010, FDA convened a meeting of the Dental Products Panel to gather input from the panel on exposure assessments for mercury vapor from dental amalgam, reference exposure levels (RELs) for mercury vapor, and the adequacy of the clinical studies on dental amalgam.[44] In particular, the panel discussed the known uncertainties associated with the risk assessments for dental amalgam and reconsidered the current RELs, in this instance the reference concentration (RfC) derived by the U.S. Environmental Protection Agency (EPA) in 1995.[45] The panel observed that there may be certain populations that are more vulnerable to mercury exposure than the general population. Overall, the panel found that a review of the available literature showed there is no causal link between the use of dental amalgam and various clinical diseases in the general population.

In 2019, FDA undertook a systematic review of the more recent epidemiological evidence for adverse health effects associated with the use of dental amalgam. Based on this review of updated scientific literature, FDA determined that none of the studies published in 2010 up to that timeframe in 2019 contain new information that would change the FDA conclusions, as discussed in the Final Rule, about the health effects of dental amalgam.[46]

## D. Discussion

### 1. Requests for a Safety Communication and to Implement a Public Information Campaign to Warn Against the Use of Dental Amalgam in Vulnerable Populations

[43] Citizen petitions in dockets FDA-2009-P-0610 (formerly FDA-2008-N-0163), FDA-2009-P-0357, and FDA-2014-P-0907 (previously FDA FDA-2008-N-0163). On January 27, 2015, FDA issued its responses to these petitions (FDA-2014-P-0907-0005, available at https://www.regulations.gov/document?D=FDA-2014-P-0907-0005; FDA-2009-P-0610-0017, available at https://www.regulations.gov/document?D=FDA-2009-P-0610-0017; and FDA-2009-P-0357-008, available at https://www.regulations.gov/document?D=FDA-2009-P-0357-0008), in which we provided analysis of a number of scientific articles presented in the petitions.

[44] See footnote 36 of this document, concerning transcripts and meeting materials for this panel meeting.

[45] See EPA, "Integrated Risk Information System (IRIS) Screening-Level Literature Review" – Mercury, elemental, 2002 (EPA IRIS Review).

[46] FDA, "Epidemiological Evidence on the Adverse Health Effects Reported in Relation to Mercury from Dental Amalgam: Systematic Literature Review (2010-Present)," September 2019, available at https://www.fda.gov/media/131151/download.

In CP-3 and CP-4, you request that FDA issue a safety communication and develop and implement a public information campaign to warn dentists, dental associations, parents, and dental consumers against amalgam use in children, pregnant women, and other vulnerable populations and to stop amalgam use altogether in children, pregnant women, and breastfeeding mothers.[47] CP-4 specifies that the requested public information campaign should include FDA's website, social media, press releases, and a press conference. In CP-4, you clarify that your requests to stop amalgam use in children pertain to children up to age 15.

These two Petitions quote the Final Rule reclassifying dental amalgam, which states: "The developing neurological systems in fetuses and young children may be more sensitive to the neurotoxic effects of mercury vapor."[48] Additionally, you assert that the Final Rule acknowledges there is "very limited to no clinical information available" regarding long-term health outcomes in children under the age of six, developing fetuses, and infants who are breastfed."[49] Your Petitions subsequently conclude that (i) experts have found that amalgam poses a substantial risk to these populations[50] and that (ii) FDA has admitted these populations are "at risk."[51] However, by confounding the higher *relative* risk for certain vulnerable populations and the unknown effects of amalgam due to the lack of scientific evidence, the cited evidence does not support these conclusions. In addition, by failing to recognize there are situations where dental treatment is needed but non-mercury restorations are not possible or appropriate, your Petitions also conclude without sufficient basis, that because there are mercury-free alternatives, "amalgam offers [these vulnerable populations] no benefits" over the alternatives or that such benefits are irrelevant.[52]

Although we are partially granting your requests in this document, we disagree with the assessment of the evidence you submitted in support of the granted requests. In CP-3 and CP-4 you cite the majority vote of scientific advisory panelists and claim that they "condemned" the conclusions of FDA's 2006 White Paper.[53] In CP-4, you additionally cite a 2012 study (Woods

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[47] We understand your request to contraindicate the use of dental amalgam in nursing mothers concerns the potential risks to breastfed infants.

[48] 74 FR at 38694.

[49] *Id*.

[50] CP-3 at 1-2, and CP-4 at 3-4.

[51] CP-3 at 2-3, and CP-4 at 4-5.

[52] CP-3 at 3, and CP-4 at 4.

[53] CP-3 at 2, and CP-4 at 3. The September 2006 advisory panel did not "condemn" FDA for its position on dental amalgam, but rather the panel stated that FDA's White Paper was not a complete review of the literature regarding the effects of mercury exposure from dental amalgam. At the meeting, FDA asked the panel if the White Paper presented the current state of

et al.)[54] finding neurotoxic effects associated in children with the CPOX4 genetic variant and a 2016 study (Yin et al.)[55] finding high mercury concentrations in the blood of subjects with dental restorations.[56] In CP-3 and CP-4 you cite a 2012 European Commission report (the 2012 EU Environmental Report)[57] for the propositions that, for children, the longevity of amalgam restorations is irrelevant and that other studies disprove mercury-free fillings do not last as long.[58] You rely on a 2005 study (Hickel et al.)[59] to prove the higher failure rate of amalgam

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knowledge about the exposure and health effects related to dental amalgam and if the conclusions of the White Paper were reasonable, to which the panel voted "no" to each question. Some of the reasons cited by the majority were that the White Paper was limited in scope and had knowledge gaps particularly regarding exposure limits and that no conclusion could be drawn based on the limited search that was conducted. The panel had a number of recommendations for FDA, including that the White Paper should be revisited to include a broader search, data from other countries, a review of data on vulnerable subpopulations, and should provide the rationale for study exclusion. See footnote 36 of this document, concerning transcripts and meeting materials for this panel meeting. As discussed in Section C.2 (Other Factual Background) above, in response to the recommendations of the 2006 panel and a review of over 1,800 public comments regarding dental amalgam, FDA updated its White Paper with the Addendum to the White Paper in 2009 but found no new information that would change the conclusions of earlier FDA assessments that exposures to mercury vapor from dental amalgam are not associated with adverse health effects.

[54] James S. Woods et. al., Modification of neurobehavioral effects of mercury by a genetic polymorphism of coproporphyrinogen oxidase in children, NEUROTOXICOLOGY AND TERATOLOGY 34 (2012), 513-521.

[55] Yin et. al., Associations of blood mercury, inorganic mercury, methylmercury and bisphenol A with dental surface restorations in the U.S. population, NHANES 2003–2004 and 2010–2012, Ecotoxicity and Environmental Safety (2016). See our discussion of the Yin et al. (2016) findings in Section D.2a below.

[56] CP-4 at 3.

[57] BIO Intelligence Service (BIOIS), Study on the potential for reducing mercury pollution from dental amalgam and batteries, Final report prepared for the European Commission-DG ENV, July 2012, available at https://ec.europa.eu/environment/chemicals/mercury/pdf/final_report_110712.pdf, p. 69. See our discussion of the 2012 EU Environmental Report in Section D.2a below.

[58] CP-3 at 3 n.8, and CP-4 at 4-5.

[59] Reinhard Hickel et al., Longevity of occlusally-stressed restorations in posterior primary teeth, AMERICAN JOURNAL OF DENTISTRY, Vol. 18, No. 3, June 2005, available at http://www.amjdent.com/Archive/2005/Hickel%20-%20June%202005.pdf (see Figure 1 and Table 11). See our discussion of the Hickel et al. (2005) study in Section D.2a below.

restorations in children, as compared to mercury-free alternatives.[60] Based on this evidence, in CP-3 you conclude that FDA needs to issue a safety communication and to develop and implement a public information campaign to warn dentists, parents, and dental consumers against the use of dental amalgam in certain vulnerable populations.[61]

As mentioned above, the Agency issued a Safety Communication in September 2020, introduced an Informational Brochure for patients, and has updated the FDA webpages to inform the public of the potential risks of using dental amalgam in certain high-risk populations. For the range of vulnerable populations that the Petitions have identified, the Safety Communication recommends against the use of dental amalgam when non-mercury restorations are possible and appropriate as determined by the dental professional treating the individual patient. The roll-out for the Safety Communication included public communications featuring FDA's website, social media, and press releases, consistent with your requests, plus the introduction of an Informational Brochure for patients and an infographics presentation in two languages in simplified terms to inform the public about the greater risk of potential adverse effects of dental amalgam, including pregnant women, breast-feeding mothers, and other vulnerable populations. However, FDA disagrees with your claim in CP-4 that FDA must take additional actions in the nature of a campaign "to stop amalgam use" altogether in certain vulnerable populations.[62] As discussed herein, there remains scientific uncertainty about the potential for adverse health effects from dental amalgam when used in certain high-risk populations. Additionally, there are situations when a dental profession may determine that non-mercury restorations are not possible or appropriate for treating their patients. Therefore, FDA does not believe that the requested warnings and/or a public campaign to stop amalgam use are necessary or appropriate at this time.

*Partial Granting of the Petitions*

We are partially granting your Petitions' requests to the extent of FDA's already issued safety communication providing information to dentists, dental associations, parents, and dental consumers regarding potential risks of dental amalgam use by vulnerable populations and use of non-mercury restorations when possible and appropriate, as identified in the September 2020 Safety Communication.

In several respects as discussed below, the Petitions fail to provide information that would cause FDA to determine that additional actions, such as the proposed public campaign to stop amalgam use in dentistry, are necessary or appropriate. We are therefore denying your requests for additional warnings and a public campaign to stop amalgam use or otherwise to contraindicate amalgam use in vulnerable populations.

[60] CP-3 at 3 n.9, and CP-4 at 5 n.25 and 13 n.75.

[61] CP-3 at 1.

[62] CP-4 at 1.

## 2. Requests for Contraindication against Dental Amalgam Use

In CP-3 and CP-4 you request FDA to take certain measures "to stop amalgam" use, by means of contraindications against amalgam use in children, pregnant women, and other sensitive populations.[63] In support of your requests, you state that in 2010 the FDA panelists expressed the need for contraindications against amalgam use in pregnant women.[64] The December 2010 advisory panel discussed that there may be certain populations that are more vulnerable to mercury exposure than the general population. With that in mind and irrespective of some of the dissenting panelists' views, both the panel and our 2019 systematic review of scientific literature[65] found that the available evidence shows there is no causal link between the use of dental amalgam and various clinical diseases in the general population.

Contraindications against using a device are limited to those situations in which the device should not be used because the risk of use clearly outweighs any possible benefit.[66] The benefits of dental amalgam include strength, durability, marginal integrity, suitability for large surfaces and wet environments, and ease of use.[67] In the Dental Amalgam Special Controls Guidance,[68] FDA identified the risks to health of dental amalgam to be exposure to mercury, allergic response including adverse tissue reaction, contamination, mechanical failure, corrosion, and use error. In the Final Rule, FDA reviewed the available valid scientific evidence for potentially vulnerable subpopulations and determined that a contraindication is warranted only "in persons with a known mercury allergy,"[69] for which FDA has previously recommended a contraindication.[70]

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[63] CP-3 at 2, and CP-4 at 3.

[64] *Id*.

[65] See Section D.7 (Review of Scientific Literature) and the accompanying text cited in footnote 46 of this document).

[66] FDA guidance document entitled "Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers" (April 2001) ("Device Patient Labeling Guidance"), at 12, available at https://www.fda.gov/media/71030/download. See FDA guidance document entitled "Device Labeling Guidance #G91-1 (Blue Book Memo)" (March 1991), Section IV, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/device-labeling-guidance-g91-1-blue-book-memo.

[67] PHS Scientific Review, cited at footnote 33 of this document.

[68] Dental Amalgam Special Controls Guidance, cited at footnote 42 of this document.

[69] 74 FR at 38693.

[70] 74 FR at 38694.

Further, as discussed in the Final Rule,[71] thereafter in the 2010 Dental Products Panel meeting,[72] and most recently in the Safety Communication,[73] FDA has repeatedly determined that there is "little to no" scientific evidence of a causal relationship between the use of dental amalgam and adverse health effects in specific subpopulations. Since issuing the Final Rule, FDA has monitored data on dental amalgam from a variety of sources, such as Medical Device Reports and data published in the scientific literature, and we have confirmed that there is still a persistent data gap concerning the existence of a causal relationship between dental amalgam and adverse health effects in vulnerable populations.

There remain enough uncertainties with regard to the dose-response assessment of mercury from dental amalgam to warrant the need for a safety communication. Accordingly, based on the available scientific evidence, FDA issued the September 2020 Safety Communication and Informational Brochure to inform the public about the most sensitive groups, who may have a greater potential for experiencing adverse health effects from exposure to the mercury vapor released from dental amalgam. We have also reviewed all the evidence described in your Petitions; and as discussed herein, FDA believes that the September 2020 Safety Communication, including the recommended Informational Brochure for patients, the infographics, and the updated FDA webpages concerning amalgam and other dental restoration materials, are the appropriate communications to provide an assurance of safety and effectiveness of amalgam use in dentistry in light of potential risks to vulnerable subpopulations, as identified in the 2020 Safety Communication. Therefore, at this time, FDA is denying your request to establish a contraindication against the use of dental amalgam in high-risk populations because, despite the potential toxic and bioaccumulative effects of mercury, the Petitions and other available information do not support a finding that there is a causal association between the use of dental amalgam in vulnerable populations and any potentially adverse health effects.

### 2a. Dental Amalgam Use in Children

The Petitions cite to various studies and other evidence to support your requests to stop amalgam use in children. In CP-4, for children under age 15,[74] you rely on Woods et al. (2012), which is an analysis of the data from the Casa Pia cohort[75] of the Children's Amalgam Trial (CAT) that

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[71] 74 FR at 38697, see 74 FR at 38693-94.

[72] See Section C.2 (Other Factual Background) of this document, discussing the Panel meeting.

[73] Recommendations About the Use of Dental Amalgam in Certain High-Risk Populations, available at https://www.fda.gov/medical-devices/safety-communications/recommendations-about-use-dental-amalgam-certain-high-risk-populations-fda-safety-communication.

[74] CP-4 at 3.

[75] De Rouen, T. et al., "Neurobehavioral Effects of Dental Amalgam in Children, A Randomized Clinical Trial," Journal of the American Medical Association, Vol. 295, 1784-1792, 2006

finds certain deficits in neurobehavioral functions associated with chronic mercury exposure and the CPOX4 genetic variant among children, especially boys. FDA has reviewed this reference and finds that the study was well-conducted and provides evidence that individuals with certain genetic polymorphisms may be at a higher risk for adverse health effects due to mercury from dental amalgam. FDA does not believe, however, that the evidence you have provided and the evidence the Agency has evaluated demonstrate an unreasonable and substantial risk of illness or injury that would justify stopping amalgam use altogether in the vulnerable subpopulations of children studied in the Casa Pia cohort (under ages 6-10) or in the sensitive child subpopulations identified in the Final Rule ("under the age six"),[76] in the 2020 Safety Communication ("younger than six years of age"), or in CP-4 (under 15 years). The Agency agrees with the 2014 SCENIHR Preliminary Report,[77] which examined Woods et al. (2012) and concluded that further research on this issue is needed. The report stated: "The studies presented…seem to indicate that genetic variation may have an influence also on responses to mercury-induced toxicity. In this case, calculated exposure limits will protect the average subject, but may be insufficient to protect those with genetic polymorphism to relevant enzymes involved in the toxicodynamics of mercury. However, no prospective clinical studies clearly showing the influence of genetic variations on the occurrence of adverse effects due to mercury from dental amalgam are available. Therefore, especially in this area further research is needed before clinical conclusions could be drawn." FDA agrees that further information is needed. The Agency will continue to consider this information and any other information that becomes available to determine whether any further action is needed, pursuant to our statutory authorities and regulations.

CP-4 also cites Yin et al. (2016) to support your claim that dental amalgam should not be used on children because amalgam restorations significantly contribute to blood mercury levels.[78] FDA has reviewed this reference and finds its conclusions are limited because, although the study found a correlation between the number of dental surface restorations (all types, including resin, ceramic, and amalgam) and increases in blood total mercury, the number of amalgam restorations, specifically, was not captured and so conclusions cannot be drawn correlating dental amalgam to any increases in blood mercury levels. Other reports do not find amalgam to be primarily responsible for blood mercury levels. The 1993 PHS Scientific Review,[79] for example,

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(groups of children had amalgam or composite restorations placed at ages 6-10 and were followed for 7 years).

[76] 74 FR at 38691.

[77] Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), European Commission, Health & Consumers Directorate, The Safety of Dental Amalgam and Alternative Dental Restoration Materials for Patients and Users-Preliminary Opinion (SCENIHR Preliminary Report), 2014.

[78] CP-4 at 3.

[79] PHS Scientific Review, cited at footnote 33 of this this document, Appendix III-12.

found moderate blood mercury levels in subjects without any amalgam restorations. Yin et al. (2016) does not present convincing evidence that amalgam should not be used in children (under either age 6 or age 15) because of its contribution to blood mercury levels, nor does it provide any new information. Rather, it confirms other studies from which FDA has concluded that amalgam contributes along with other sources of mercury, such as diet, to mercury blood levels and results in increased accumulation in tissues. However, evidence is inconclusive that these levels contribute to adverse health responses.

Your Petitions cite the 2012 EU Environmental Report[80] to support your claim that dental amalgam should not be used in vulnerable children because it requires the removal of more tooth structure than composite resins and because the longer service life of dental amalgam is not a significant benefit for primary teeth. FDA disagrees with the report's conclusion that amalgam is not suitable for children because its larger size may lead to premature tooth fracture or failure. FDA believes the size of a restoration is not the only determinant of device failure. As stated in the Final Rule, the two primary reasons dental restorations fail have been found to be secondary caries (as the result of marginal leakage) and fracture.[81] Many factors, including material properties, type and size of restoration, patient hygiene and diet, and skill of the dentist can contribute to the failure of a device. FDA agrees that preservation of the tooth is the primary objective. What material to use to best accomplish this for primary or permanent teeth, in a particular patient situation, is a decision that a dentist should make in consultation with his/her patient.

Your Petitions cite Hickel et al. (2005)[82] to support your claim that dental amalgam should not be used on vulnerable children because dental amalgam has a higher mean annual failure rate (7.6%) for occlusal restorations in primary teeth than do alternatives, i.e., composite (5.9%) and resin-modified glass ionomer (4.2%). FDA has reviewed this reference and believes it is difficult to draw conclusions from the wide variability of values (0 to 35%) presented in this literature review. Note that the same study also shows a mean annual failure rate of 13.9% for glass ionomer cements.

In the 2009 Final Rule, FDA identified another study, a randomized clinical study on children ages 8 through 12, that reported annual failure rates ranging from 0.16 to 2.83 percent for amalgam restorations and from 0.94 to 9.43 percent for composite restorations.[83] The study shows higher secondary caries rates for composite resins, and roughly equivalent fracture rates

[80] CP-3 at 3 n.8, and CP-4 at 4-5.

[81] 74 FR at 38703.

[82] CP-3 at 3 n.9, and CP-4 at 5 n.25 and 13 n.75.

[83] Bernardo, M. et al., "Survival and Reasons for Failure of Amalgam Versus Composite Posterior Restorations Placed in a Randomized Clinical Trial," Journal of the American Dental Association, Vol. 138, pp. 775-783, June 2007; see 74 FR at 38703, 38714.

for composite and amalgam restorations. Secondary caries was the main reason for failure in both materials and the risk of secondary caries was 3.5 times greater in the composite group. The references you cited do not present convincing evidence that dental amalgam should not be used in vulnerable children because of a higher risk of device failure.

In CP-4 you request FDA to implement measures to contraindicate and restrict amalgam use for children "under age 15"[84] and to expand the age range of the children identified as special or "potentially sensitive subpopulations" in the Final Rule (defining children as the population "under six years of age").[85]

In the Final Rule, FDA did consider the potential health effects of dental amalgam on children older than the age of six.[86] As stated in the Final Rule,[87] two prospective amalgam trials in children six years of age and older did not find that kidney injury is associated with exposure to dental amalgam. In the New England trial,[88] groups of children had amalgam or composite restorations placed at ages 6-8 and were followed for five years. Results showed that, although microalbuminuria levels were higher in the amalgam treatment group, the levels of three other biomarkers of kidney injury were not different between the amalgam versus composite restoration groups. The authors of the study noted that they were unable to determine whether the increase in microalbuminuria was related to treatment or may have occurred by chance, since albuminuria may be caused by strenuous physical exercise, urinary tract infections, or other conditions with fever, or be related to orthostatic proteinuria. In another children's prospective trial (Casa Pia),[89] groups of children had amalgam or composite restorations placed at ages 6-10 and were followed for seven years. There were no differences between the amalgam and composite groups with respect to the urinary excretion of microalbumin or albumin, a biomarker

[84] The earlier Petitions, including CP-3, which makes the same requests as CP-4, requested protection categorically for all children without specifying an upper age limit. See footnote 150 and accompanying discussion in Section 4a (EU Regulation on Mercury) below, concerning the designation of children under age 15 years as a vulnerable population.

[85] 74 FR at 38691. Based on the available scientific evidence, FDA issued the September 2020 Safety Communication, which discusses use in children under the age of six.

[86] 74 FR at 38688.

[87] 74 FR at 38693.

[88] Barregard, L. et al., "Renal Effects of Dental Amalgam in Children: The New England Children's Amalgam Trial," Environmental Health Perspectives, Volume 116, 394-399, 2008.

[89] De Rouen, cited at footnote 75 of this document.

of renal glomerular injury, and GST-alpha and GST-pi, two biomarkers[90] of renal proximal and distal tubule injury, respectively. As stated in the Final Rule,[91] FDA concluded that the data from these studies support a finding that exposures to mercury vapor at levels associated with dental amalgams do not result in renal damage in the population age six and older. Based on the findings for children older than six in the New England and Casa Pia trials, FDA cannot conclude that dental amalgam should be contraindicated or that use should stop altogether in children, including those up to age 15.

The Petitions fail to provide information that would cause FDA to determine that additional actions, such as additional proposed warnings or a public campaign to contraindicate or to stop the use of dental amalgam in children under age 15, are necessary or appropriate. Consistent with the Safety Communication, there may be situations where dental treatment is needed but non-mercury restorations are not possible or appropriate in this subpopulation as determined by the dental professional responsible for treating the individual patient. We are therefore denying your requests for such warnings and a public campaign.

**2b. Dental Amalgam Use in Women and Sensitive Populations**

The Petitions request that FDA stop amalgam use in pregnant women, breastfeeding mothers, and other sensitive populations. In the Final Rule,[92] FDA considered the potential health effects of dental amalgam on pregnant women and breast-feeding mothers, specifically. Although mercury has the ability to cross the placental barrier,[93] the limited human data available[94, 95, 96] do not demonstrate an association between exposure to the mercury in dental amalgam and

[90] Woods, J.S. et al., "Biomarkers of Kidney Integrity in Children and Adolescents with Dental Amalgam Mercury Exposure: Findings from the Casa Pia Children's Amalgam Trial," Environmental Research, Vol. 108, pp. 393-399, 2008.

[91] 74 FR at 38691.

[92] 74 FR at 38687-88, 38691-92, 38694, 38697, and 38700.

[93] Lindbohm, M.L. et al., "Occupational exposure in dentistry and miscarriage," *Occupational Environmental Medicine,* Vol. 64 (2), pp. 127-133, 2007.

[94] Elghany, N.A. et al., "Occupational exposure to inorganic mercury vapour and reproductive outcomes," *Occupational Medicine*, Vol. 47 (6), pp. 333-336, 1997.

[95] Hujoel, P.P. et al., "Mercury exposure from dental filling placement during pregnancy and low birth weight risk," American Journal of Epidemiology, Vol. 161(8), pp. 734-740, 2005.

[96] Morgan DL, Chanda SM, Price HC, Fernando R, Liu J, Brambila E, O'Connor RW, Beliles RP, Barone Jr S: "Disposition of inhaled mercury vapor in pregnant rats: Maternal toxicity and effects on developmental outcome." *Toxicol Sci*, 2002; 66:261-273.

adverse reproductive outcomes.[97] And although mercury present in a nursing mother's body is transmitted to her infant through breast milk[98] and maternal exposure to elemental mercury vapor is expected to affect the concentration of inorganic mercury in breast milk,[99] the existing data[100, 101, 102] support a finding that inorganic mercury absorption through breast milk is not a significant source of mercury exposure to infants.[103]

Although the data are limited, FDA concluded in the Final Rule that the existing data do not suggest that fetuses are at risk for adverse health effects due to maternal exposure to mercury vapors from dental amalgam.[104] FDA also concluded that the existing data support a finding that infants are not at risk for adverse health effects from the breast milk of women exposed to mercury vapors from dental amalgam.[105] Even so, FDA did include the following language concerning the recommended professional labeling for dental amalgam in the "Information for Use" section of the Dental Amalgam Special Controls Guidance: "The developing neurological systems in fetuses and young children may be more sensitive to the neurotoxic effects of mercury vapor. Very limited to no clinical information is available regarding long-term health outcomes in pregnant women and their developing fetuses, and children under the age of six, including infants who are breastfed."[106]

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[97] 74 FR at 38691-92.

[98] Norouzi, E., et al., Effect of teeth amalgam on mercury levels in the colostrums human milk in Lenjan, Environmental Monitoring and Assessment, January 2012, Volume 184, Issue 1, pp 375-380.

[99] FDA Final Response, document FDA-2009-P-0610-0017, cited at footnote 43 of this document, at 16, n. 46. See also 74 FR at 38692.

[100] Review and Analysis of the Literature on the Potential Adverse Health Effects of Dental Amalgam, Life Sciences Research Office, July 2004.

[101] Vimy M.J. et al., "Mercury from maternal "silver" tooth fillings in sheep and human breast milk: A source of neonatal exposure," *Biol. Trace Elem. Res.*, Vol. 56 (2), pp.143-152, 1997.

[102] Herr DW, Chanda SM, Graff JE, Barone SS, Jr., Beliles RP, Morgan DL: Evaluation of sensory evoked potentials in Long Evans rats gestationally exposed to mercury (Hg0) vapor. Toxicol Sci 2004; 82(1):193-206.

[103] 74 FR at 38692.

[104] 74 FR at 38691.

[105] 74 FR at 38692.

[106] Dental Amalgam Special Controls Guidance, cited at footnote 42 of this document.

Subsequent to the Final Rule, FDA held an advisory committee meeting in December 2010 to discuss and make recommendations on these issues related to pregnant women and breast-feeding mothers.[107] Several panel members expressed concern about the effects of mercury vapor on these and other potentially vulnerable populations. Of particular concern to the panel was the lack of clinical data available regarding health outcomes in these subpopulations. FDA has acknowledged there is very limited to no clinical information relevant to these subgroups. Since that panel meeting, FDA has been monitoring literature on dental amalgam, including literature discussing pregnant women and fetuses, and will continue to evaluate new information as it becomes available.

Based on the available scientific evidence, FDA issued the September 2020 Safety Communication to inform the public about who may be at greater risk of potential adverse effects of dental amalgam, including pregnant women, breast-feeding mothers, and other vulnerable populations.

The Petitions fail to provide information that would cause FDA to determine that additional actions, such as additional proposed warnings or a public campaign to stop the use of dental amalgam in these vulnerable populations, are necessary or appropriate. Consistent with the Safety Communication, there may be situations where dental treatment is needed but non-mercury restorations are not possible or appropriate as determined by the dental professional responsible for treating the individual patient. We are therefore denying your requests for such warnings and a public campaign.

### 3. Request to Require Manufacturers to Distribute Labeling for Patients

In CP-2,[108] you request FDA to require manufacturers to distribute the following labeling information for parents and dental consumers: amalgam's mercury content, amalgam's risks to children and fetuses, the damage amalgam can do to tooth structure, the damage caused by amalgam in the environment, and the benefits of mercury-free fillings.[109]

In the Petition, you quote the statements of individual advisory panel members to support your contention that the "public is not getting the information that it needs" and wants about dental amalgam.[110] You argue that the Agency is not following the recommendations of its own

[107] See footnote 36 of this document, concerning transcripts and meeting materials for this panel meeting.

[108] CP-3 and CP-4 also briefly mention such request, without further elaboration.

[109] CP-2 at 1.

[110] CP-2 at 3.

guidance document covering patient labeling.[111] Specifically, you contend that "giving patients labeling with 'direct information that would include the presence of mercury in amalgam'" would reduce mercury exposure,[112] and that the patient's choice of dental restoration is "a very simple thing" and not a complex matter requiring the participation of a dental professional.[113] In addition, you state that manufacturers need to communicate information about the risk/benefit of amalgam to patients and parents and about other exposure to mercury in the patient's diet or workplaces so that patients have the opportunity to give vital personal health information to dentists in the case of pre-existing hypersensitivities or allergy to mercury so that all these factors are appropriately weighed when dentists determine whether amalgam is appropriate.[114]

Citing the World Dental Federation, you raise concerns that the risk-benefit information currently reaching patients and caregivers is inadequate, that their dentists are not providing adequate information,[115] and that it is "unethical" to not involve patients in dental treatment decisions.[116] You cite to a 2014 Zogby poll finding that most Americans do not know that mercury is amalgam's main component, and when notified, 75% choose mercury-free dental restoration.[117] Additionally, your Petition states that patient labeling is contrary to FDA's findings in the Final Rule that vulnerable subpopulations are at risk and that mercury is bioaccumulative.[118]

In classifying dental amalgam into Class II (Special Controls) in the Final Rule, FDA also established special controls that, together with general controls, provide reasonable assurance of the safety and effectiveness for amalgam use. The Final Rule states the following:

> "FDA believes that the recommended labeling statements in the special controls guidance document will provide dentists with important information that will improve their

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[111] CP-2 at 4-5 (referring to the Device Patient Labeling Guidance, cited at footnote 66 of this document).

[112] CP-2 at 2.

[113] CP-2 at 3.

[114] CP-2 at 4.

[115] CP-2 at 2.

[116] CP-2 a 4.

[117] CP-2 at 2. See FDA's response to citizen petition in FDA-2014-P-0907-0005 (available at https://www.regulations.gov/document?D=FDA-2014-P-0907-0005). The introductory page of FDA's consumer website has been updated to specify that the main component of dental amalgam is elemental mercury.

[118] CP-2 at 4.

> understanding of the devices and help them make appropriate treatment decisions with their patients. In addition, FDA notes that dental amalgam is a prescription device and, therefore, patients cannot receive the device without the involvement of a learned intermediary, the dental professional. Based on the reasons described above, FDA has concluded that it is not necessary to require that dentists provide this information to patients in order to provide reasonable assurance of the safety and effectiveness of the device."[119]

Concerning vulnerable populations specifically, the "Information Section" of the Dental Amalgam Special Controls Guidance recommends that the labeling for dental professionals should contain the following statement: "The developing neurological systems in fetuses and young children may be more sensitive to the neurotoxic effects of mercury vapor. Very limited to no clinical information is available regarding long-term health outcomes in pregnant women and their developing fetuses, and children under the age of six, including infants who are breastfed."[120] Additionally, the Dental Amalgam Special Controls Guidance also recommends the following warning: "WARNING – CONTAINS MERCURY – may be harmful if vapors are inhaled." [121]

As you point out, however, this information is provided in professional labeling that dental professionals are not *required* to give to patients. In the 2009 Final Rule, FDA considered the option to require labeling to be provided directly to the patient.[122] Subsequent to the Final Rule, the question of whether patient labeling should be required for dental amalgam was reconsidered at the FDA Advisory Committee meeting of the Dental Products Panel held on December 14-15, 2010.[123] The panel meeting was held to discuss this and other issues raised in then-pending petitions regarding the safety of dental amalgam. As you point out in the Petition, several members of the panel suggested that patient labeling would have some benefit. After consideration, and based on all available scientific evidence, including evidence submitted in your Petitions, FDA does not believe it is necessary or appropriate to require that dental health care providers provide this information to patients.

The Agency believes that, at this time, other methods are appropriate for conveying this information to achieve the same result of educating patients about benefits/risks and treatment options for dental restorations. For example, it is anticipated that the September 2020 Safety Communication and Informational Brochure, accessible on FDA's webpage, will be used to

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[119] 74 FR at 38703.

[120] Dental Amalgam Special Controls Guidance, cited at footnote 42 of this document, p. 10.

[121] *Id*, p. 8.

[122] 74 FR at 38697.

[123] See footnote 36 of this document, concerning transcripts and meeting materials for this panel meeting.

facilitate a discussion between the dental care provider and patient on the benefits, risks, and treatment options for a dental restorative procedure. Further, the infographics and bilingual translation added in 2021 make this information even more accessible to patients. We believe providing patient information in these formats are the appropriate methods to provide patients with access and time to consider this information and help to facilitate the type of informed discussion with their dental care provider that FDA believes is necessary based on the available scientific evidence.

You state that we should "amend FDA's mercury amalgam rule to require patient labeling."[124] As explained above, we disagree that this is needed to provide for a reasonable assurance of the safety and effectiveness of the device. Given the recent availability of the September 2020 Safety Communication, the Informational Brochure, and the updated FDA webpages concerning amalgam and other dental restorations, we do not believe that FDA must take additional actions to require manufacturers to distribute labeling to parents and dental consumers concerning the risks of dental amalgam.

In summary, FDA does not believe, based on the information you included in your Petitions, that further action regarding patient labeling is warranted at this time. We do not agree with your suggestion that the required labeling for dental amalgam is unethical because it somehow excludes patient participation in treatment decisions. To the contrary, we believe the current amalgam labeling distributed to dental professionals, together with the patient and user information described in the Safety Communication, the Informational Brochure, and on FDA's webpage updates (which are available to both patients and parents, as well as to dental professionals), can help facilitate a robust discussion about risk-benefit information regarding amalgam use that enables the patient and dentist to determine the patient's best treatment option. The Agency continues to hold the view it expressed in the Final Rule and is denying your request to amend the Final Rule to require manufacturers to include patient labeling at this time.

**4. <u>Requests for FDA to Conform to the Minamata Convention, to "Catch Up" with Governmental Regulatory Actions in Other Countries and International Guidance, and to Exercise a Leadership Role in the International Regulation of Mercury</u>**

In support of your requests to phase down and/or stop amalgam use in pregnant women, breastfeeding mothers, and other sensitive populations, the Petitions cite the U.S. Government's acceptance of the Minamata Convention. To comply or conform with this Convention, in your view, FDA must amend the Final Rule as requested in CP-1,[125] require patient labeling as requested in CP-2,[126] and provide an environmental assessment for each action not categorically

[124] CP-2 at 2 and 4.

[125] CP-1 at 2.

[126] CP-2 at 1-2.

excluded in the event that FDA amends the Final Rule as requested in CP-3[127] and CP-4.[128] In CP-1, you quote the September 2015 letter of 60 environmental organizations urging the U.S. State Department "to bring FDA into line" with the Convention obligations of the U.S. Government.[129] You also cite a press article concluding that FDA's "standing behind" the Final Rule is inconsistent with U.S. Government participation in the Convention.[130]

The Convention identifies dental amalgam as a mercury-added product for which the participant countries must take countervailing measures. Specifically, Part II of Annex A of the Convention lists nine measures for phasing down the use of mercury in dental amalgam,[131] and the Convention itself states that the parties are to consider their domestic circumstances and relevant international guidance and to implement at least two of these nine phase-down measures.[132]

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[127] CP-3 at 4. See 21 CFR 25.30 and 25.34.

[128] CP-4 at 5.

[129] CP-1 at 2.

[130] *Id*.

[131] Convention, Annex A, Part II provides that:

> Measures to be taken by a Party to phase down the use of dental amalgam shall take into account the Party's domestic circumstances and relevant international guidance and shall include two or more of the measures from the following list:
> (i) Setting national objectives aiming at dental caries prevention and health promotion, thereby minimizing the need for dental restoration;
> (ii) Setting national objectives aiming at minimizing its use;
> (iii) Promoting the use of cost-effective and clinically effective mercury-free alternatives for dental restoration;
> (iv) Promoting research and development of quality mercury-free materials for dental restoration;
> (v) Encouraging representative professional organizations and dental schools to educate and train dental professionals and students on the use of mercury-free dental restoration alternatives and on promoting best management practices;
> (vi) Discouraging insurance policies and programmes that favour dental amalgam use over mercury-free dental restoration;
> (vii) Encouraging insurance policies and programmes that favour the use of quality alternatives to dental amalgam for dental restoration;
> (viii) Restricting the use of dental amalgam to its encapsulated form;
> (ix) Promoting the use of best environmental practices in dental facilities to reduce releases of mercury and mercury compounds to water and land.

[132] *Id*.; Convention, Art. 4, Para. 3.

It should be noted that the President did not submit the Convention to the U.S. Senate for ratification as a treaty under the Treaty Clause,[133] and Congress has taken no legislative action to ratify or approve the Convention.[134] The State Department press release announcing the U.S. Government's acceptance of the Minamata Convention expressly stated that the United States "can implement Convention obligations under existing law."[135] In various notifications made under terms of the Convention, the U.S. Government has identified the existing law that enables it to implement its Convention obligations.[136] None of these notifications refer to the FDA's authorities on regulation of medical devices under the FD&C Act.

The U.S. Government is committed to complying with the Convention, by taking at least two of the nine specific measures set forth in Part II of Annex A with respect to dental amalgam, including the June 2017 EPA action to reduce discharges of mercury from dental offices by requiring dental offices to use amalgam separators.[137] However, we disagree with your assertion that the obligations of the U.S. Government under the Minamata Convention necessarily require amendment of FDA's regulations. We do not find any mention of FDA regulation of dental amalgam in the U.S. Government acceptance of the Convention or in the notifications submitted by the United States under the Convention. As noted above, there is no Federal statutory restriction to phase down or prohibit use of mercury in dental amalgam.

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[133] See U.S. Constitution, Art. II, § 2, cl. 2. There is a longstanding practice of the President entering into binding "executive agreements" with foreign nations, without the need for compliance with the Senate review and approval formalities required by the Treaty Clause. Dames & Moore v. Regan, 453 U.S. 654, 679-80 (1981); U.S. v. Pink, 315 U.S. 203, 228-29 (1942); U.S. v. Belmont, 301 U.S. 324, 330-31 (1937).

[134] The failure of Congress to review an executive agreement does not imply disapproval of the action taken by the Executive Branch. 453 U.S. 654, at 678-79.

[135] U.S. Dept. of State, "United States Joins Minamata Convention on Mercury" (press release), Nov. 6, 2013, available (archived content) at https://2009-2017.state.gov/e/oes/eqt/mercury/index.htm.

[136] See the U.S. Government notifications available at https://www.mercuryconvention.org/en/parties/notifications (search under the heading "Article 4.2" in the row "United States of America"). In the document entitled "Measures to Implement the Minamata Convention on Mercury," the U.S. Government describes with specificity the existing Federal laws that enable it to phase down amalgam use: "The United States will implement at least two measures listed in part II of Annex A under the Public Health Service Act, 42 U.S.C. §241(a), and the Clean Water Act [33 U.S.C. 1251(a)]," also available at https://www.mercuryconvention.org/sites/default/files/documents/notification/USA%2520declaration_Art%252030%2520para%25204.pdf.

[137] 82 FR 27154, Jun. 14, 2017 (Effluent Limitations Guidelines and Standards for the Dental Category). See http://water.epa.gov/scitech/wastetech/guide/dental/index.cfm.

### 4a. EU Regulation on Mercury

In particular, in CP-4 you refer to the 2017 actions of the European Union (EU) to prohibit amalgam use in the treatment of children under 15 years and of pregnant and breastfeeding mothers beginning on July 1, 2018.[138] The EU actions as implemented in May 2017 called on member countries to phase down dental amalgam use in order to align EU legislation with the Convention, to develop national plans by July 2019 to implement phase down, and to assess in June 2020 the feasibility of complete phase out of amalgam use by 2030 (the EU Regulation).[139]

As an initial matter, the EU Regulation is an environmental regulation applicable to EU members, not a health regulation binding FDA.[140] Having said that, the Agency has reviewed the legislative record of the EU Regulation to evaluate the scientific evidence available in that record. The prior 2008 EU Regulation on mercury did not address the use of dental amalgam.[141] And in 2014, the Scientific Committee on Health and Environmental Risks (SCHER), an independent body providing scientific advice to the European Commission concluded at that time: "The contribution of environmental mercury coming from dental amalgam use…to soil are not considered as a concern for human health…At present, there is insufficient scientific evidence to support the statements" of the World Alliance for Mercury-Free Dentistry that the ecological risk of the alternatives is very low or lower than those of amalgam.[142] Similarly, in 2015 another scientific panel, the Scientific Committee on Emerging and Newly Identified

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[138] CP-4 at 1.

[139] Regulation (EU) 2017/852 of the European Parliament and of the Council of 17 May 2017 on mercury repealing Regulation (EC) No.1102/2008, OJ L 137/1-137/21, 24.5.2017, available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0852&from=EN.

[140] In noting the progress of international negotiations on the global mercury treaty and considering the EU policy option of banning the use of mercury in dentistry, the 2012 EU Environmental Report observed: "[T]here is currently no scientific consensus on the *direct* health effects of dental amalgam (except with regard to possible allergies caused by dental amalgam). For this reason, future policy actions concerning dental amalgam addressed in this study focus on the *environmental side* of the problem and *indirect* health effects [italics included in the Report]." 2012 EU Environmental Report, cited at footnote 57 of this document, p. 14.

[141] Regulation (EC) No. 1102/2008 on the banning of exports of metallic mercury and certain mercury compounds and mixtures and the safe storage of metallic mercury, OJ L 304, 14.11.2008, available at http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1102&from=EN.

[142] SCHER, "Opinion on the environmental risks and indirect health effects of mercury from dental amalgam (update 2014), March 2014, pp. 17, 20 and 22-23, available at https://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_165.pdf.

Health Risks (SCENIHR) reported to the Commission: "The current evidence does not preclude the use of dental amalgam in restorative treatment of the general population. The SCENIHR recognizes that dental amalgam is an effective restorative material for the general population, with low risk of adverse health effects. The choice of material should be based on patient characteristics."[143]

In light of these scientific panel conclusions, the European Commission's 2016 legislative proposal was to amend the 2008 EC Regulation on mercury to address dental amalgam through two measures: (1) by permitting amalgam use in encapsulated form only, and (2) by requiring dental offices to have an amalgam separator.[144] Focusing specifically on EU legislation that would be required to comply with the Minamata Convention, the Commission Staff concluded that, at the minimum, the EU would have to take at least one of these two measures;[145] and the Commission Staff specifically declined to recommend or to assess the impact of phasing out amalgam use in dentistry.[146]

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[143] SCENIHR, "[Scientific Experts Opinion on] The safety of dental amalgam and alternative dental restoration materials for patients and users" (April 2015), p. 76, available at https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_046.pdf.

[144] Proposal for a Regulation of the European Parliament and of the Council on mercury, and repealing Regulation (EC) No. 1102/2008, Art. 10, 2016/0023(COD), Feb. 2, 2016, available at http://eur-lex.europa.eu/resource.html?uri=cellar:f1bacfbb-c995-11e5-a4b5-01aa75ed71a1.0002.02/DOC_1&format=PDF. In May 2016, the European Economic and Social Committee (EESC) of the European Parliament "unreservedly recommend[ed]" the adoption of the Proposal and commented as follows: "The Committee appreciates the balanced approach taken by the European Commission on the use of amalgam in dentistry based on the latest available scientific knowledge. It considers that requirements on equipment in dental care establishments – namely the obligation to install mercury separators and restriction on the use of dental amalgam to its encapsulated form – are enough to effectively limit the release of mercury into the environment and to protect human health." ECSC, Opinion on the Proposal for a Regulation on Mercury repealing Regulation (EC) No. 1102/2008, May 25, 2016, at 5.9, available at https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=OJ:C:2016:303:FULL&from=BG (search for EESC document 2016/C 303/17).

[145] European Commission Staff, Impact Assessment of Ratification and Implementation by the EU of the Minamata Convention on Mercury, accompanying the Proposal for a Regulation repealing Regulation (EC)_No 1102/2008, Feb. 2, 2016, p. 16 , available at http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52016SC0017&from=EN.

[146] Because the SCHER and SCENIHR scientific panels had "clearly indicate[d] that significant negative impacts of dental amalgam on health are not proven," the Commission Staff impact-assessment document found that phase out of amalgam use "would not be a proportionate

The European Environmental Bureau (EBB), a non-governmental organization, criticized the Commission, saying that the Proposal set a low ambition level for the EU and did not incorporate the results of public consultation; and further, the EBB called for phasing out of mercury use in dentistry.[147] In parallel action, the Committee on the Environment, Public Health and Food Safety (ENVI), the European Parliament's committee with legislative jurisdiction to review the matter, revised the Proposal to mandate the staged phase-out of mercury in dentistry by 2022 and, as the first stage, to prohibit its use for pregnant or breastfeeding women and children.[148]

In the EU inter-institutional negotiations in December 2016,[149] the European Commission, Council, and Parliament reached a compromise agreement on dental amalgam favoring the ENVI revision that would require the Commission to pursue phasing out amalgam use by 2030 and, as a first step, prohibit its use by July 2018 in "children under 15 years"[150] and in pregnant or breastfeeding women "except when strictly deemed necessary by the practitioner on the ground of specific medical needs of the patient."[151] The compromise was enacted as the EU Regulation on May 17, 2017, including the "children under 15 years" grouping. There is no scientific data

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measure and it is not retained for further assessment" in its impact-assessment report. *Id.* at 40-41.

[147] EBB, Input to the EU Environment Council Meeting, Brussels, 4 March 2016, Feb. 15, 2016, p. 3 and Annex 5, available at http://archive.eeb.org/index.cfm/library/eeb-letter-to-environment-council-march-2016/.

[148] ENVI, Report on the Proposal for a Regulation on mercury repealing Regulation (EC) No. 1102/2008, Oct. 20, 2016, p. 34-36 (Amendments 60, 61, 63, and 65), available at http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+REPORT+A8-2016-0313+0+DOC+PDF+V0//EN.

[149] European Parliamentary Research Service (EPRS), EU Legislation in Progress Briefing, "Mercury, Aligning EU legislation with Minamata" (May 2017), available at http://www.europarl.europa.eu/RegData/etudes/BRIE/2017/595887/EPRS_BRI%282017%2959 5887_EN.pdf..

[150] In the earlier legislative history of the EU Regulation, children in general (without an age limitation) would have been treated as a vulnerable population.

[151] European Parliament, Provisional Agreement Resulting from Interinstitutional Negotiations on Proposal for a Regulation on mercury repealing Regulation (EC) No. 1102/2008, Feb. 24, 2017, GEDA/T/(2017)013299, p. 30 (Article 10), p. 47 (Article 15a), available at http://www.europarl.europa.eu/RegData/commissions/envi/inag/2017/02-24/ENVI_AG(2017)600906_EN.docx.

provided either in the legislative history of the EU Regulation (or in CP-4)[152] supporting a definition of the vulnerable-child population as being children under age 15.[153]

In the legislative record of the EU Regulation, we do not find valid scientific evidence or conclusions that would support your requests that FDA amend the Final Rule to phase down and/or prohibit amalgam use in the treatment of children and of pregnant and breastfeeding mothers. FDA does not believe that such proposed action is necessary or appropriate at this time to protect "children under age 15" or in younger groups. FDA will continue to keep the public informed if significant new information about dental amalgam applicable to children becomes available.

### 4b. National and Multilateral Actions and International Guidance

To support your requests, in CP-3 and CP-4 you cite several national and multilateral actions, such as a 2011 report of the World Health Organization (WHO).[154] In CP-2, you rely on the 2016 report of the U.N. Environment Programme (UNEP).[155] CP-2, CP-3, and CP-4 refer to governmental actions in eight European countries to restrict the use of dental amalgam.[156] In CP-1, you urge FDA to amend the Final Rule in order "to maintain the leadership role of the United States on mercury issues."[157]

The national and multilateral/intergovernmental actions of other countries that you cite do not require the U.S. to take similar actions to alter U.S. domestic law. The FDA actions that you have requested are not necessary under the FD&C Act or other relevant authorities, as explained in the other sections of this document; and they are not required for compliance with the

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[152] Contemporaneously, CP-4 defined the vulnerable child population in the Petitions as children under age 15 (p. 1) and references the EU's decision "to ban amalgam use in children under age 15" (p. 4).

[153] "Children under 15 years" appears to be a legislated category delineating by age one of the "vulnerable members of the population" to be protected from amalgam exposure. See Regulation (EU) 2017/852 cited in footnote 139, at 137/3-4 (clauses 21 and 23); see also *id.*, Annex IV(i), at 137/20 ("vulnerable populations, particularly children"). See also Centers for Disease Control and Prevention (CDC) information on Child Development (age 15 is the accepted age threshold *in behavioral and developmental research* for distinguishing "teenagers" from younger minors), available at https://www.cdc.gov/ncbddd/childdevelopment/positiveparenting/adolescence2.html.

[154] CP-3 at 3 and CP-4 at 4.

[155] CP-2 at 3.

[156] Sweden, Norway, and Denmark (CP-2 at 2), and additionally: Finland, Germany, Canada, Australia, and the United Kingdom (CP-3 at 3-4 and CP-4 at 2).

[157] CP-1 at 2.

Minamata Convention. Nor are these requested actions appropriate, either based on governmental actions taken in other countries or in response to foreign-policy considerations.[158]

Accordingly, based on the scientific evidence available and consistent with FDA's statutory and regulatory authorities, FDA is denying your requests for additional actions to phase down and/or prohibit amalgam use in the treatment of children under 15 years or in younger groups, of pregnant and breastfeeding mothers, and other sensitive populations. FDA does not believe that such proposed actions are necessary or appropriate at this time. Even though we are denying these requests in your Petitions, the Agency continues to evaluate the safety of dental amalgam and will take further action as needed in accordance with our statutory authorities and regulations.

### 5. Environmental Assessment of FDA Actions

Your Petitions argue that, with the need for the requested actions now recognized by the Minamata Convention, an extraordinary circumstance exists[159] and conclude that FDA must renew its consideration of the "negative environmental impact" of dental amalgam."[160] However, your contentions do not reflect FDA's applicable statutory and regulatory requirements.

Your claim presumes either that FDA will initiate amendment of the Final Rule, during which process environmental impacts under the National Environmental Policy Act (NEPA) may be considered or that FDA has a general obligation under NEPA to continuously assess the impact on the environment of FDA's current regulations pertaining to mercury and the cumulative effects of mercury attributable to dental devices. Such presumptions do not comport with applicable law, or with the fact that FDA is denying your request to amend the Final Rule. No major federal action is being proposed in this letter or at this time that would require

[158] Earth Island Inst. v. Evans, 2004 U.S.Dist.LEXIS 15729, 26 Int'l Trade Rep. (BNA) 1993 (N.D. Cal., Civ. No. C-03-0007, 2004 ("'[I]nternational concerns' and 'competing policies' [have] no place in [agency] decision-making because such factors had already been weighed by Congress," at 77-78); aff'd, 494 F.3d 757, 769 (9th Cir. 2007) (holding arbitrary and capricious "the agency's decision-making process, which…was influenced to at least some degree by foreign policy considerations rather than by science alone, in contravention of the Congressional mandate" for the agency to make such decisions).

[159] CP-1 at 3 and CP-2 at 5, CP-3 at 4, and CP-4 at 5 (each Petition alleging that "…this is not an ordinary circumstance").

[160] CP-1 at 3 and CP-2 at 5, CP-3 at 4, and CP-4 at 5 (each Petition concluding that "FDA can no longer categorically dismiss mercury amalgam's negative environmental impact").

consideration of new environmental impact of such action under NEPA or FDA regulations, as applicable.[161]

Additionally, NEPA does not require FDA to continually assess changing environmental conditions with respect to previously proposed actions.[162] Nor is the Agency required to assess changing environmental effects when there is no "reasonably close causal relationship" between the environmental effect and the alleged cause.[163]

Under FDA regulations, absent extraordinary circumstances, the Agency is not required to prepare an environmental assessment or environmental impact statement before taking an action that is "categorically excluded."[164] An extraordinary circumstance exists only where a *proposed* action may have a significant environmental effect.[165] The Final Rule finalized the proposed action in 2009. As part of that action, FDA considered the environmental effects and determined under the categorical exclusion in 21 CFR 25.34(b) that it did not individually or cumulatively have a significant effect on the human environment and that neither an environmental assessment nor an environmental impact statement was required.[166]

The evidence and arguments presented in the Petitions, including your reference to the Minamata Convention and the governmental actions of other countries, do not present proposed actions *by FDA*. In partially granting and otherwise denying your requests, FDA is not taking any major federal action that changes the quality of the human environment. Therefore, the absence of any major federal action on dental amalgam forecloses any Agency requirement to prepare an environmental assessment or an environmental impact statement.

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[161] See 21 CFR part 25; Karst Envtl. Educ. and Protection, Inc. v. EPA, 475 F.3d 1291, 1295 (D.C. Cir. 2007).

[162] 42 U.S.C. 4321, et seq.; 40 CFR 1500.1, et seq.

[163] DOT v. Public Citizen, 541 U.S. 752, 767 (2004).

[164] See 21 CFR 25.30 (General) and 25.34 (Devices and electronic products).

[165] 74 FR 38706, citing Utah Envtl. Cong. v. Bosworth, 443 F.3d 732 (10th Cir. 2006).

[166] 74 FR 38704-06; see 21 CFR 25.21 (Extraordinary circumstances) and 25.22(b) (Actions requiring the preparation of an environmental impact statement). See also NEPA memo archived here: https://wayback.archive-it.org/7993/20170403223455/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/UCM236360.pdf.

### 6. Continued Use of Dental Amalgam

The Petitions claim that the Final Rule discourages a decrease in mercury exposure contrary to FDA's mercury policy commitment under the Minamata Convention. Specifically, in CP-1, you quote the Final Rule out of context and imply it means that FDA has valid scientific evidence that "any change towards use of dental amalgam is likely to result in positive public health outcomes" and that "any change away from use of dental amalgam is likely to result in negative public health outcomes."[167]

In the Final Rule, the quoted statements are not an FDA finding about the safety and effectiveness of amalgam that weighs probable benefits and probable risks. The statements appear in the Analysis of Impacts section of the Final Rule[168] as working assumptions to measure the *economic* impact of various hypothecated "public health outcomes," such as delayed dental treatments or increased or decreased costs of treatment, that by assumption are associated with alternative methods for regulating amalgams.[169] Acknowledgement of these public health outcomes are not FDA findings about the safety and effectiveness of dental amalgam and do not serve as an announcement of a policy to discourage mercury exposure reduction.

The Agency is statutorily required to classify medical devices based on the level of regulatory control necessary to provide reasonable assurance of the safety and effectiveness of the device. In the Final Rule, FDA reclassified the components of dental amalgam into class II and designated a special control guidance document to establish sufficient regulatory controls to provide such reasonable assurance. The Final Rule reclassified dental amalgam from class I into class II, in accordance with section 513(e) of the FD&C Act, which provides that FDA may do so based upon "new information." The Final Rule does not establish a general mercury policy concerning the use or non-use of dental amalgam.

While developing the Final Rule, the Agency determined that, "during 2008, there were an estimated 154.1 million dental restorations in the United States.[[170]] This number represents a decrease of almost 12 million restorations from 2005, with the decrease associated with better dental care. We assume that the trends to reduce the use of dental amalgam as a restorative material will continue as patients and dentists take advantage of improved alternative materials for restorative and cosmetic purposes."[171] The Final Rule, FDA's implementation of our current regulations, and our recent Safety Communication pertaining to amalgam use are not intended to stop the continued use of dental amalgam; but, given recent trends, we do not expect an increase

[167] CP-1 at 1.

[168] 74 FR at 38706-38708 and 38710.

[169] See Executive Order 12866 (Sep. 30, 1993), as amended.

[170] See American Dental Association, "Survey of Dental Practice—Dental Services," 2006.

[171] 74 FR at 38708.

from the existing levels of use. Based on these trends, to the contrary, FDA expects the use of dental amalgam as a restorative material to continue to decrease over time, irrespective of current FDA regulations.

### 7. Review of Scientific Literature

The Petitions claim that FDA cannot offer any reasonable assurance that amalgam is safe for children, pregnant women, and breastfeeding mothers, and has failed to recognize studies demonstrating the hazards of mercury exposure from dental amalgam.[172] FDA disagrees with your claim.

Prior to issuing the Final Rule, FDA carefully examined extensive information related to the safety and effectiveness of dental amalgam. This information included a comprehensive safety analysis of dental amalgam performed by the U.S. Public Health Service, U.S. Government research related to dental amalgam, several national and international comprehensive reviews of scientific information about the risks and benefits of the device, comprehensive safety analyses of dental products that contain mercury by international health organizations and foreign countries, and the scientific literature reviewed by the September 6-7, 2006 Panel meeting.[173] Several studies from the 2008-2009 search were reviewed in the Addendum to the White Paper.[174]

As part of the rulemaking proceeding for the Final Rule, FDA reviewed more than 200 scientific articles, published from 1997 to 2008, on the potential health effects of dental amalgam.[175] FDA has reconsidered the information and evaluations reviewed in the rulemaking proceeding for the Final Rule, and the evaluations developed since the publication of the Final Rule, including the 2004 Life Sciences Research Office (LSRO) Report.[176] FDA also reviewed the more than 3,200

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[172] CP-3 at 2-3 and CP-4 at 3-5.

[173] This panel meeting was held to discuss FDA's review of the amalgam literature in the White Paper. White Paper, cited at footnote 35 of this document.

[174] See Addendum to the White Paper, cited at footnote 38 of this document and accompanying text.

[175] 74 FR at 38697.

[176] Review and Analysis of the Literature on the Potential Adverse Health Effects of Dental Amalgam, Life Sciences Research Office, July 2004. The LSRO report examined studies published from 1996 through 2003. In conducting its review, LSRO engaged an independent panel of academic experts in the fields of immunotoxicology, immunology, and allergy; neurobehavioral toxicology and neurodevelopment; pediatrics; developmental and reproductive toxicology; toxicokinetics and modeling; occupational health and epidemiology; pathology; and general toxicology.

comments combined, many of which contained scientific journal articles, submitted to our public dockets on dental amalgam.[177] In addition, to support the review of primary studies published from 1997-2008, FDA evaluated the most recent U.S. government agency reviews of mercury toxicity.[178]

In an effort to determine if articles published subsequent to 2008 would have an impact on FDA's analysis, FDA has undertaken several literature searches during and covering the period 2008-2018. In each of these reviews, three databases (PubMed, Biosis, and Embase) thoroughly and others more generally were searched with key words, such as mercury, toxicity, mercury vapor, adverse effect, dental, etc. In the abstracts reviewed in our most recent search, FDA determined that none of the studies published in 2010-19 contained new information that would change FDA conclusions of the Final Rule about the health effects of dental amalgam.[179]

For these reasons, FDA does not agree with your contention that there is no valid scientific evidence of safety of amalgam use in these populations and that the risks clearly outweigh any possible benefit.

### E. Conclusion

Except for your Petition requests granted in part that address the potential risks and vulnerable populations identified in the September 2020 Safety Communication, we are denying your Petitions for the reasons discussed above. Even so, FDA continues to evaluate the safety of dental amalgam and will take further action as needed in accordance with our statutory authorities and regulations.

Sincerely,

Ellen J. Flannery -S Digitally signed by Ellen J. Flannery -S
Date: 2022.05.26 20:35:47 -04'00'

Ellen J. Flannery, JD
Deputy Center Director for Policy
Director, Office of Policy
Center for Devices and Radiological Health

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[177] See FDA dockets FDA-2001-N-0067 (for FDA's proposed rule on dental amalgam; this docket was later folded into FDA-2008-N-0163), FDA-2006-N-0543 (comments relating to the September 6 & 7, 2006 joint panel meeting on dental amalgam, formerly docket number 2006N-0352), and FDA-2008-N-0163 (reopening of the comment period on FDA's proposed rule on dental amalgam).

[178] See EPA IRIS Review, cited at footnote 45 of this document.

[179] See 2019 FDA Scientific Literature Review cited in footnote 46 of this document.