

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 872

[Docket No. FDA-2008-N-0163] (formerly Docket No. 2001N-0067)

RIN 0910-AG21

Dental Devices: Classification of Dental Amalgam, Reclassification of Dental Mercury,  
Designation of Special Controls for Dental Amalgam, Mercury, and Amalgam Alloy

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule classifying dental amalgam into class II, reclassifying dental mercury from class I to class II, and designating a special control to support the class II classifications of these two devices, as well as the current class II classification of amalgam alloy. The three devices are now classified in a single regulation. The special control for the devices is a guidance document entitled, "Class II Special Controls Guidance Document: Dental Amalgam, Mercury, and Amalgam Alloy." This action is being taken to establish sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of these devices. Elsewhere in this issue of the FEDERAL REGISTER, FDA is announcing the availability of the guidance document that will serve as the special control for the devices.

DATES: This rule is effective [insert date 90 days after date of publication in the FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT: Michael E. Adjodha, Food and Drug Administration, Center for Devices and Radiological Health, 10903 New Hampshire Ave., Bldg. 66, rm. 2606, Silver Spring, MD 20993-0002, 301-796-6276.

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## I. BACKGROUND

The following section provides an overview of the final rule, applicable statutory authority for classifying devices, the regulatory history of these dental devices, scientific information and safety assessments involving the devices, and the development of this rule.

### A. Overview

Dental amalgam is a metallic restorative material that is used for direct filling of carious lesions or structural defects in teeth. It is a combination of mercury (liquid) and amalgam alloy (powder), which is composed primarily of silver, tin, and copper.

As discussed in detail in this preamble, this final rule classifying dental amalgam reflects FDA's careful consideration of the valid scientific evidence related to dental amalgam's benefits, which include its effectiveness as a restorative material, strength, and durability, and its potential risks, which include those related to the release of low levels of mercury vapor. FDA is required

by statute to classify devices (21 USC 360c). This final rule classifies the device “dental amalgam” into class II and reclassifies the device “dental mercury” (hereinafter “mercury”) from class I to class II. Importantly, the rule also establishes special controls for dental amalgam, mercury, and amalgam alloy (mercury and amalgam alloy are combined to form dental amalgam). Special controls are established to provide a reasonable assurance of safety and effectiveness for class II devices and are in addition to the general controls already applicable to any device.<sup>1</sup> This rule designates a special controls guidance document with performance data and labeling recommendations as the special controls for dental amalgam.

The Agency has determined that class II with special controls is the appropriate classification for dental amalgam after evaluating the valid scientific evidence related to dental amalgam, including comprehensive reviews of the scientific literature and safety assessments. Based on its review of this scientific evidence, FDA made the two findings it is required by law to make when classifying a device (21 CFR 860.7(d)(1)): First, FDA found that, when subject to the general controls of the act and the designated special control, the probable benefits to health from the use of the device for its intended use and conditions for use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. Second, FDA found that, when subject to the general controls of the act and the designated special control, the scientific evidence adequately demonstrates the absence of unreasonable risk of illness or injury associated with the intended use of dental amalgam.

In developing this final rule, FDA reviewed scientific evidence and also considered the classification recommendation of the Dental Products Panel (Ref. 1), which concluded that there

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<sup>1</sup> General controls are specifically identified in the statute and include requirements such as adverse event reporting and good manufacturing practices. General controls are applicable to any class of device. Special controls are controls identified and designated by the Agency as controls in addition to the general controls that apply to a specific device to address the specific risks to health of that device.

are no major risks associated with encapsulated dental amalgam, when used as directed, but recognized there is a small population of patients who may experience allergic hypersensitive reactions to the materials in the device. The Panel also noted that improper use exposes dental professionals to risks associated with mercury toxicity, with improper storage, trituration, and handling contributing to this risk.

As part of its assessment, FDA considered the important public health benefits of dental amalgam and the advantages it presents as a restorative material.

Dental amalgam has been used since the 1890s.<sup>2</sup> Millions of patients have received dental amalgam restorations to treat dental caries.<sup>3</sup>

A dentist's decision concerning the use of a particular restorative material is complex, involving factors related to the tooth, the patient, the clinician and the properties of the restorative materials. The dentist must, among other considerations, take into account the patient's age, caries history, oral hygiene, ability to maintain a dry field, degree of tooth destruction and the necessity to perform a procedure quickly and efficiently due to a patient's ability to cooperate. Specific clinical situations may limit the restoration options. Dental amalgam provides advantages in that it may be placed quickly in a wet field while providing high strength, durability, longevity, and marginal integrity, features that may help prevent recurrent decay. Dental amalgams are typically used:

- In stress-bearing areas and in small to moderate sized cavities in posterior teeth;
- In teeth with severe destruction;
- As a foundation for cast-metal, metal-ceramic and ceramic restorations;
- When a patient's commitment to oral hygiene is poor; and/or

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<sup>2</sup> Earlier prototypes were available beginning in the 1830s.

<sup>3</sup> Over 50 million dental amalgam restorations are placed per year in the United States (Ref. 2).

- When moisture control is problematic.

Dental amalgam may provide benefits over other dental restorative materials because amalgam fillings offer a broad range of applicability in clinical situations, ease of use and relative insensitivity to variations in handling technique and oral conditions (Refs. 3-7).

FDA also considered the potential risks of dental amalgam. Dental amalgam is a combination of elemental mercury (liquid) and amalgam alloy (powder), which is composed primarily of silver, tin, and copper. FDA's assessment focused on the risks associated with the presence of mercury in the device.

Mercury is a toxic metal that exists naturally in several forms in the environment: elemental metallic mercury, inorganic mercury (ionic salt forms), and methylmercury (Ref 70, Ref. 69). Elemental metallic mercury is highly volatile and releases mercury vapor. This form of mercury has a well-studied toxicity profile and its toxicity is dependent on dose and exposure conditions. The toxicokinetics and adverse effects associated with mercury vapor are different from those associated with methylmercury. These differences include route of exposure (mercury vapor is inhaled while methylmercury is ingested), percent of dose that is absorbed (80% in the case of mercury vapor; 95% in the case of methylmercury), and toxicity profiles (Ref. 69, Ref. 70).

Dental amalgam releases low levels of mercury vapor, with higher amounts released with mastication and gum chewing (Ref. 3). Higher levels of exposure to elemental mercury vapor are also associated with placement and removal of dental amalgams. For example, urinary mercury concentrations in 43 children ages 5 to 7 years before and after amalgam placement (1-4 teeth filled) were  $3.04 \pm 1.42 \mu\text{g Hg/L}$  ( $2.34 \mu\text{g Hg/g Cr}$ ) and  $4.20 \pm 1.60 \mu\text{g Hg/L}$  ( $3.23 \mu\text{g Hg/g Cr}$ ), respectively (Ref. 8). Removal of amalgams resulted in an increase in urinary mercury;



values were  $1.8 \pm 1.2 \mu\text{g Hg/L}$  ( $1.4 \mu\text{g Hg/g Cr}$ ) before removal compared to  $2.8 \pm 2.1 \mu\text{g Hg/L}$  ( $2.2 \mu\text{g/g Cr}$ ) at 10 days post-removal (Ref. 9).

After inhalation, approximately 70-80% of a mercury vapor dose is absorbed by the lung, enters the systemic circulation, distributes to several organ systems in varying amounts, and excretion occurs generally via the urinary route (Ref. 70). Because of its high lipid solubility, mercury vapor readily diffuses into erythrocytes and is oxidized by the catalase-hydrogen peroxide complex to divalent mercuric ion ( $\text{Hg}^{2+}$ ) (Ref. 70). Despite this rapid oxidation and intracellular localization, a fraction of the elemental mercury dose crosses the blood-brain barrier. Once inside cells, mercury vapor is also oxidized to mercuric ions ( $\text{Hg}^{2+}$ ) that are unable to diffuse back across the cell membrane (Ref. 70). The mercuric ion is believed to be the proximate toxic species responsible for the adverse health effects of inhaled mercury vapor. The mercuric ion has a biological half-life of two months (Ref. 69, Ref. 70).

While mercury toxicity has been demonstrated in a variety of organ systems in laboratory studies, the central nervous system (CNS) and the kidneys are both target organs sensitive to mercury vapor (Ref. 69).

The first signs of mercury vapor toxicity at high doses are subtle effects on the nervous system, such as changes in nerve conduction, slight tremor, abnormalities in electroencephalography (EEG) patterns, and changes in motor functions, cognitive functions, and behavior. (Ref. 69, Ref. 70). With progressively higher exposures, these effects become more pronounced and include prominent tremor, ataxia (incoordination), memory loss, psychological distress, irritability, excitability, depression, and gingivitis (inflammation of the gums) (Refs. 69, 70).

Mercury also accumulates in the kidneys. Adverse renal effects can range from reversible proteinuria (protein in the urine) to irreversible nephrotic syndrome, depending on the degree of exposure to mercury vapor (Ref. 69, Ref. 70).

In addition to crossing the blood-brain barrier, mercury vapor has been shown in animal studies to cross the placenta and reach the fetal brain (Ref. 48, Ref. 44) is also able to cross the placenta and reach the fetal brain. Inorganic mercury, most likely in the form of  $\text{Hg}^{2+}$ , is found in breast milk after maternal exposure to mercury vapor and, therefore, may be present in breastfed infants (Ref. 55). Because maternal exposure to mercury vapor from dental amalgam may lead to prenatal and postnatal exposure of offspring, FDA considered the potential health effects of dental amalgam on developing fetuses and breastfed infants.

#### 1. Review of Scientific Evidence

As already noted, this rule and the special controls guidance reflect FDA's evaluation of the valid scientific evidence related to the use of dental amalgam in the population age six and older and in potentially sensitive subpopulations (developing fetuses, breastfed infants, and children under age six). The White Paper (Ref. 10) and Addendum (Ref. 11) referenced in this rule include more details regarding FDA's examination.<sup>4</sup> These documents are included as references and are available on FDA's website.

In developing the White Paper and Addendum, FDA drew from the expertise of other groups<sup>5</sup> that had previously conducted reviews related to the potential health effects of dental amalgam. FDA's approach was to build upon these reviews, rather than to duplicate the work other groups had already undertaken. FDA reviewed more than 200 scientific articles, published

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<sup>4</sup> FDA decided to conduct this comprehensive review of the literature and prepare the Addendum rather than revise the White Paper.

<sup>5</sup> These groups included the U.S. Public Health Service and the Environmental Health Policy Committee's Working Group on Dental Amalgam (Refs. 3, 12).

from 1997 to 2008, on the potential health effects of dental amalgam. In addition to considering these studies, FDA also considered information and assessments reviewed in the proposed rule, and other risk assessments developed since the publication of the proposed rule, including the 2004 Life Sciences Research Office (LSRO) Report (Ref. 13).<sup>6</sup> In an effort to determine if any very recent articles would have an impact on FDA's analysis, a literature search was conducted for 2008 – July 2009 (even though FDA had already reviewed studies published through October 2008). Three databases (PubMed, Biosis, and Embase) were searched with key words, such as mercury, toxicity, mercury vapor, adverse effect, dental, etc. Several studies from this search had already been reviewed in the FDA Addendum to the White Paper. After review of the total of 70 abstracts from the search, FDA determined that no studies have been published in 2008-2009 that would change FDA conclusions about the health effects of dental amalgam.

FDA also considered the fact that dental amalgam is a commonly used device with a low frequency of adverse events reported to the Agency. FDA received 141 adverse event reports related to dental amalgam from 1988 to 2008. It is estimated that over one billion amalgam restorations were placed during this time period. The majority of the dental amalgam adverse event reports submitted to FDA were anecdotal, lacked specific details, and were often reported years after placement of the restoration, making it difficult for the Agency to perform a causal analysis.

An overview of the available evidence and FDA's conclusions follows.

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<sup>6</sup> 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. (Ref. 13)

a. Evidence Related to the Population Age Six and Older:

i. Air Monitoring Standards for Elemental Mercury Vapor

The Agency for Toxic Substance and Disease Registry (ATSDR) has established a Minimal Risk Level (MRL)<sup>7</sup> for elemental mercury vapor at 0.2 µg/m<sup>3</sup>. The Environmental Protection Agency (EPA) has established a Reference Concentration (RfC)<sup>8</sup> for elemental mercury vapor at 0.3 µg/m<sup>3</sup>. These reference values were derived using a standard risk assessment approach employing uncertainty factors, including an uncertainty factor to account for variability in sensitivity of the human population. They are considered to represent chronic or lifetime inhalation exposures that are free from adverse health outcomes and protective of human health for all individuals, including potentially sensitive populations such as children prenatally or postnatally exposed to mercury vapor (Refs. 14, 15).<sup>9</sup>

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<sup>7</sup> ATSDR defines a Minimal Risk Level (MRL) as follows: “An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. ... [MRLs] are set below levels that, based on current information, might cause adverse health effects in the people most sensitive to such substance induced effects” (<http://www.atsdr.cdc.gov/mrls/>).

<sup>8</sup> EPA defines a Reference Concentration (RfC) as follows: “An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL [No Observed Adverse Event Level], LOAEL [Lowest Observed Adverse Event Level], or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used” ([http://www.epa.gov/ncea/iris/help\\_gloss.htm#r](http://www.epa.gov/ncea/iris/help_gloss.htm#r)).

<sup>9</sup> After considering a large body of literature, ATSDR derived the MRL for elemental mercury from a study of 26 workers exposed to low levels of mercury (0.026mg/m<sup>3</sup>) in three industrial settings for an average of 15.3 years (range 1-41 years) (Ref. 16). Urinary mercury concentrations for this study averaged 11.3µmol/mol creatinine (Cr) (approximately 20.1µg/g Cr; 26.1µg/L urine). Continuous exposure was taken into account by converting workplace exposures of 8hr/day-5days/week into exposures of 24hr/day-7days/week. Uncertainty factors (UFs) were used in deriving the MRL included variability in sensitivity to mercury within the human population (UF = 10) and the use of a lowest observed adverse effect level (LOAEL) – in this study, increased average velocity of naturally-occurring hand tremors – instead of a no observed adverse effect level (NOAEL). In deriving the MRL, the ATSDR applied a less conservative uncertainty factor for the LOAEL (UF = 3), an approach commonly used when the endpoint is determined to be a less serious effect. In total, an uncertainty factor of 30 was applied. Application of the exposure conversions and uncertainty factors yielded a tolerable mercury vapor intake concentration of 0.2µg/m<sup>3</sup> for chronic inhalation exposure. The derivation of the ATSDR MRL for chronic exposure to mercury vapor also considered supporting evidence from several more recent studies that showed effect levels and adverse outcomes similar to those reported in Fawer et al. (Ref. 16), including Ngim et al. (Ref. 17) and Piikivi and Tolonen (Ref. 18). (See ATSDR, Ref. 14) EPA derived its RfC for chronic inhalation exposure to mercury vapor using the same occupational exposure study (Fawer et al., Ref. 16) and supporting studies (including Ngim et al. (Ref. 17) and Piikivi and Tolonen, (Ref. 18) used by ATSDR in deriving the MRL for chronic mercury vapor

Using widely accepted values for the respiratory rate and tidal volume in individuals at various ages, the following ventilation rates were calculated: 16.2 m<sup>3</sup>/day for the average adult; 7.6 m<sup>3</sup>/day for the average five-year-old child; and 5.8 m<sup>3</sup>/day for the average one-year-old child.<sup>10</sup>

At these ventilation rates, chronic exposure at the level of the MRL would result in an estimated dose of mercury vapor of 3.2 µg/day in the average adult, 1.5 µg/day in the average five-year-old child, and 1.2 µg/day in the average one-year-old child. Chronic exposure at the level of the RfC would result in an estimated dose of mercury vapor of 4.9 µg/day in the average adult, 2.3 µg/day in the average five-year-old child, and 1.7 µg/day in the average one-year-old child.

ATSDR assumes a slightly higher ventilation rate of 20 m<sup>3</sup>/day for the average adult (Ref. 14). At this ventilation rate, chronic exposure at the level of the MRL would result in an estimated dose of elemental mercury vapor of 4 µg/day in the average adult. Chronic exposure at the level of the RfC would result in an estimated dose of elemental mercury vapor of 6 µg/day in the average adult.

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exposure (Ref. 15). EPA conducts periodic screening level reviews for chemicals and in 2002 decided that the RfC for mercury vapor would remain unchanged (Ref. 15).

<sup>10</sup> These ventilation rates were calculated as follows, using standard physiological parameters from several sources and handbooks (Refs. 19 and 20) **Adult:** The tidal volume per kilogram body weight in adults is 10.7 mL/kg. The weight of the average adult is 70 kg. Given these two values, the tidal volume of the average adult is 750 mL. The respiratory rate of the average adult is 12-15 breaths/minute. At a rate of 15 breaths/minute, the average adult would have a respiratory minute volume of 11.25 L/min. Given that there are 1440 minutes/day and 1 m<sup>3</sup>/1000 L, this would result in a ventilation rate of 16.2 m<sup>3</sup>/day. **Five-year-old child:** The tidal volume per kilogram body weight in five-year-old children is 10.7 mL/kg. The weight of the average five-year-old child is 20 kg. Given these two values, the tidal volume of the average five-year-old child is 217 mL. The respiratory rate of the average five-year-old child is 21-25 breaths/minute. At a rate of 25 breaths/minute, the average five-year-old child would have a respiratory minute volume of 5.3 L/min. Given that there are 1440 minutes/day and 1 m<sup>3</sup>/1000 L, this would result in a ventilation rate of 7.6 m<sup>3</sup>/day. **One-year-old child:** The tidal volume per kilogram body weight in one-year-old children is 10 mL/kg. The weight of the average one-year-old child is 10 kg. Given these two values, the tidal volume of the average one-year-old child is 100 mL. The respiratory rate of the average one-year-old child is 40 breaths/minute. At a rate of 40 breaths/minute, the average one-year-old child would have a respiratory minute volume of 4 L/min. Given that there are 1440 minutes/day and 1 m<sup>3</sup>/1000 L, this would result in a ventilation rate of 5.8 m<sup>3</sup>/day.

The U.S. Public Health Service (PHS) reviewed several studies estimating the daily dose of elemental mercury from dental amalgam (Ref. 3). In some of the studies, investigators measured the mercury concentration of intraoral and exhaled air in small populations of individuals with and without amalgams. In these studies, estimates of the daily dose of mercury from dental amalgams ranged from 1-29  $\mu\text{g}/\text{day}$ . However, the reliability of these studies is questionable. Problems have been cited with the instruments used to measure mercury vapor in the oral cavity. Questions have also been raised about whether the small size of the oral cavity is appropriate for accurately measuring vapor concentrations, and about how to control for variable factors such as the dilution of vapor with inhaled air within the oral cavity and inhalation/exhalation rates, analytical quality control, and differences in sampling methodology (Ref. 20). According to PHS, the best estimates of daily intake of mercury from dental amalgam restorations have come from measurements of mercury in blood among subjects with and without amalgam restorations, and subjects before and after amalgams were removed. For adults, these estimates range from 1-5  $\mu\text{g}/\text{day}$ .

The World Health Organization (WHO) also reviewed several studies estimating the daily dose of elemental mercury from dental amalgam (Ref. 21). WHO found that values generally in the range of 1-5  $\mu\text{g}/\text{day}$  were estimated in the U.S. adult population, which is consistent with the PHS determination. WHO noted three studies that made higher estimates of the daily dose. The highest estimate that WHO reports was a dose of 12  $\mu\text{g}/\text{day}$ , for middle-aged individuals with approximately 30 amalgam surfaces (Ref. 22).

According to these estimates, the daily dose of mercury from dental amalgam is generally expected to be in the same range as the daily dose that would result from chronic exposure at the level of the MRL (4  $\mu\text{g}/\text{day}$ ) or the RfC (6  $\mu\text{g}/\text{day}$ ) in adults. Moreover, exceeding these

protective reference levels does not necessarily mean that any adverse effects will occur (Refs. 14-15). FDA assumes that the daily dose from amalgam in children under six years old is below those in adults since children under six years old have fewer and smaller teeth and lower ventilation rates as compared to adults.

Given that the MRL and the RfC were derived to be protective and are set below air mercury concentrations associated with observed adverse health effects,<sup>11</sup> chronic exposure at these levels would not generally be expected to produce such effects. Chronic exposure to air mercury concentrations several times higher than the MRL and the RfC would also generally not be expected to result in adverse effects, because of the conservative approach of incorporating uncertainty factors in the derivation of these reference levels.<sup>12</sup> Moreover, both the MRL and the RfC assume lifetime chronic exposure. FDA has taken a conservative approach by applying these reference levels to children, who have experienced less than a full lifetime of exposure.

#### ii. Biological Monitoring Standards for Urine Mercury

##### Occupational Studies

Several studies have assessed the risk of adverse health effects in workers occupationally exposed to high doses of mercury vapor. Strong correlations have been found between daily, time-weighted air concentrations, adverse health outcomes, and urinary mercury levels in workers (Refs. 14, 21).

Based on a number of occupational studies, the American Conference of Government Industrial Hygienists (ACGIH) has determined that the biological threshold for preclinical

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<sup>11</sup> As described in Footnote 9, ATSDR used a total uncertainty factor of 30 to derive the MRL.

<sup>12</sup> As discussed by EPA in their Staff Paper on Risk Assessment Principles and Practices, "EPA risk assessments tend towards protecting public and environmental health by preferring an approach that does not underestimate risk in the face of uncertainty and variability. In other words, EPA seeks to adequately protect public and environmental health by ensuring that risk is not likely to be underestimated." See EPA 2004 An examination of EPA Risk Assessment Principles and Practices, EPA/100/B-04/001 available at: <http://www.epa.gov/osa/pdfs/ratf-final.pdf>.

changes for central nervous system and kidney effects is 50 µg Hg/g Cr (Ref. 24).<sup>13</sup> However, occupational studies published since 1996 report that increases in urinary levels of early biomarkers predictive of renal injury have been observed at urinary mercury concentrations of 16-28 µg Hg/g Cr (Refs. 25-28).

#### *Studies of Amalgam Bearers*

Studies of large cohorts indicate that urinary mercury concentrations in individuals without dental amalgam restorations are approximately 0.5-0.6 µg Hg/g Cr in adults (Refs. 29, 30) and 0.5-2 µg Hg/g Cr in children, aged 6-17 (Refs. 31, 32).

Studies of adults with dental amalgam restorations have found a positive correlation between the number of dental amalgam restorations in the mouth and urinary mercury concentration. In a study of 1,626 women, aged 16-49, urinary mercury concentrations ranged from 0.83-1.25 µg Hg/g Cr (Ref. 29). The average urinary mercury concentration for the 75 percent of the women who had 12 amalgam surfaces or less was reported to be 0.81 µg Hg/g Cr. In a study of 550 adults, aged 30-49, urinary mercury concentrations ranged from 0.75-2.9 µg Hg/g Cr in individuals with 1-46 amalgam surfaces (Ref. 33). In one study of 1,127 men, aged 40-78, with dental amalgam restorations, 47 percent of the participants had a urinary mercury concentration less than 1.5 µg Hg/g Cr, and 1.3 percent of the participants had urinary mercury concentrations over 12 µg Hg/g Cr (Ref. 30). A urinary mercury concentration of 1.9 µg Hg/g Cr was reported for men with approximately 20 amalgam surfaces. Based on the study's analysis, an individual with 60 amalgam surfaces would be expected to have a urinary mercury concentration of 4-5 µg Hg/g Cr.

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<sup>13</sup> Given that 50 µg Hg/g Cr is the threshold urinary mercury concentration associated with preclinical nervous and renal system effects, ACGIH recommends that the urinary mercury concentration of occupationally exposed individuals not exceed 35 µg Hg/g Cr. This urinary mercury concentration is associated with chronic occupational exposure of a healthy worker to an air concentration of 25 µg Hg/m<sup>3</sup>.



Studies have also assessed urinary mercury concentrations in amalgam-bearing children age six or older. Two prospective studies assessed urinary mercury concentrations in children age six and older after placement of dental amalgam restorations. In a seven-year study of children ages eight to ten at baseline, the highest average urinary mercury concentration reported during the study period was 3.2  $\mu\text{g Hg/g Cr}$  (Ref. 31); this level occurred during the second year of the follow-up and progressively declined through year seven. The subjects had an average total of 19 amalgam surfaces at the end of the study period. In a five-year study of children ages six to ten at baseline, average urinary mercury concentrations were 0.9  $\mu\text{g Hg/g Cr}$  (range 0.1-5.7) five years after dental amalgam placement (Ref. 34). The subjects had an average total of 12 amalgam surfaces at the end of the study period. The highest outlier in this study had a reported urinary mercury concentration of 10.5  $\mu\text{g Hg/g Cr}$ . Children from the composite restoration-only group averaged 0.6  $\mu\text{g Hg/g Cr}$  (range 0.1-2.9). In a study of 60 children aged 4-8 years (Ref. 89), those with amalgam restorations had higher urinary mercury concentrations (1.4  $\mu\text{g Hg/g Cr}$ ) compared to those without amalgams (0.436  $\mu\text{g Hg/g Cr}$ ).

The urinary mercury concentrations generally observed in adults and children age six and older with dental amalgam restorations is approximately one order of magnitude less than the threshold levels associated with preclinical neurological and renal health effects in persons occupationally exposed to mercury vapor. Reported high outliers in adults and children age six and older are also below this threshold level.

FDA has concluded that exposures to mercury vapor from dental amalgam do not put individuals age six and older at risk for mercury-associated adverse health effects.

### iii. Clinical Studies

In order to assess potential health effects of mercury exposure from dental amalgam in the population age six and older, FDA reviewed studies evaluating neurological and renal outcomes. Studies of persons occupationally exposed to mercury vapor are also helpful for assessing risks of potential toxicity in the population age six and older from exposure to mercury vapors released from dental amalgams because occupationally-exposed individuals are exposed to higher mercury levels than those associated with dental amalgams.

### Neurological Effects

#### Occupational Studies

In a study of chloralkali workers and age-matched controls evaluated twice at five years apart, no correlations were found between multiple neurobehavioral (motor and cognitive) and tremor tests and mercury vapor exposure (Ref. 35). Performance on only one test, the Digital Symbol Test, showed improvement when subjects were tested five years later after exposure ceased suggesting that these individuals experienced some neurological toxicity while still being exposed to mercury at the time of the initial testing. Those subjects who demonstrated improvement had the highest inorganic mercury blood concentrations.<sup>14</sup>

In another study, 38 chloralkali workers with average urinary mercury concentration of 9 µg Hg/g Cr were compared with non-exposed controls (average urinary mercury concentration 2 µg/g Cr (Ref. 36). No differences in results of multiple neurobehavioral tests were observed between the two groups.

#### Studies of Amalgam Bearers

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<sup>14</sup> The authors noted that “[w]hen summarizing the available evidence, one could suggest that long-term neurobehavioral effects on a group basis may occur when the average [urinary mercury] concentration has been in the range of 30-40 nmol/mmol Cr [53.1 – 70.8 µg Hg/g Cr] or higher, but not when the average [urinary mercury] concentration has been lower than 10 nmol/mmol Cr [17.7 µg HG/g Cr].”

Studies have shown a lack of association between amalgam exposure and neuropsychological and neurobehavioral deficits. In a retrospective study of 550 adults, no significant associations between neuropsychological function and indices of cumulative amalgam exposure over many years were found (Ref. 33). In a report evaluating 1,127 men (Ref. 37), no effects on tremor, coordination, gait, strength, sensation, muscle stretch, or peripheral neuropathy were associated with amalgam exposure.

It has been suggested that exposure to mercury vapor from dental amalgam may be linked to various neurological or neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and autism. There is a paucity of studies that evaluate a link between dental amalgam and these conditions.

In one study, regional brain levels of mercury were determined at autopsy in subjects with Alzheimer's disease and controls (Ref. 38). Brain mercury levels did not correlate with the number of amalgams and there were no differences between the Alzheimer's disease and control groups with respect to number of amalgams. In another study, the mean number of dental amalgam surfaces and urinary mercury concentrations for Alzheimer's disease patients were not different from those of control patients (Ref. 39). In a study of aging and Alzheimer's disease evaluating 129 Catholic nuns, aged 75-102, no effect of dental amalgam number and surfaces was observed for eight tests of cognitive function (Ref. 38). These findings do not support the hypothesis that mercury from dental amalgam plays a role in the pathogenesis of Alzheimer's disease.

Several reports of results from prospective clinical studies of dental amalgam numbers (Refs. 31, 32, 34, and 40) found no neurological deficits in children who first received dental amalgam restorations at ages six to ten and were followed for five or seven years.

FDA concludes that the existing data support a finding that exposures to mercury vapor at levels associated with dental amalgams do not result in neurological deficits, tremors, peripheral neuropathies, or Alzheimer's Disease in the population age six and older. Although the existing clinical data on purported links between dental amalgam and other neurological or neurodegenerative diseases, such as Parkinson's Disease are limited, FDA concludes that, in light of the air monitoring and biological monitoring evidence described above, there is information from which to determine that general and special controls are sufficient to provide a reasonable assurance of safety and effectiveness.

#### Renal Effects

The kidneys accumulate the highest organ concentration of mercury (as Hg<sup>2+</sup>) following exposure to mercury vapor. The concentration of mercury in the kidney has been associated with the number of dental amalgams (Refs. 41, 42).

#### Animal Studies

Renal mercury concentrations increased in proportion to increasing mercury vapor exposure concentrations in rats (Refs. 43,44). Pregnant rats exposed to high concentrations of mercury vapor through gestation exhibited increases in two biomarkers of renal injury at gestation day 15, but no changes were observed for three other biomarkers at any time evaluated during gestation (Ref. 44).

#### Occupational Studies

Numerous occupational studies of mercury vapor exposure indicate that effects on the kidney begin to manifest when urinary mercury concentrations reach or exceed 50 µg Hg/g creatinine (Ref. 24). However, occupational studies published since 1996 report that increases in urinary levels of early biomarkers predictive of renal injury have been observed at urinary

mercury concentrations of 16-28  $\mu\text{g Hg/g creatinine}$ . In a study of chloralkali workers exposed to mercury vapor for 13 years (mean urinary mercury concentrations of 16.5  $\mu\text{g/g Cr}$ ), no significant differences in urinary biomarkers of renal function were found between the exposed and non-exposed groups (Ref. 45). Urinary biomarkers of renal function may be reversible upon cessation of exposure at the levels of exposure in this study. In several occupational studies of exposed workers (Refs. 25-28), increases in urinary N-acetylglucosaminidase (NAG), a preclinical renal biomarker, were correlated with urinary mercury concentrations of 16-28  $\mu\text{g Hg/g Cr}$ . In another study, 38 chloralkali workers with average urinary mercury concentration of 9  $\mu\text{g Hg/g Cr}$  were compared with non-exposed controls (average urinary mercury concentration 2  $\mu\text{g Hg/g Cr}$  (Ref. 36). No differences in renal expression as measured by multiple preclinical urinary biomarkers were observed between the two groups.

#### Studies of Amalgam Bearers

Two prospective amalgam trials in children age six and older demonstrated that kidney injury is not associated with exposure to dental amalgam. In the New England trial (Ref. 46) groups of children had amalgam or composite restorations placed at ages 6-8 and were followed for 5 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 (Ref. 46). In another children's prospective trial (Casa Pia), groups of children had amalgam or composite restorations placed at ages 6-10 and were followed for 7 years. There were no

differences between the amalgam and composite groups with respect to the urinary excretion of microalbumin or albumin (Ref. 31), a biomarker of renal glomerular injury, and GST-alpha and GST-pi, two biomarkers of renal proximal and distal tubule injury, respectively (Ref. 47).

FDA concludes 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. The conclusions from studies of amalgam mercury exposure and neurological and renal endpoints are supported by independent investigations by other scientific bodies, such as the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), which stated in 2007 that "no risks of adverse systemic effects exist and the current use of dental amalgam does not pose a risk of systemic disease" (Ref. 6).

In light of the evidence from air monitoring, biological monitoring, and clinical studies, FDA concludes that exposures to mercury vapor from dental amalgam are not associated with adverse health effects in the population age six and older.

b. Evidence Related to Special Populations:

i. Potentially Sensitive Subpopulations (Developing Fetuses, Breastfed Infants, and Children under Age Six)

*Fetal Development*

Elemental mercury is transported through the placenta, which results in fetal exposure with the potential for subsequent developmental toxicity in offspring.

*Animal Studies*

FDA reviewed several well-conducted studies designed to assess high-level mercury vapor exposure on developmental effects in pregnant animals and their offspring. High levels of

maternal mercury vapor exposure were associated with the accumulation of mercury in fetal tissues. In one study (Ref. 48), no effects were observed on peripheral, somatosensory, auditory, or visual neurological functions in offspring of rats exposed to mercury vapor prenatally. In another study, prenatal exposure of pregnant rats was associated with adverse effects on fetal development only in cases where maternal exposure to mercury vapor was so high that it became toxic to the mother (leading to decreased maternal body weight, which can directly alter fetal development) (Ref. 44). The 2004 Life Sciences Research Office (LSRO) Report (Ref. 13) reviewed several studies of exposure of pregnant squirrel monkeys to high concentrations of mercury vapor. Although mercury accumulated in brain tissues *in utero*, only modest effects were observed on learning, motor function, and adaptive behaviors. In all of the aforementioned studies, maternal mercury vapor exposures were considerably higher than those estimated for individuals with dental amalgam restorations.

#### Occupational Studies

Very few available studies have evaluated the effects of elemental mercury exposure on pregnancy outcomes in humans. Although mercury has the ability to cross the placental barrier, the limited human data do not demonstrate an association between exposure to the mercury in dental amalgam and adverse reproductive outcomes such as low birth weight babies or increased rates of miscarriage. In a retrospective study (Ref. 49), no strong association or clear dose-response relationship between occupational exposure to chemical agents or restorative materials and the risk of miscarriage was observed. A slight but non-significant increase in risk was found for exposure to some acrylate compounds, mercury amalgam, solvents and disinfectants leading the authors to conclude that they could not rule out the possibility of a slightly increased risk of miscarriage among exposed dental workers. In a study of female factory workers exposed to a

median concentration of 90  $\mu\text{g Hg}/\text{m}^3$  (maximum 600  $\mu\text{g}/\text{m}^3$ ), no significant differences in stillborn or miscarriage rates were observed between exposed and unexposed subjects (Ref. 50). The mercury vapor concentrations to which these workers were exposed were over an order of magnitude higher than those associated with dental amalgam.

### Studies in Amalgam Bearers

Very few well-controlled animal studies or human epidemiological studies have evaluated the potential effect of low-level mercury vapor exposure on fetal development, especially at exposures experienced by dental amalgam bearers. In one retrospective study (Ref. 51), no association was found between the number of amalgam fillings in women and low birth weight of their babies. However, there is limited clinical information concerning the effects of prenatal exposure from maternal sources of mercury vapor at relevant concentrations.

Although the data are limited, FDA concludes 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. As described earlier in this document, maternal exposures are likely to increase temporarily when new dental amalgams are inserted or existing dental amalgam restorations are removed.

### *Breastfed Infants*

Mercury present in the mother's body is transmitted to her infant through breast milk. Maternal exposure to elemental mercury vapor would be expected to affect the concentration of inorganic mercury in breast milk.

The EPA has set a Reference Dose (RfD)<sup>15</sup> for oral exposure to inorganic mercury at 0.3  $\mu\text{g Hg}/\text{kg}/\text{day}$  (Ref. 52). This value represents the daily exposure to inorganic mercury that is

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<sup>15</sup> EPA defines a Reference Dose (RfD) as follows: "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be



likely to be without an appreciable risk of deleterious health effects during a lifetime. Reference values are derived to be protective against adverse health effects in sensitive subpopulations, such as developing fetuses and children.

Seven studies reviewed in the 2004 Life Sciences Research Office Report evaluated concentrations of total mercury in breast milk. In some of the reviewed studies, the number of amalgams correlated with the concentration of total mercury in breast milk (Refs. 53, 54, 55). However, the LSRO report concluded from its review that inorganic mercury absorption through breast milk is not a significant source of mercury exposure to infants (Ref. 13).

One study (Ref. 56) determined the concentration of breast milk mercury attributable to dental amalgam. In this study, the concentration of mercury in subjects with dental amalgam restorations was subtracted from the level in subjects without dental amalgam restorations. The level of mercury attributable to amalgam was 0.09 µg Hg/L (Addendum, p. 13). A standard value used in risk assessment for daily breast milk consumption is 0.85 L/day. Based on this value, the typical daily dose of inorganic mercury from breastfeeding in an individual with dental amalgam restorations would be 0.075 µg Hg/day. For a 5 kg infant, the daily exposure to inorganic mercury from breastfeeding would be 0.015 µg Hg/kg/day.

The estimated concentration of mercury in breast milk attributable to dental amalgam exposure is low and is an order of magnitude below the health-based exposure reference value for oral exposure to inorganic mercury established to protect the health of adults and children.

FDA concludes 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 amalgams.

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without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL [no observed adverse effect level], LOAEL [lowest observed adverse effect level], or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used" ([http://www.epa.gov/ncea/iris/help\\_gloss.htm#r](http://www.epa.gov/ncea/iris/help_gloss.htm#r)).

*Children under six years of age*<sup>16</sup>

No clinical studies have evaluated the effects of mercury vapor exposure from dental amalgam in children under six years of age. FDA assumes that the daily dose of mercury from amalgams in children less than six years old would not be higher than the estimated daily dose for adults (1-5 µg/day). FDA expects that the daily dose in children will be lower than the estimated dose for adults since children less than six have fewer and smaller teeth and lower ventilation rates, as compared to adults. The MRL and the RfC are derived using a conservative approach by applying uncertainty factors, and therefore are protective against adverse health effects, in populations including potentially sensitive subpopulations such as young children. Therefore, chronic exposure at these or slightly higher levels would not generally be expected to produce adverse health effects, suggesting that these children are not at risk for adverse health effects from mercury vapor released from dental amalgams.

*Summary*

Based on comparisons between the expected daily dose in these potentially sensitive subpopulations and the MRL and RfC, the exposure estimated from breast milk in breastfed infants, and clinical studies, we would not expect to see any adverse health effects in these subpopulations from mercury vapors released from dental amalgam. However, the data regarding risk in these subpopulations is not as robust as in adults due to the absence of measured urinary mercury concentrations and limited clinical data in these subpopulations.

## ii. Dental Professionals

Dentists and their staff may be exposed to mercury vapor in the workplace during the preparation, placement, and removal of dental amalgams. As noted by the Dental Products Panel,

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<sup>16</sup> Table 4 of this final rule (section V), “Projected Amalgam Restorations for Specific Populations” projects for 2009 that total amalgam in children under age 6 will be 2.6 million.

improper use of dental amalgam exposes dental professionals to risks associated with mercury toxicity. Improper storage, trituration, and handling contribute to this risk (Ref. 1).

Dental professionals are generally exposed to lower levels of mercury vapor than those that have been reported in industrial settings, and they have urinary mercury concentrations approaching those observed in non-occupationally-exposed population.

Several studies, primarily from one laboratory group, provide the most information about the potential health effects of low-level mercury exposure among dental professionals. In four of these studies, mean urinary mercury concentrations in dentists and hygienists ranged from 0.9 to 3  $\mu\text{g Hg/L}$  ( $\sim 0.7$  to  $2.3 \mu\text{g Hg/g Cr}$ ) and were associated with some neurobehavioral effects. In a fourth study which pooled results from six earlier studies, urine mercury concentrations ranged from less than 1  $\mu\text{g Hg/L}$  ( $\sim 0.8 \mu\text{g Hg/g Cr}$ ) to greater than 50  $\mu\text{g Hg/L}$  ( $\sim 38 \mu\text{g Hg/g Cr}$ ). A significant weakness of these studies was that no non-mercury-exposed dental professionals were evaluated; therefore, the effect of exposure to other chemicals in the workplace (gases, organic solvents) cannot be ruled out. Nor was a non-dental workplace control group studied, which would have been informative about effects of the dental work environment in general. The neurobehavioral measures reported in several studies of dentist/dental assistant populations as being significantly correlated with mercury exposure (urine mercury levels) have not been shown in some cases to be similarly affected in other occupationally-exposed groups where urinary mercury concentrations were much higher (e.g., chloralkali workers) than in the dental professional cohorts.

In one study (Ref. 57), 34 dentists and 15 hygienists exposed to mercury vapor in the workplace (mean number of amalgams placed was 16.1) were chelated to allow assessment of recent mercury exposure (pre-chelation) and body burden from longer-term exposures (post-

chelation). Mean urinary mercury concentrations for each group were:  $0.9 \pm 0.5 \mu\text{g Hg/L}$  ( $0.7 \mu\text{g Hg/g Cr}$ ) before chelation;  $9.1 \pm 6.9 \mu\text{g Hg/L}$  ( $7 \mu\text{g Hg/g Cr}$ ) after chelation. Subtle but statistically significant associations were demonstrated for recent exposure (pre-chelation) and measures of mood, motor function and cognition, and mercury body burden (post-chelation) was associated with symptoms, mood, and motor function. Chelation of mercury in dental professionals suggests that the mercury body burden in this population of workers is much greater than indicated solely by pre-chelation urinary mercury levels.

Another study (Ref. 58) 230 dentists (data pooled from six previous studies) had urinary mercury concentrations ranging from less than  $1 \mu\text{g Hg/L}$  ( $\sim 0.8 \mu\text{g Hg/g Cr}$ ) to greater than  $50 \mu\text{g Hg/L}$  ( $\sim 38 \mu\text{g Hg/g Cr}$ ); 50% subjects had urine concentrations less than  $3 \mu\text{g Hg/L}$  ( $\sim 2 \mu\text{g Hg/g Cr}$ ) and 30% had concentration greater than  $20 \mu\text{g Hg/L}$  ( $\sim 15 \mu\text{g Hg/g Cr}$ ). Dentists stratified into three urine mercury concentration groups: less than  $1 \mu\text{g Hg/L}$  ( $\sim 0.8 \mu\text{g Hg/g Cr}$ ),  $1\text{-}20 \mu\text{g Hg/L}$  ( $\sim 0.8\text{-}15 \mu\text{g Hg/g Cr}$ ) and greater than  $20 \mu\text{g Hg/L}$  ( $\sim 15 \mu\text{g Hg/g Cr}$ ). An association of urine mercury concentrations to a hand steadiness test was highly significant; however, associations with motor function tests were not significant.

Two studies (Refs. 59, 60) evaluated 194 dentists (average exposure of 26 years; average amalgam surfaces = 16; urine mercury =  $3.32 \pm 4.87 \mu\text{g/L}$ ,  $\sim 2.6 \mu\text{g/g Cr}$ ) and 233 hygienists (average exposure of 15 years; average amalgam surfaces = 12; urine mercury =  $1.98 \pm 2.29 \mu\text{g/L}$ ,  $\sim 1.48 \mu\text{g/g Cr}$ ) for neurological effects. No effects were observed on verbal intelligence and reaction time. Significant correlations with urine mercury concentrations were found on 9 measures in dentists and 8 measures in hygienists, including visual discrimination, hand steadiness, finger tapping and trail making tests. A weakness of the study was that no non-mercury-exposed dental professionals were studied; therefore, the effect of exposure to other

chemicals in the workplace (gases, organic solvents) cannot be ruled out. Nor was a non-dental workplace control group studied, which would have been informative about effects of the dental work environment in general.

FDA concludes that existing data indicate that dental professionals are generally not at risk for mercury toxicity except when dental amalgams are improperly used, stored, triturated, or handled.

### iii. Individuals with Mercury Allergies

Some individuals are hypersensitive or allergic to mercury and/or other metals. FDA reviewed several epidemiological and case studies related to the effects of mercury vapor exposure from dental amalgam on allergic individuals.

According to some of the studies that were reviewed, some patients develop adverse tissue reactions such as dermatological conditions or lesions of the skin, mouth, and tongue as a result of exposure to dental amalgam (Ref. 61, 62). In mercury-allergic individuals, clinical improvements were reported after dental amalgam restorations were removed. Other studies reported that dental amalgam may exacerbate pre-existing autoimmune disease in mercury-allergic individuals (Refs. 63, 64). After dental amalgam restorations were removed, the health status of these patients reportedly improved.

FDA concludes that existing data indicate that certain individuals with a pre-existing hypersensitivity or allergy to mercury may be at risk for adverse health effects from mercury vapor released from dental amalgam.

## 2. Rationale for Special Controls

In light of the above information, FDA has identified the following as the potential risks to health associated with the use of dental amalgam devices, requiring the establishment of

special controls: (1) exposure to mercury; (2) allergic response including adverse tissue reaction; (3) contamination; (4) mechanical failure; (5) corrosion; and (6) improper use. FDA is establishing a special controls guidance document that includes recommendations to address these risks as follows.

a. Risk of Exposure to Mercury

As discussed above, dental amalgam releases mercury vapor and is associated with a risk of human exposure to this vapor. The special controls to address this risk are recommendations for: (i) specific labeling, (ii) an information for use statement, and (iii) a performance test for mercury vapor release.

i. Specific Labeling Recommendation

The special controls guidance recommends the following specific labeling:

- **WARNING: CONTAINS MERCURY**
- Warning: May be harmful if vapors are inhaled
- Precaution: Use with adequate ventilation
- Precaution: Store in a cool, well ventilated place
- Contains [ ]% mercury by weight

The recommended warning about the presence of mercury in a dental amalgam device and the recommended disclosure of mercury content by weight will alert dental professionals of the potential for exposure to mercury vapor and will remind them of the need for protective measures, such as the use of gloves when handling the device. The recommended precautions about the need for adequate ventilation and the need to store in a cool, well ventilated place will encourage professionals to ensure there is adequate ventilation when in proximity to the device

and to use a vacuum pump and adequate ventilation during placement of dental amalgams to minimize the amount of mercury vapor that they or their patients may inhale.

ii. Information for Use Recommendation

Dental amalgam has been and remains one of the most commonly used restorative materials in dentistry. In the recent past the use of dental amalgam has gradually declined due to the improved properties of composite resin materials. Although amalgam has been used successfully for many years, the risks associated with this device have been controversial. Some scientists, professional groups, clinicians and patient advocacy groups have expressed concern about the potential hazards to health arising from mercury vapor release from amalgam restorations. Other groups of scientists, clinicians, and professional organizations have disagreed with these concerns. These opposing view points were voiced at the 2006 FDA joint panel meeting (Ref 66).

In order for dentists to make appropriate treatment decisions with their patients, it is important to provide information to help dentists understand the complexities of the science related to dental amalgam and its mercury content.

FDA recommends the inclusion of an “information for use” statement in dental amalgam labeling as a special control:

“Dental amalgam has been demonstrated to be an effective restorative material that has benefits in terms of strength, marginal integrity, suitability for large occlusal surfaces, and durability.<sup>17</sup> Dental amalgam also releases low levels of mercury vapor, a chemical that at high exposure levels is well-documented to

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<sup>17</sup> 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.

cause neurological and renal adverse health effects.<sup>18</sup> Mercury vapor concentrations are highest immediately after placement and removal of dental amalgam but decline thereafter.

Clinical studies have not established a causal link between dental amalgam and adverse health effects in adults and children age six and older. In addition, two clinical trials in children aged six and older did not find neurological or renal injury associated with amalgam use.<sup>19</sup>

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.

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<sup>18</sup> Liu, J. et al., "Toxic effects of metals," Casarett & Doull's Toxicology: The Basic Science of Poisons, Chapter 23, pp. 931-979, McGraw-Hill Medical, New York, New York, 2008.

Clarkson, T.W. et al., "The Toxicology of Mercury and Its Chemical Compounds," Critical Reviews in Toxicology, Vol. 36, pp. 609-662, 2006.

<sup>19</sup> 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, No. 15, April, 19, 2006.

Bellinger, D.C. et al., "Neuropsychological and Renal Effects of Dental Amalgam in Children: A Randomized Clinical Trial," Journal of the American Medical Association, Vol. 295, No. 15, April 19, 2006, 1775-1783, 2006.

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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.

Lauterbach, M. et al., "Neurological Outcomes in Children with and Without Amalgam-Related Mercury Exposure: Seven Years of Longitudinal Observations in a Randomized Trial," Journal of the American Dental Association, Vol. 139, 138-145, February 2008.



The Agency for Toxic Substances and Disease Registry's (ATSDR) and the Environmental Protection Agency (EPA) have established levels of exposure for mercury vapor that are intended to be highly protective against adverse health effects, including for sensitive subpopulations such as pregnant women and their developing fetuses, breastfed infants, and children under age six.<sup>20</sup> Exceeding these levels does not necessarily mean that any adverse effects will occur.

FDA has found that scientific studies using the most reliable methods have shown that dental amalgam exposes adults to amounts of elemental mercury vapor below or approximately equivalent to the protective levels of exposure identified by ATSDR and EPA. Based on these findings and the clinical data, FDA has concluded that exposures to mercury vapor from dental amalgam do not put individuals age six and older at risk for mercury-associated adverse health effects.

Taking into account factors such as the number and size of teeth and respiratory volumes and rates, FDA estimates that the estimated daily dose of mercury in children under age six with dental amalgams is lower than the estimated daily adult dose. The exposures to children would therefore be lower than the protective levels of exposure identified by ATSDR and EPA.

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<sup>20</sup> Agency for Toxic Substances and Disease Registry (ATSDR) and Research Triangle Institute, Toxicological profile for mercury, U.S. Dept. of Health and Human Services, Public Health Service, Atlanta, Georgia, 1999.  
United States Environmental Protection Agency (EPA), "Integrated Risk Information System (IRIS) Screening-Level literature Review" – Mercury, elemental, 2002.

In addition, the estimated concentration of mercury in breast milk attributable to dental amalgam is an order of magnitude below the EPA protective reference dose for oral exposure to inorganic mercury. FDA has 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.”

The purpose of this labeling recommendation is address potential misunderstandings about the risk of exposure to mercury from the device and to help dental professionals plan appropriate treatment recommendations for their patients by providing them with FDA’s assessment of the most current, best available evidence regarding potential risks to health from mercury vapor released from dental amalgams.

### iii. Performance Test Recommendation

The special controls guidance recommends a performance test to determine the amount of mercury vapor released by a dental amalgam device during corrosion ( $\text{ng}/\text{cm}^2$  in 4 hrs).

Dental amalgam releases the highest levels of mercury vapor when it corrodes (Ref. 65). By measuring the amount of mercury vapor released during corrosion, the recommended performance test will quantify the highest levels of vapor release that can be expected from a dental amalgam device. The results of this test will enable FDA, through a premarket notification (510(k)) submission, to determine if these levels are acceptable and are comparable to legally marketed devices.<sup>21</sup>

### b. Risk of Allergic Response Including Adverse Tissue Reaction

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<sup>21</sup> Dental amalgam devices currently on the market must also be in conformance with the special controls guidance.

Dental amalgam is associated with a risk of adverse tissue reaction, particularly in individuals with a mercury allergy, who may experience additional allergic reactions. The special controls to address this risk are recommendations for: (i) specific labeling and (ii) a performance test for biocompatibility.

i. Specific Labeling Recommendation

The special controls guidance recommends the following specific labeling:

- Contraindication: do not use in persons with a known mercury allergy.

The recommended contraindication is designed to prevent exposure and resultant adverse tissue reactions in allergic individuals.

ii. Performance Test Recommendation

The special controls guidance recommends a performance test to assess the biocompatibility of a dental amalgam device. Specifically, the guidance recommends that devices be tested in conformance with the following consensus standard: “ISO 7405:1997(E), Dentistry – Preclinical evaluation of biocompatibility of medical devices used in dentistry – Test methods for dental materials.”

Biocompatibility refers to the appropriate interaction between the device and the human body, and the minimization of risk of rejection or toxicity. Conformance to the recommended consensus standard will minimize the potential of a dental amalgam device to cause toxic or injurious effects by ensuring that the device will have the appropriate biological response for its intended use.

c. Risk of Mercury Contamination

When the mercury used to form dental amalgam is contaminated with impurities, such as oil, water, or other foreign matter, the amalgam may not harden properly. This may cause the

device to be less effective. The special control to address this risk is a recommendation for a quality control test.

The special controls guidance recommends a quality control test for the production of dental amalgam devices. Specifically, the guidance recommends that devices be tested in conformance with the ISO 24234:2004(E) consensus standard. This standard includes quality control procedures for mercury, setting specific guidelines for visually inspecting mercury during production and observing its pouring characteristics. Among other things, this standard describes what visual signs indicate that a mercury sample is contaminated and therefore unsuitable for dental amalgam.

The recommended quality control test will ensure that the mercury used in dental amalgam devices is free from contamination.

#### d. Risk of Mechanical Failure

If a dental amalgam device is not sufficiently strong, it will not be able to withstand the force of regular chewing. As a result, it may fracture and require replacement. The special controls to address the risk of mechanical failure are recommendations for (i) specific labeling and (ii) a performance test.

##### i. Specific Labeling Recommendation

The special controls guidance recommends the following specific labeling:

- Compressive strength (MPa) @ 24 hrs
- Dimensional change during hardening (%)
- Trituration time (s)
- Working time (min)

The recommended labeling will ensure that dental professionals are aware of the key physical properties of a dental amalgam device. This information will be useful in helping the professional decide if the device is suitable for an intended application.

#### ii. Performance Test Recommendation

The special controls guidance recommends that dental amalgam devices be tested in conformance with the ISO 24234:2004(E) performance standard. This standard calls for evaluation of the following physical properties:

- Complete chemical composition
- Compressive strength (MPa) @ 1 hr
- Compressive strength (MPa) @ 24 hrs
- Maximum creep (%)
- Dimensional change during hardening (%)
- Particle size distribution ( $\mu$ ) and shape, i.e., spherical, irregular, etc.
- Trituration time (s)
- Working time (min)

The recommended performance test will evaluate key physical properties of dental amalgam devices that could affect their function. Analysis of these properties will enable FDA, through a premarket notification (510(k)) submission, to determine if a device has physical properties that are acceptable and are comparable to legally marketed devices.

#### e. Risk of Corrosion

Dental amalgam devices may corrode under certain conditions, including when they are placed in direct contact with other metals. If a dental amalgam device corrodes, it will lose its strength and will need to be replaced. Corrosion also increases the amount of mercury vapor a

dental amalgam device releases. The special controls to address the risk of corrosion are recommendations for: (i) specific labeling and (ii) a performance test for corrosion potential.

i. Specific Labeling Recommendation

The special controls guidance recommends the following specific labeling:

- Precaution: Do not place the device in direct contact with other types of metals.

This labeling precaution recommendation will alert dental professionals of a potential material incompatibility between dental amalgam and other metal restoratives that may be present in the mouth, such as stainless steel, titanium, base metal alloys, and noble metal alloys. It will help ensure that a dental amalgam device is not placed in contact with a metal that will cause the device to corrode.

ii. Performance Test Recommendation

The special controls guidance recommends that dental amalgam devices be tested to assess their corrosion potential. Specifically, the guidance recommends that dental amalgam devices be tested in conformance with the ISO 24234:2004(E) performance standard. This standard calls for an evaluation of corrosion byproducts, identifying the type and amount of substances leached from the device when corrosion occurs.

The recommended performance test will provide information about what chemical products could be expected to be leached if the device were to corrode. This information will enable FDA, through a premarket notification (510(k)) submission, to determine if the device is acceptable and is comparable to legally marketed devices.

f. Risk of Improper Use

“Improper use” of a device can result from misuse of the device. The special controls to address the risk of improper use are recommendations for specific labeling.

The special controls guidance recommends the following specific labeling:

- Contraindication: Do not use in persons with a known mercury allergy
- Precaution: Single-use only

The recommended labeling contraindication will alert dental professionals of situations in which the use of a dental amalgam device is not recommended, such as in patients with a known mercury allergy. The recommended labeling precaution will inform dental professionals that a dental amalgam device is not intended to be reused.

#### B. Statutory Authority

FDA regulates devices, including dental devices, under the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 et seq.), and the act’s implementing regulations (parts 800 through 898 (21 CFR parts 800 through 898)). The Medical Device Amendments of 1976 (Public Law 94-295) amended the act to add premarket review authority and other authorities related to devices. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I devices, which are subject to general controls; class II devices, which are subject to general and “special” controls; and class III devices, for which premarket approval applications generally must be submitted.

General controls include requirements for registration, listing, adverse event reporting, and good manufacturing practice (section 513(a)(1)(A) of the act). Special controls are controls that, in addition to general controls, are applicable to a class II device to help provide reasonable

assurance of that device's safety and effectiveness (section 513(a)(1)(B) of the act). Under the 1976 amendments, class II devices were defined as devices for which there was insufficient information to show that general controls themselves would provide reasonable assurance of safety and effectiveness, but for which there was sufficient information to establish performance standards to provide such assurance. The Safe Medical Devices Act of 1990 (SMDA) (Public Law 101-629) broadened the definition of class II devices to mean those devices for which the general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish special controls to provide such assurance, including performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and any other appropriate actions the agency deems necessary (section 513(a)(1)(B) of the act). The premarket approval requirements specify data and information that must be provided to FDA to obtain approval of a class III device (section 515 of the act (21 U.S.C. 360e)).

Devices that were in commercial distribution before the enactment of the Medical Device Amendments of 1976 (May 28, 1976) are commonly referred to as "preamendments devices." Under section 513 of the act, FDA classifies preamendments devices according to the following steps: (1) FDA receives a recommendation from a device classification panel (an FDA advisory committee); (2) FDA publishes the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) FDA publishes a final regulation. FDA has classified most preamendments devices under these procedures.

Section 513(e) of the act governs reclassification of preamendments devices. This section provides that FDA may reclassify a device by rulemaking based upon "new information." FDA may initiate reclassification under section 513(e) or an interested person may petition FDA



to reclassify a preamendments device. The term “new information,” as used in section 513(e) of the act, includes information developed as a result of a reevaluation of the data before the agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, e.g., Holland Rantos v. United States Department of Health, Education, and Welfare, 587 F.2d 1173, 1174 n.1 (D.C. Cir. 1978); Upjohn v. Finch, 422 F.2d 944 (6th Cir. 1970); Bell v. Goddard, 366 F.2d 177 (7th Cir. 1966)).

Reevaluation of the data previously before the agency is an appropriate basis for subsequent regulatory action where the reevaluation is made in light of newly available regulatory authority (see Bell v. Goddard, supra, 366 F.2d at 181; Ethicon, Inc. v. FDA, 762 F. Supp. 382, 389-91 (D.D.C. 1991)), or in light of changes in “medical science.” (See Upjohn v. Finch, supra, 422 F.2d at 951). Whether data before the agency are past or new data, the “new information” to support reclassification under section 513(e) must be “valid scientific evidence,” as defined in section 513(a)(3) of the act (21 U.S.C. 360c(a)(3)) and 21 CFR 860.7(c)(2). (See, e.g., General Medical Co. v. FDA, 770 F.2d 214 (D.C. Cir. 1985); Contact Lens Assoc. v. FDA, 766 F.2d 592 (D.C. Cir.), cert. denied, 474 U.S. 1062 (1985)).

FDA relies upon “valid scientific evidence” in the classification process to determine the level of regulation for devices (§ 860.7). For the purpose of reclassification, the valid scientific evidence upon which the agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending premarket approval application (PMA). (See section 520(c) of the act (21 U.S.C. 360j(c)).

### C. Regulatory History of the Devices

#### 1. Regulatory Status

Dental amalgam<sup>22</sup> is a metallic restorative material that has been used for direct filling of carious lesions or structural defects in teeth since the 1890s<sup>23</sup>. It is a combination of two devices, mercury<sup>24</sup> (liquid) and amalgam alloy (powder), which is composed primarily of silver, tin, and copper. At the time FDA proposed to classify mercury and amalgam alloy, the devices were most commonly marketed individually in tablet/sachet or bulk form to be prepared by mixing the two devices in a dentist's office, although the devices were also available in an already combined predosed, encapsulated form. Since the mid-1980s, the device has been marketed most frequently in the predosed, encapsulated form.

FDA classified mercury and amalgam alloy separately in accordance with the classification procedures for preamendments devices. In 1980, FDA published a proposed rule to classify amalgam alloy into class II, based on the recommendation of a device classification panel (Dec. 30, 1980, 45 FR 85979), and finalized the classification of amalgam alloy into class II in the FEDERAL REGISTER of August 12, 1987 (52 FR 30099). Although FDA proposed classifying mercury into class II, in the FEDERAL REGISTER of August 12, 1987 (52 FR 30089) FDA issued a final rule classifying mercury into class I. FDA explained that it believed that the general controls of the act, particularly the requirement that the device bear adequate directions for use, were sufficient to provide reasonable assurance of the safety and effectiveness of the device and to address the risk of rare allergic reactions among patients as well as the risk of toxicity among dental health professionals.

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<sup>22</sup> "Dental amalgam," as it is referred to in this final rule, is a device that is a combination of two component devices, mercury and amalgam alloy.

<sup>23</sup> Earlier prototypes were available from the 1830s.

<sup>24</sup> FDA is no longer using the term "dental mercury," but instead is using "mercury," to more accurately reflect the fact that the mercury used in dental amalgam is elemental mercury.

FDA did not classify dental amalgam at the time it classified its two components, mercury and amalgam alloy. However, in accordance with its customary practice regarding regulation of devices composed of two or more devices, FDA has regulated the predosed, encapsulated form of dental amalgam in accordance with the requirements applicable to its component with the highest classification, i.e., amalgam alloy. Accordingly, dental amalgam devices entering the market have been regulated as class II devices under 21 CFR 872.3050, amalgam alloy.

## 2. Proposed Rule

In the FEDERAL REGISTER of February 20, 2002 (67 FR 7620), FDA published a proposed rule entitled “Dental Devices: Classification of Dental Amalgam and Reclassification of Dental Mercury; Issuance of Special Controls for Amalgam Alloy.” The proposed rule was based on the recommendation of the device advisory panel, information submitted in citizen petitions requesting the agency to take various actions with respect to the devices, a substantial amount of scientific data, and the results of several government safety assessments related to the devices (Refs. 3, 4, 12).

The Dental Products Panel<sup>25</sup> (the Panel) unanimously recommended that FDA classify dental amalgam in its encapsulated form into class II (Ref. 1). The Panel concluded that there are no major risks associated with encapsulated dental amalgam, when used as directed, but recognized there is a small population of patients who may experience allergic hypersensitive reactions to the materials in the device. The Panel also noted that improper use of the device exposes professionals to risks associated with mercury toxicity. To address these risks, the Panel recommended that the device be subject to voluntary performance standards, voluntary testing

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<sup>25</sup> A panel of FDA’s Center for Devices and Radiological Health Medical Devices Advisory Committee.

guidelines, and requirements that the device be used only on the written or oral authorization of a licensed practitioner, and only by persons with training or expertise in its use.

The proposed rule included the following actions: (1) classify encapsulated dental amalgam into class II (special controls); (2) amend the class II classification for amalgam alloy by designating special controls; and (3) reclassify mercury from class I (general controls) to class II (special controls). In the 2002 proposed rule, FDA identified risks to health associated with the use of dental amalgam, mercury, and amalgam alloy that it believed required the imposition of special controls that, in conjunction with the general controls of the act, would provide reasonable assurance of the safety and effectiveness of the device. The risks identified were mercury toxicity associated with the improper use of dental amalgam and allergic reactions in a small subpopulation of individuals. To mitigate these risks, FDA proposed a labeling guidance and compliance with recognized consensus standards as special controls for these devices. FDA proposed that all three devices be subject to the same special control guidance document, “Special Control Guidance Document on Encapsulated Amalgam, Amalgam Alloy, and Dental Mercury Labeling,” dated February 20, 2002, as well as the following consensus standards, as relevant: (1) International Standards Organization (ISO) 1559:1995 Dental Materials-Alloys for Dental Amalgam, and (2) American National Standards Institute/American Dental Association (ANSI/ADA) Specification No. 6-1987 for Dental Mercury. The comment period on the proposed rule was reopened on July 17, 2002 (67 FR 46941), and again on April 28, 2008 (73 FR 22877), to permit additional opportunities for public comment (Docket No. FDA-2008-N-0163).

3. Scientific Information, Safety Assessments, and Adverse Event Reports Regarding Dental Amalgam

a. Information and Assessments Discussed in the Proposed Rule

Before issuing the proposed rule, FDA carefully examined extensive information related to the safety and effectiveness of dental amalgam. This information included a comprehensive safety assessment of dental amalgam performed by the U.S. Public Health Service (PHS), U.S. government research related to dental amalgam, studies and other information submitted in citizen petitions to the agency, several national and international comprehensive reviews of scientific information about the risks and benefits of the device, comprehensive safety assessments of dental products that contain mercury by international health organizations and foreign countries, and the scientific literature reviewed by the Panel. See 67 FR 7621-7625 (Feb. 20, 2002).

b. Information and Assessments That Have Become Available Since Publication of the Proposed Rule

i. Life Sciences Research Office (LSRO) Report

In 2004, the Trans-agency Working Group on the Health Effects of Dental Amalgam completed a comprehensive review of approximately 300 peer-reviewed studies of dental amalgam and mercury vapor published from 1996 through 2003 (LSRO report) (Ref. 13). The project was completed under contract by Life Sciences Research Office, Inc. (LSRO), and was funded by the National Institutes of Health (NIH), in cooperation with FDA, the Centers for Disease Control and Prevention (CDC), and the Office of the Chief Dental Officer of the Public Health Service. In conducting the review, LSRO engaged an independent panel of experts from academia 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. The LSRO report concluded that there is little evidence to support claims of a causal relationship between mercury fillings and human health problems, such as kidney or cognitive dysfunction; neurodegenerative disease, specifically Alzheimer's disease or Parkinson's disease; or autoimmune disease (Refs. 13, 67). The report also identified important data gaps, including whether low-level mercury vapor results in neurotoxicity, whether low-level in utero exposure to mercury vapor affects the developing brain, and whether occupational exposure to mercury vapor affects reproductive and/or pregnancy outcomes.

ii. White Paper and Addendum Scientific Reviews

In an effort to assess whether peer-reviewed literature published since FDA's 1997 safety assessment of dental amalgam (Ref. 12) presented new information on the potential health risks of dental amalgam, FDA's National Center for Toxicological Research (NCTR) prepared a White Paper review (Ref. 10). Rather than duplicate previous extensive reviews of the scientific literature by U.S. government agencies and international organizations, NCTR chose to build on the previous reviews and conducted an in-depth evaluation of 34 primary research articles that were chosen for their scientific merit, relevance, and potential to provide the most significant current information regarding the potential health risks associated with exposure to mercury in dental amalgam. The conclusion in the draft White Paper was that the peer-reviewed scientific information published since 1997 was consistent with FDA's previous assessment that, except for persons with rare allergic or hypersensitivity reactions, individuals with dental amalgam restorations do not experience adverse effects from the device.

On September 6 and 7, 2006, FDA presented the findings of the White Paper in draft to a joint meeting of the Dental Products Panel and the Peripheral and Central Nervous System Drugs Advisory Committee (the 2006 Panel). At that time, FDA also opened a docket related to the

meeting to facilitate public submission of information regarding the potential health risks of mercury in dental amalgam (Docket No. FDA-2006-N-0543 (formerly 2006N-0352)).

The 2006 Panel heard from numerous public speakers, and then deliberated and made recommendations on a series of questions FDA had posed on its draft White Paper (Ref. 66). The committee concluded that FDA's draft White Paper had significant limitations, such as the fact that the literature search used a single database (PubMed), the Paper did not satisfactorily explain how the scientific references were chosen,<sup>26</sup> and it failed to identify significant gaps in the scientific knowledge, particularly with respect to exposure limits and possible health risks for sensitive subpopulations. The majority of the 2006 Panel voted that it could not find the conclusions of the draft White Paper to be "reasonable" in light of these limitations. In their closing comments, the panelists provided individual recommendations, including the individual (not consensus) recommendations that FDA consider labeling requirements related to the use of dental amalgam in pregnant women and small children, that manufacturers be required to provide information to patients to ensure that they understand that the devices contain mercury, and that the federal government (public health agencies) research the effects of dental amalgam mercury on reproductive health and developing fetuses.

In response to the deliberations and recommendations of the 2006 Panel, FDA conducted a more comprehensive review of the scientific literature in an Addendum to the White Paper (Ref. 11). In total, more than 200 scientific articles, including 33 case studies, were considered in the White Paper and its Addendum.<sup>27</sup>

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<sup>26</sup> Appendix A of the draft White Paper did list the inclusion and exclusion criteria for identification of relevant studies.

<sup>27</sup> FDA decided to conduct this comprehensive review of the literature and prepare the Addendum rather than revise the White Paper. FDA finalized the White Paper with the addition of the Addendum.

The conclusions of the Addendum generally confirmed the conclusions of the White Paper and previous assessments by other organizations and agencies regarding the potential health risks presented by the presence of mercury in dental amalgam. More specifically, the articles and case studies reviewed in the Addendum to the White Paper were consistent with the conclusion in earlier government safety assessments (Refs. 3, 4, 12 ) that exposures to mercury vapor from dental amalgam are not associated with adverse health effects in the population age six and older (see also section I.A.). As discussed in the Addendum, FDA also concluded that prospective clinical studies of dental amalgam published to date (Refs. 31, 32, 34, 40, 46, 47, 68) found no neurological deficits in children who first received dental amalgam restorations at ages six to ten and were followed for five or seven years. FDA concluded, however, that the clinical data are limited regarding certain subpopulations (pregnant women and their developing fetuses, and children under the age of six, including breastfed infants).

#### c. Adverse Event Reports

As part of FDA's effort to determine the appropriate regulatory controls to provide reasonable assurance of the safety and effectiveness of dental amalgam, FDA reviewed all adverse event reports submitted to MedWatch for dental amalgam devices through 2008. The review identified 141 reports, dating back to 1988, including 102 reports of injuries, 12 reports of malfunctions, 26 miscellaneous complaints, and 1 misreported death.<sup>28</sup> The large majority of the injury reports were submitted voluntarily by individual patients. The malfunction reports were submitted primarily by health professionals and two reports were submitted by manufacturers.

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<sup>28</sup> The death report appears to have been misclassified because it was self reported (an actual death had not occurred). This report attributes symptoms of joint pain, neurological spasms, a compromised immune system, and a variety of other physical symptoms to dental amalgam.



The malfunction reports described problems with encapsulated amalgam such as product shrinkage, inaccurate powder to liquid ratios, and capsule leaking. There were also some reports of mercury spills as a result of mixing (tritulating) amalgam capsules.

The injury reports described a wide array of conditions and symptoms that individual patients believed to be caused by their dental amalgam fillings. The conditions and symptoms reported included fatigue, headaches, joint pain, brain “fog,” depression, neuropathy, rheumatoid arthritis, hypothyroidism, visual impairments, hearing loss, allergies, kidney damage, attention deficit disorder, irritable bowel syndrome, seizures, abnormal menstrual cycle, weight loss, and developmental problems, such as autism, attention deficit hyperactivity disorder, and unidentified congenital defects. Several reporters stated that they experienced relief from their symptoms when their amalgam fillings were removed, while others stated that their symptoms did not appear until after their fillings were removed.

The great majority of the adverse event reports submitted to FDA regarding dental amalgam are anecdotal and lack specific details, such as when symptoms first appeared, how they progressed, and what may have caused onset or relief of certain symptoms. In addition, the reports frequently were not made until years after the events occurred. Because of these factors, FDA is unable to assess the relationship of the reported adverse effects with the device. FDA notes, however, that the number of adverse event reports it has received regarding dental amalgam is quite low in light of the device's long history of use in tens of millions of dental restorations in the United States each year.<sup>29</sup>

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<sup>29</sup> FDA estimates that dental amalgam has been used in approximately one billion restorations between 1988 and 2008.

## II. DEVELOPMENT OF THE FINAL RULE

In developing this final rule, FDA considered the comments and information submitted in response to the proposed rule, the scientific reviews, studies, and safety assessments described above, and its analysis of the adverse event reports submitted. The final rule and the special controls guidance document are consistent with the proposed regulation, although they reflect several changes made in response to the comments and information received. As proposed, the final rule classifies dental amalgam into class II, reclassifies mercury from class I to class II, and designates a special control for dental amalgam, mercury, and amalgam alloy. However, the final rule classifies the three devices together in a single regulation and uses the term “mercury” instead of “dental mercury.”

The special controls guidance document specifically revises the draft special controls guidance document as follows:

- Includes recommendations related to the updated relevant consensus standards, rather than designating these standards as separate special controls.
- Includes recommendations regarding device composition, performance data, warnings, and labeling precautions.
- Recommends a contraindication against use in persons with a known mercury allergy.
- Recommends that the labeling include an information for use (IFU) statement.
- Updates recommendations regarding performance testing to be included in 510(k) submissions to include strength, creep, dimensional change, particle shape and distribution, corrosion products, and amount of mercury vapor released.

- Replaces the recommendation that each ingredient of the device be listed in the labeling with the recommendation that the primary ingredients be listed, and that the labeling state that the device contains mercury.

- Replaces the recommendation that the labeling warn that the device contains zinc with the recommendation that the labeling warn that the device contains mercury. FDA believes that the effects of zinc on the expansion of dental amalgam are well understood and that a warning that the device contains zinc is not necessary to provide a reasonable assurance of the safety and effectiveness of the device. In contrast, as discussed in section I.A., FDA recommends that the device bear a warning that the device contains mercury because FDA believes such a warning is necessary to provide a reasonable assurance of safety and effectiveness because of the potential risks to health of exposure to mercury and toxicity and adverse tissue reaction.

- Deletes recommendations regarding packaging and handling because FDA has concluded that these recommendations are not necessary to provide a reasonable assurance of the safety and effectiveness of the device.

In this final rule, FDA is designating a special controls guidance document (described in section I.A.) that, along with the general controls under the act, will provide reasonable assurance of the safety and effectiveness of the device. Elsewhere in this issue of the FEDERAL REGISTER, FDA is announcing the availability of the special controls guidance. Following the effective date of this final rule, any firm submitting a 510(k) premarket notification for dental amalgam, as well as any firm currently marketing the device, must address the risks to health identified in the special controls guidance document. Firms marketing or intending to market mercury or amalgam alloy must address the risks to health identified in the special controls guidance document that apply to those devices.

When a guidance document is established as a special control by rulemaking, manufacturers are required to address the issues identified in the guidance, either by following the recommendations in the guidance or by some other means that provides equivalent assurances of safety and effectiveness. If a manufacturer proposes to use a means other than the recommendations set forth in the special controls guidance, it is required to demonstrate that the alternative means provides equivalent assurances of safety and effectiveness.

### III. COMMENTS AND FDA'S RESPONSES

As stated previously, in addition to the comment period provided when the proposed rule was issued in 2002, FDA reopened the comment period on the rule in July 2002 and again in April 2008. Altogether, FDA received more than 1,400 comments on the proposed rule and the draft special controls guidance document. The commenters included consumers, health professionals, industry, academia, State and Federal agencies, professional societies, and organizations. Because of the intertwined nature of the documents and the significant duplication of comments, FDA is summarizing and responding to the comments it received on both the proposed rule and the draft special controls guidance document in this preamble.<sup>30</sup>

In the 2008 FEDERAL REGISTER notice reopening the comment period on the proposed rule, FDA requested comments supported by empirical data and scientific evidence on specific topics relating to the classification of the devices and the special controls that should apply to them if they were classified into class II. FDA requested comments on whether the proposed special controls (materials and labeling) would provide reasonable assurance of the safety and effectiveness of the devices if they were placed in class II, and on whether the

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<sup>30</sup> FDA also received more than 1,800 comments to the docket for the 2006 Panel meeting on dental amalgam (Docket No. 2006N-0352), which had been established to permit persons to comment and provide information on the issues and questions raised at the meeting. FDA reviewed and considered those comments in finalizing this regulation.

proposed special controls guidance document should be revised in light of the recommendations and discussions of the 2006 Panel. FDA also sought information related to the agency's analysis of the benefits and costs of the various regulatory options for classifying the devices, including the number of annual procedures in which the devices are used, trends in the use of various restorative devices, information regarding alternatives to dental amalgam, how labeling describing the risks in certain populations might affect demand, how such risks should be communicated, information regarding the current level of mercury to which patients and professionals are exposed, and whether that exposure might be reduced by using alternatives to dental amalgam.

#### A. Classification

(Comment) FDA received many comments regarding the appropriate classification of these devices. The comments generally did not distinguish among dental amalgam, mercury, and amalgam alloy, treating them as one device, dental amalgam. Many comments urged the agency to classify the device into class III (premarket approval), frequently stating safety concerns. For example, some commentators urged the agency to classify dental amalgam into class III because, as a class III device, “[it would be] presumed as unsafe and needing to be proven safe before general use can be allowed” and that “it should be placed in class III where manufacturers are forced to prove that it is safe, not the class II where it can continue to be grandfathered.” Others believed the device should be classified into class II because there is sufficient information to establish special controls for the device that would provide reasonable assurance of its safety and effectiveness. One comment stated that special controls were unnecessary because it believed that the general controls of the act are sufficient to provide reasonable assurance of the safety and effectiveness of the device.

(Response) FDA has determined that class II with a designated special controls guidance document will provide a reasonable assurance of safety and effectiveness for dental amalgam. In reaching this determination, FDA made the findings required by § 860.7(d)(1) that, first, when subject to the general controls of the act and the designated special control, and when accompanied by warnings against unsafe use in individuals who are allergic to mercury, the probable benefits to health from use of the device outweigh any probable risks. Second, FDA has determined that, when subject to the general controls of the act and the designated special control, valid scientific evidence demonstrates the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

FDA classifies devices in accordance with the statutory criteria in section 513 of the act. As provided in section 513, class I devices are devices for which the general controls of the act are sufficient to provide reasonable assurance of safety and effectiveness. Class II devices are devices for which general controls are not sufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish special controls that, along with the general controls of the act, will provide such assurance. Class III devices are devices for which premarket approval is necessary to provide reasonable assurance of safety and effectiveness.

As stated above, FDA relies on valid scientific evidence in making determinations regarding classification. Valid scientific evidence is defined as "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, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device

under its conditions of use." § 860.7(c)(2). Consistent with the regulation, FDA does not rely on isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, or unsubstantiated opinions. The valid scientific evidence to support classification of a device may vary according to, among other things, the existence and adequacy of warnings and restrictions, and the extent of experience with use of the device. § 860.7(c)(2).

The standard for determining whether there is reasonable assurance that a device is safe is described in § 860.7(d)(1).<sup>31</sup> According to that section, "[t]here is reasonable assurance that a device is safe when it can be determined, based on 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. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

In determining the appropriate classification of dental amalgam, FDA has relied on valid scientific evidence, including, as described in detail in section I.A., several comprehensive reviews of the scientific literature and safety assessments, air monitoring standards for mercury vapor, biological monitoring standards for urine mercury, and clinical studies. Based on its review of this information, FDA concludes that exposures to mercury vapor from dental amalgam are not associated with adverse health effects in the population age six and older. With respect to potentially sensitive populations, i.e., fetuses, breastfed infants, and children under six years of age, FDA would not expect to see any adverse health effects in these subpopulations from mercury vapors released from dental amalgam, although clinical data are limited. These

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<sup>31</sup> There is no question regarding the effectiveness of the device. It is undisputed that the device has been used effectively in millions of dental restorations over 100 years.

conclusions are supported by independent investigations by other scientific bodies, such as the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), which stated in 2007 (Ref. 6) that "no risks of adverse systemic effects exist and the current use of dental amalgam does not pose a risk of systemic disease."

Consistent with the regulation defining valid scientific evidence, in determining the appropriate classification of dental amalgam, FDA has considered the device's long history of use in tens of millions of procedures in the United States each year, as well as the information available regarding that use. FDA has also considered the adequacy of warnings and the fact that the device is a prescription device and, therefore, available to patients only with the involvement of a health care provider. Finally, FDA has considered the probable benefits to health from use of the device, such as its strength, marginal integrity, suitability for large occlusal surfaces, durability, ease of placement, and low failure and complication rates.

FDA recognizes that dental amalgam releases low levels of mercury, and that there are scientific data showing mercury vapor, at high enough exposures, to be a neurotoxicant and nephrotoxicant. FDA also recognizes that certain individuals are allergic to mercury. In addition, 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. FDA believes that, in order to provide reasonable assurance of the safety of dental amalgam, it is important that dentists are informed that the device contains mercury, that it is contraindicated against use in persons with a known allergy to mercury, and that the labeling include an information for use statement discussing the benefits, risks, and scientific study information.



FDA has concluded that general controls alone are not sufficient to address the identified risks to health presented by dental amalgam and thus provide reasonable assurance of its safety and effectiveness. FDA has also determined that premarket approval is not necessary to provide such assurance because there is sufficient information to establish special controls that, in conjunction with the general controls under the act, will provide reasonable assurance of the safety and effectiveness of the device. Specifically, FDA has concluded that the recommendations in the special controls guidance document, including the recommended labeling statements, along with the general controls of the act, are sufficient to provide a reasonable assurance of the safety and effectiveness of the device.

In accordance with § 860.7(d)(1), FDA has also concluded that, when subject to the general controls of the act and the designated special control, and when accompanied by warnings against unsafe use in individuals who are allergic to mercury, the probable benefits to health from use of the device outweigh any probable risks. Finally, FDA has determined that, when subject to the general controls of the act and the designated special control, valid scientific evidence demonstrates the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

(Comment) Some comments were opposed to “FDA reclassifying mercury-encapsulated amalgam dental fillings as a class II,” stating that “FDA is moving quickly to approve mercury.”

(Response) These comments reflect a misunderstanding of the device classification process. Mercury, amalgam alloy, and dental amalgam are legally marketed preamendments devices. As explained above, preamendments devices are subject to specific classification procedures. In 1987, FDA classified mercury and amalgam alloy through notice and comment rulemaking, as required by the statute. Although FDA did not classify dental amalgam (the

combination of those two devices) at that time, the device has been regulated in accordance with the requirements applicable to its component with the highest classification, i.e., amalgam alloy. In 2002, the agency issued a proposed rule to classify dental amalgam. Consistent with that proposed rule, FDA is now classifying the device into class II subject to a special control that, along with the general controls under the act, will provide reasonable assurance of its safety and effectiveness. Thus, this rule does not constitute an “approval” for marketing, but rather establishes additional regulatory controls for the device.

(Comment) One comment stated that dental amalgam should be regulated as a class III device because it is an implant.

(Response) FDA disagrees with the comment. As explained in the FEDERAL REGISTER of December 30, 1980 (45 FR 85962 at 85964), FDA does not consider restorative materials placed in the teeth, such as dental amalgam, to be implants<sup>32</sup>. Moreover, even if the devices were considered to be implants, FDA would not be required to classify them into class III. In accordance with section 513(d)(2)(B) of the act (21 U.S.C. 360c(d)(2)(B)) and 21 CFR 860.93, an implant may be classified into class I or class II if FDA determines that premarket approval is not necessary to provide reasonable assurance of its safety and effectiveness. As stated above, FDA has made this determination with respect to dental amalgam.

### B. Banning

(Comment) Some comments stated that dental amalgam should be banned because it is poisonous and not safe for use in dentistry. Other comments requested that dental amalgam be banned for children 18 and under, women of childbearing age, pregnant women, nursing mothers,

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<sup>32</sup> The classification panel identified a dental implant 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). Dental restorative materials such as amalgam do not protrude through the mucosa of the oral cavity and, therefore, are not considered implants.

and persons with compromised immune systems and kidney problems. Some comments suggested that FDA employ the “precautionary principle” adopted by other countries to protect these populations. In contrast, other comments noted that no scientific study or assessment has found a causal link between dental amalgam and adverse health effects in either the general population or in any sensitive subpopulation, and that the device has been used safely for many years in millions of dental restorations.

(Response) As discussed in detail above, FDA disagrees that the levels of mercury released from dental amalgam contribute to adverse health outcomes or is unsafe for use in dentistry when used with appropriate occupational health controls for dental offices. FDA recognizes that certain countries, e.g., Norway, Sweden, and Denmark, have banned dental amalgam, adopting a “precautionary principle” approach (taking preventive action despite uncertainty regarding the need for such action). However, FDA regulates devices, like dental amalgam, in accordance with the requirements of the act. As explained above, in accordance with the statutory criteria for classifying devices, FDA has concluded that there is sufficient information from which to establish special controls that, along with the general controls of the act, will provide reasonable assurance of the safety and effectiveness of the device. Specifically, FDA has determined that the risks to health presented by dental amalgam can be addressed through the general controls of the act in conjunction with the recommendations in the special controls guidance document. Because of this determination, FDA disagrees with comments suggesting that the device should be banned.

### C. Mercury Content and Toxicity

(Comment) One comment stated that the labeling of the device should disclose the fact that it contains mercury, citing to a recent poll showing that 76 percent of Americans do not

know that the primary component of amalgam fillings is mercury. Another comment stated that the amount of mercury vapor released from dental amalgam also should be disclosed.

(Response) FDA agrees that the labeling of the device should disclose the fact that it contains mercury. Accordingly, the special controls guidance recommends that the labeling include a warning that the device contains mercury and disclose the total mercury content (% by mass). FDA has concluded that labeling disclosing the amount of mercury vapor released from the device would not provide useful information because the mercury vapor released in a clinical setting varies among patients and is dependent on several variables, such as age and wear of the restoration, as well as the diet and chewing habits of the patient. FDA believes, however, the recommended warning about the presence of mercury in a dental amalgam device and the recommended disclosure of mercury content by weight will alert dental professionals of the potential for exposure to mercury vapor and will remind them of the need for protective measures, such as the use of gloves when handling the device. The recommended precaution about the need for adequate ventilation will encourage professionals to use a vacuum pump and adequate ventilation during placement of dental amalgams to minimize the amount of mercury vapor that they or their patients may inhale. Moreover, FDA is recommending that, to establish substantial equivalence to a legally marketed device in a 510(k) premarket notification, manufacturers conduct a test showing that the amount of mercury vapor released due to corrosion is acceptable when evaluated using an FDA-recognized standard or an equivalent method of evaluating the amount of mercury vapor released due to corrosion.

(Comment) Several comments were submitted in response to FDA's request for information on the current level of exposure to the mercury in dental amalgam for patients and dental professionals. One comment stated that dental amalgams release 0.53 micrograms of

mercury per surface per day, resulting in an uptake into the blood stream of 0.081 micrograms of mercury per surface per day, well below the World Health Organization (WHO) Acceptable Daily Intake (ADI) levels of 40 micrograms/day or 300 micrograms/day for demonstrable health effects to the most sensitive individual. Another comment stated that dental amalgam fillings release 4 to 22 micrograms/cm<sup>2</sup> per day, that those amounts are increased further by galvanism, heat, or chewing, and that data show an average of 60 micrograms of mercury are excreted daily in the feces of the average patient with amalgam fillings. Another comment stated that the average urinary mercury concentrations in children (age six and older) with amalgam fillings range from 0.1 to 5.7 micrograms/gram creatinine, as compared to 0.1 to 2.9 micrograms/gram creatinine for children with composite fillings. Another comment stated that health screenings of dental professionals from 1997-2007 found an average urinary mercury concentration of approximately 2.5 micrograms/L and that this level is within the range of the urinary mercury concentration found in individuals who are not exposed to mercury in their occupations. Finally, one comment stated that there are 0.2 micrograms of mercury in the breathing zone of dentists during placement and removal of amalgam.

(Response) FDA agrees with the comments that the current level of exposure to mercury in dental amalgam, for patients with restorations and dental professionals exposed occupationally, is below the accepted threshold levels for the most subtle health effects and is consistent with the conclusions of previous safety assessments (Refs. 3, 6, 12, 13) that the mercury in dental amalgam does not present a risk to health for the population age six and older. While the fact that dental amalgam releases mercury vapor has been known for a long time, it is difficult to make accurate estimates of the amount of mercury released from amalgam and subsequent absorption of mercury in the body using an air monitoring approach. These difficulties account

for the disparate range of values reported in the literature, some of which are noted in the comment above. Because of the difficulties noted in determining a robust estimate of daily dose of mercury resulting from monitoring of mercury vapor in the oral cavity, as discussed in section I. A., FDA is primarily relying on a consensus estimate of 1-5 µg/day for adults (Refs. 3, 22).

FDA also recognizes that good dental hygiene practices, such as the use of vacuum pumps and chair-side traps, have greatly reduced the level of mercury to which dental professionals are exposed. Nevertheless, because dental amalgam releases mercury vapor and is associated with a risk of human exposure to this vapor, and because some individuals have a known allergy to mercury, FDA is recommending that the labeling warn that the device contains mercury, contain a precaution that it should be used with proper ventilation, and include a contraindication against use in persons with a known allergy to mercury.

(Comment) A few comments stated that dental amalgam fillings contribute to the majority of the mercury body burden in the general population and that urinary mercury concentrations are not measures of mercury body burden, but rather represent a combination of the amount of mercury to which an individual has been exposed and his or her ability to excrete mercury. The comments added that 90 percent of mercury is excreted from the body through the fecal route, and that low urinary mercury concentrations are not an accurate predictor of mercury exposure. Some comments stated that data obtained from autopsies demonstrate that high mercury levels are present in the brain and kidneys, despite dental amalgam mercury exposure levels being below safety limits. A few comments noted that mercury passes through both the umbilical cord and the blood/brain barrier.

(Response) FDA recognizes that dental amalgam contributes to the majority of the body burden of mercury for many people not occupationally exposed to mercury (Ref. 22). FDA

recognizes that urine and feces are major routes of mercury excretion, but also recognizes that which excretion route predominates is dependent on the mercury species. The “90% mercury excreted by the fecal route” relates to excretion of organic methylmercury, and this high percent is not the case for inorganic forms of mercury, where the urinary route predominates, especially in the case of chronic mercury vapor exposure (Refs. 14, 69, 70 ). The amount of mercury excreted into feces is not a well-accepted index of exposure to elemental mercury vapor. Further, the correlation of fecal mercury levels, mercury vapor exposure, and adverse health effects has not been reliably established, as has been shown for urinary mercury concentrations. Fecal mercury concentrations might increase during removal of dental amalgams due to swallowing amalgam particles. Fecal levels might also be elevated from dietary exposure to methylmercury, which undergoes extensive enterohepatic recycling between the GI tract and liver biliary excretion system.

FDA disagrees with the comment that urinary mercury concentrations are not accurate measures of inorganic mercury, including mercury vapor, exposure. In fact, FDA and other public health agencies, such as ATSDR (Ref. 14), and WHO (Refs. 21, 22), consider urinary mercury concentrations to be the most accurate and widely used biomarker for assessing the absorbed dose that results from chronic mercury vapor exposure. For example, in a number of occupational studies, strong correlations have been found between daily, time-weighted air concentrations (which are considerably higher than exposures to dental amalgam mercury) and urinary mercury concentrations in workers (Refs.14, 21). In studies evaluating dental amalgam mercury exposure, urinary mercury concentrations have been shown to be proportional to the number of amalgam restorations and/or surfaces in the mouth.

FDA is aware that, in autopsy studies, mercury has been found to accumulate in the brain. However, it is difficult to draw conclusions from autopsy studies regarding a potential association between exposure to dental amalgam and adverse health outcomes without information concerning the individual's lifetime history of exposure to mercury from fish and other environmental sources. Similarly, even in cases attempting to find an association, meaningful conclusions could not be drawn between neurodegenerative disorders, the number of dental amalgams, and the amount of accumulated mercury, because it is possible that damaged neuronal cells in patients with neurodegenerative disorders are able to accumulate more mercury than healthy cells (Ref. 70).

In response to the comments noting that mercury passes through both the umbilical cord, FDA agrees that mercury vapor has the ability to cross the placental barrier. As discussed in detail in section I.A., FDA found that the limited human data do not demonstrate an association between exposure to the mercury in dental amalgam and adverse reproductive outcomes such as low birth weight babies or increased rates of miscarriage. Moreover, FDA also reviewed several well-conducted studies designed to assess high-level mercury vapor exposure on developmental effects in pregnant animals and their offspring. In one study no effects were observed on peripheral, somatosensory, auditory, or visual neurological functions in offspring of rats exposed to mercury vapor prenatally (Ref. 48). In another study, prenatal exposure of pregnant rats was associated with adverse effects on fetal development only in cases where maternal exposure to mercury vapor was so high that it became toxic to the mother (leading to decreased maternal body weight) (Ref. 44). More details are provided in section I.A.

(Comment) One comment stated that mercury in dental amalgam is more toxic than mercury in fish.



(Response) The form of mercury in dental amalgam (mercury vapor) is different from the form of mercury in fish (methylmercury). These two types of mercury differ in terms of kinetic behavior, mechanism of action, exposure routes, and tissue targets. For the purpose of classifying dental amalgam, FDA is addressing only the form of mercury in that device. As discussed in detail above, FDA disagrees that the levels of mercury released from dental amalgam are unsafe.

(Comment) A few comments stated that toxic/allergic reactions to mercury in dental amalgam may produce autoimmune conditions such as lichen planus lesions, eczema, pustulosis, and dermatitis, and often play a role in the pathogenesis of periodontal disease.

(Response) After reviewing 23 case studies and several epidemiological studies in the Addendum to the White Paper and conclusions from other reviews, FDA concluded that various dermatological conditions or lesions of the skin, mouth, and tongue were attributed to direct or indirect contact with dental amalgam, and may have been related to a pre-existing hypersensitivity or allergy to mercury and/or other metals. To help ensure that the device is not used in patients who are allergic to mercury, FDA is recommending that the labeling of the device contain a warning that the device contains mercury and a contraindication against use in persons with a known allergy to mercury.

FDA disagrees that the mercury from dental amalgam plays a role in the pathogenesis of periodontal disease. Based on its review of the scientific literature on this subject (Refs. 71- 75), FDA has concluded that the mercury in dental amalgam is not an etiological or aggravating agent for the initiation, propagation, or aggravation of any form of periodontitis.

(Comment) Several comments suggested that the mercury in dental amalgam causes or contributes to chronic neurological or neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and autism.

(Response) FDA discusses in detail in section I.A the available clinical information related to these diseases and its conclusions. In addition to the studies discussed in section I. A., and explained in the White Paper and Addendum reports (Refs. 10, 11), no evidence of neurodegenerative diseases have been reported in occupational cohorts exposed to much higher levels of mercury vapor in the workplace compared to the low levels in non-occupational groups with exposure from amalgams.

(Comment) One comment claimed that dental amalgam may cause kidney damage in children, as evidenced by a recent clinical trial (New England) (Ref. 46) that showed that children with amalgam restorations had higher levels of microalbuminuria (protein in urine), which is a marker of kidney injury, than children with non-amalgam restorations.

(Response) FDA disagrees with this comment. FDA reviewed the New England trial (Ref. 46) in the Addendum to the White Paper and concluded 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 (Ref. 46). However, in another children's prospective trial (Casa Pia), there were no differences between the amalgam and composite groups with respect to the urinary excretion of microalbumin or albumin (Ref. 31), a biomarker

of renal glomerular injury, and GST-alpha and GST-pi, two biomarkers of renal proximal and distal tubule injury, respectively (Ref. 47) (see also section I.A).

#### D. Patient Information

(Comment) Several comments stated that FDA should require dentists to inform their patients that dental amalgam contains mercury, and to advise them of the risks and benefits of the device, as well as the various restoration choices available to them. Many comments expressed concern that the labeling information would be provided only to dentists and not to patients. Several comments suggested that informed consent should be obtained from patients before they are treated with the device.

(Response) As a preliminary matter, FDA believes the comments that suggested that “informed consent” be obtained before patients receive dental amalgam were not using the term as it is used in 21 CFR part 50, which applies to the protection of human subjects in clinical investigations (for example, investigations of devices that have not been cleared or approved for marketing). Rather, these comments appear to be concerned about ensuring that patients are informed about the risks, benefits, and alternatives to dental amalgam.

FDA recognizes that selection of an appropriate restorative material for an individual patient, and hence an appropriate treatment plan, is a complex matter that requires the expertise of the dental professional. In selecting the appropriate restorative material for an individual patient, the dentist routinely considers many factors, such as the patient's oral health, the material properties of the various options, and the patient's medical history, including whether the patient has a known allergy to mercury.

FDA believes that the recommended labeling statements in the special controls guidance document will provide dentists with important information that will improve their 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 can not 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.

#### E. Alternative Materials

Several comments were submitted in response to FDA's request for information on the relative costs and replacement lives of dental amalgam and alternative materials, particularly composite resins.

(Comment) With respect to cost, one comment stated that composites cost 46 percent more than equivalent amalgam restorations and are more likely to fail, resulting in the need for crowns on large surfaces. Another comment stated that alternative materials cost 20 percent more than amalgam restorations. One commenter stated that data from 2007 indicate that the average fee submitted to insurance companies for one to four or more surfaces of dental amalgam ranged from \$107 to \$186, while the average submitted fee for composite resins ranged from \$135 to \$242 for the same surfaces. One comment stated that amalgam remains the best choice for deeper carious lesions of the posterior teeth and for patients seeking effective, lower cost dentistry.

(Response) FDA agrees that, in general, composite resin restorations are more costly than dental amalgam restorations.

(Comment) FDA received conflicting comments on the durability of composite resins versus dental amalgam. Some comments stated that composite resins are inferior to amalgam

with respect to durability, stiffness, wear resistance, marginal stability, and service life, and that they must be replaced more frequently. One comment stated that amalgam fillings can last for 35 years, while composites need to be replaced every 5 years. In contrast, other comments stated that amalgam is inferior to composites. For example, one comment stated that amalgam-filled teeth have a tendency to crack more frequently than composite-filled teeth, inevitably leading to more expensive restorations, such as crowns. The commenter stated further that composite resins better preserve the structural integrity of the tooth because they do not expand and because less natural tooth structure is removed in preparation for their placement. Other comments stated that the service lives of composite resins and dental amalgam are equivalent. One comment stated that the process for placing composite restorations is technique-sensitive and, if done properly, a composite restoration can last as long as an amalgam restoration.

(Response) FDA believes that the durability of dental restorations is dependent on many factors related to material properties, the type and size of the restoration, the dentist's skill, and patient use. According to the literature, the two primary reasons dental restorations fail are secondary caries (as the result of marginal leakage) and fracture. Studies have shown higher secondary caries rates for composite resins, but equivalent fracture rates for composite and amalgam restorations (Ref. 76).

#### F. Need for Public Hearings

(Comment) FDA received many comments on the proposed rule in 2002 requesting the agency to hold a public hearing or advisory committee meeting on dental amalgam, noting that dental amalgam had not been discussed in an FDA public meeting since 1994. Many comments requested that individual consumers, consumer advocacy organizations, and scientists and health professionals opposed to the use of dental amalgam be included in such a meeting.

(Response) FDA believes the concerns expressed by these comments were addressed in 2006 when FDA held a joint meeting of the Dental Products Panel and the Peripheral and Central Nervous Drugs Advisory Committee. One of the principal purposes of that meeting was to provide a transparent, public forum where all parties might share information. The panelists at the meeting were selected from a wide range of disciplines and interests, including neurology, dentistry, toxicology, statistics, epidemiology, and consumer advocacy. The 2006 meeting included an opportunity for the public to provide presentations, and a docket was opened to permit additional information to be submitted to the agency (Docket No. FDA-2008-N-0163). The 2006 Panel listened to presentations from more than 50 members of the public and FDA's presentation of its White Paper. At the conclusion of the meeting, the 2006 Panel provided individual and panel recommendations to the Agency.

#### G. Accusations of FDA Bias

(Comment) Several comments accused FDA of being biased in this rulemaking in support of the continued use of dental amalgam. The comments stated that the agency is too closely aligned with the interests of professional dental organizations and, as a result, has unfairly discounted evidence regarding the health risks presented by dental amalgam.

(Response) FDA disagrees with the comments suggesting that it has been biased in its approach to regulating these devices. This final rule and the special controls guidance document reflect FDA's careful and impartial consideration of all the comments and information it has received, the scientific information and safety assessments discussed previously, the White Paper and Addendum reports, and the adverse event reports submitted regarding these devices.

FDA has been proactive in obtaining as much information as practicable regarding the safety of these devices. As described previously, FDA has undertaken or supported several

safety assessments since the early 1990s regarding dental amalgam. In 2006, in an effort to ensure a transparent, public forum for discussion, FDA convened a joint committee of panelists with diverse backgrounds, including neurology and toxicology experts, to consider FDA's most recent review of the scientific literature related to dental amalgam (the White Paper) as well as presentations from members of the public. In response to the recommendations of the 2006 Panel, FDA updated its White Paper in the Addendum report.

(Comment) Some comments suggested that FDA did not consider the report on mercury by the Agency for Toxic Substances and Disease Registry, and that FDA ignored the toxicological and adverse health effects identified in Toxicological Profiles for Mercury, which was published by the U.S. Department of Health and Human Services.

(Response) FDA disagrees with the comments. FDA reviewed and evaluated both of these reports in preparing the White Paper (Ref. 10).

#### H. Preemption

(Comment) FDA received several comments requesting the agency to explain the preemptive effect of this rule on state requirements involving dental amalgam and on the tort liability of dentists.

(Response) FDA has imposed a special control to address the risks of exposure to mercury, toxicity and adverse tissue reaction, corrosion and mechanical failure, and improper use presented by these devices. This special control creates "requirements" for the manufacturer's labeling and other aspects of dental amalgam devices under 21 U.S.C. 360k, even though product sponsors have some flexibility in how they meet those requirements. Papike v. Tambrands, Inc., 107 F.3d 737, 740-42 (9<sup>th</sup> Cir. 1997). With respect to the tort liability of dentists, the special control in this rule requires manufacturers to properly inform dentists about dental amalgam in

the labeling, but does not impose any requirements on dentists. Dental amalgam is a prescription device, and properly informed dentists will be able to make the most appropriate treatment decisions for their patients, taking individual concerns into account. FDA does not intend to regulate the practice of dentistry. State consumer protection laws that concern the practice of dentistry, not manufacturer labeling, are therefore not implicated by this final rule. See Cal. Bus. & Prof. Code §§ 1648.10-1648.20 (requiring dentists to provide factual information to patients about dental amalgam); Maine (32 M.R.S. § 1094-C) (same); N.H. R.S.A. § 317-A:38 (same); N.Y. C.L.S. E.C.L. § 27-0926 (precluding dentists from using mercury in dentistry unless it is encapsulated for environmental reasons).

#### I. Environmental Concerns

(Comment) Many comments stated that dental amalgam should not be used because it is a toxic metal that pollutes the environment and frequently referenced concerns related to water and air pollution. Several comments stated, in general, that FDA has never prepared an Environmental Assessment for dental amalgam and should do so considering mercury is a bioaccumulative toxicant. One comment specifically addressed FDA requirements under the National Environmental Policy Act of 1969 (NEPA). The comment stated that FDA has a statutory duty to prepare an Environmental Impact Statement (EIS) or, at a minimum, an Environmental Assessment (EA) before promulgating any final action relating to the classification of dental amalgam, reclassification of mercury or the issuance of a special control. Moreover, the comment characterized the categorical exclusion in 21 CFR 25.34(b) as being "overbroad" and seemed to fault FDA for not finding extraordinary circumstances in the context of this rulemaking. The comment cited to *Louisiana v. Lee*, 758 F.2d 1081 (5th Cir. 1985), *cert. denied*, 475 U.S. 1044 (1986) as support for its assertion that an FDA action to classify or



reclassify dental mercury devices does not perpetuate the status quo and has significant effects. The comment suggests that FDA must evaluate the continued introduction of mercury into the environment attributable to dental devices.

(Response) Under the National Environmental Policy Act of 1969 (NEPA), all federal agencies must assess the environmental impact of any "major federal action" they take (42 U.S.C. 4332(C)). A regulation to classify or reclassify a device constitutes a major federal action under NEPA (*see* 40 CFR 1508.18). The Council on Environmental Quality (CEQ) is responsible for overseeing federal efforts to comply with NEPA and issued regulations on procedural requirements of NEPA (40 CFR Parts 1500-1508). CEQ directs federal agencies to adopt procedures, as necessary, to supplement the CEQ regulations (40 CFR 1507.3). FDA promulgated its supplemental NEPA regulations in 21 CFR Part 25.

For major federal actions "significantly affecting the quality of the human environment," an agency must prepare an Environmental Impact Statement (EIS) (*see id.*; 40 CFR 1501.4; 21 CFR 25.22). If the action "may" have such a significant environmental effect, an agency must prepare an Environmental Assessment (EA) to provide sufficient evidence and analysis for the agency to determine whether to prepare an EIS or a finding of no significant impact (FONSI) (40 CFR 1501.3; 21 CFR 25.20).

However, agencies can establish categorical exclusions for categories of actions that do not individually or cumulatively have a significant effect on the human environment and for which, therefore, neither an EA nor an EIS is required (*see* 40 CFR 1508.4). FDA promulgated such an exclusion, under 21 CFR 25.34(b), for agency actions that classify or reclassify a device and that may include the establishment of a special control, if the action will not result in increases in the existing levels of use of the device or changes in the intended use of the device

or its substitutes. FDA considered the application of this categorical exclusion to its classification/reclassification decision in this final rule, and to the establishment of the special control for mercury, amalgam alloy, and dental amalgam. (Ref. 77) Consistent with its NEPA obligations, the agency considered whether there were any extraordinary circumstances that would preclude its reliance on this categorical exclusion for this final rule (agency procedures must "provide for extraordinary circumstances in which a normally excluded action may have a significant environmental effect" (40 CFR 1508.4; *see also* 21 CFR 25.21)). The agency determined that the action it is taking in this final rule is appropriately categorically excluded under 21 CFR 25.34(b).

These comments reflect a misunderstanding of the action FDA is taking in this final rule and its obligations under NEPA for such action. The comments presume that FDA has a general obligation under NEPA, in the context of promulgating this final rule, to assess the impacts of mercury on the environment and the effects of any continued introduction of mercury attributable to dental devices. FDA disagrees with such a presumption, particularly where there is "no reasonably close causal relationship" between the actions in the final rule and such general impacts. DOT v. Public Citizen, 541 U.S. 752, 767 (2004) (rejecting a "but for" causal relationship as sufficient to require agency environmental review under NEPA) (citation omitted)). The comments ignore the scope of the action FDA is taking in this final rule and the categorical exclusion that applies to it.

Specifically, FDA is classifying dental amalgam into class II, reclassifying mercury from class I to class II, and designating a special control to support the class II classifications of dental amalgam, mercury, and amalgam alloy (currently classified as class II). The action is being taken to establish sufficient regulatory controls that will provide reasonable assurance of the

safety and effectiveness of these devices. This action does not constitute a decision to permit any individual's particular use of any of these devices in the market. It simply provides a classification regulation establishing sufficient regulatory controls that will provide reasonable assurance of safety and effectiveness as to the particular class of these devices. The introduction into interstate commerce of amalgam alloy, mercury, or dental amalgam requires FDA clearance under section 510(k) of the act (21 U.S.C. 360(k)). An FDA decision to clear a device under section 510(k) of the act would be a "major federal action" (as defined in 40 CFR 1508.18) and would be independent of FDA's action in this final rule. Thus, FDA would evaluate, independent of this final rule, its obligations under NEPA for a decision to clear a particular use of amalgam alloy, mercury, or dental amalgam in the context of a 510(k) submission. Such a decision is not before the agency in this final rule. Manufacturers currently or intending to market amalgam alloy, mercury, or dental amalgam are expected to comply with the requirements of special controls and address the issues of safety and effectiveness identified in the special controls guidance, either by following the recommendations in the guidance or by some other means that provides equivalent assurances of safety and effectiveness, on or before effective date of rule (see the DATES section of this document).

Further, the reference in the comment to Louisiana v. Lee is misplaced. In that case, the court vacated a lower court's judgment and remanded the case for more careful review to ascertain whether an environmental assessment and finding of no significant impact by the United States Army Corps of Engineers was reasonable. 758 F.2d 1081 at 1086. To the extent the comment likens the issuance of permits that would allow for continued dredging of the Louisiana Gulf Coast area to a decision on a classification, the comparison is not on point. As

previously stated, this final rule does not constitute a decision on a particular submission to "permit" any particular introduction into the environment of any of these devices.

FDA appropriately focuses its environmental review in this final rule on its action to classify, reclassify, and establish a special control for amalgam alloy, mercury, and dental amalgam. FDA disagrees, as one comment asserts, that FDA is required to prepare an environmental assessment or an environmental impact statement under NEPA for this final rule. FDA has evaluated the application of the existing categorical exclusion in 21 CFR 25.34(b) to the actions it is taking in this final rule and concludes, based on the reasons set forth below, that it is proper to rely on that categorical exclusion for this final rule.

In 1985, FDA finalized a categorical exclusion in 21 CFR 25.24(e)(2) for the "classification or reclassification of a device under Part 860" (50 FR 16635 at 16661; April 26, 1985). FDA identified this as a class of actions that would not result in the production or distribution of any substance, and therefore, would not result in the introduction of any substance into the environment. (44 FR 71742 at 71745; December 11, 1979). In other words, changing the classification of a device from, e.g., class I to class II, would not, by itself, result in the introduction of any substance into the environment. Therefore, such an action would not normally require the preparation of an environmental assessment (44 FR 71742 at 71745; December 11, 1979). In 2005, FDA expanded the categorical exclusion for the classification and reclassification of devices to include, within its scope, an action that establishes special controls, if such action will not result in increases in the existing levels of use of the device or changes in the intended use of the device or its substitutes (70 FR 69276; November 15, 2005). Thus, FDA would evaluate the application of the categorical exclusion for classification and reclassification decisions that include the establishment of special controls on a case-by-case basis to determine

whether its action would result in increases in the existing levels of use or changes to the intended use of the device or its substitutes. FDA does not consider such a categorical exclusion to be "overbroad" as one comment asserts.

FDA has determined that its action to classify dental amalgam, reclassify dental mercury, and to establish a special control are all within the scope of the categorical exclusion in 21 CFR 25.34(b). This final rule reclassifies mercury from the lower risk class I to the higher risk class II and classifies dental amalgam as class II. The final rule does not change the requirements in place prior to this final rule and that remain in effect after this final rule publishes, e.g., premarket review and general controls. The change in classification alone does not result in the introduction of any substance into the environment, does not increase the existing levels of use, and does not change the intended use of these devices or their substitutes (Ref. 77).

In addition, FDA undertook a careful review of the special control designated by this final rule to determine whether the special control would increase the existing levels of use or change the intended use of amalgam alloy, mercury, and dental amalgam or their substitutes. (Ref. 77) FDA has determined that the labeling recommendations in the special controls guidance imposed by the final rule would not result in increases in the existing levels of use of the devices or changes in the intended use of the devices or their substitutes. (Ref. 77) The labeling statements should help ensure that dentists are more fully informed regarding the devices. We have no basis to suggest or expect that the labeling recommendations would result in any increase in use of these devices or changes in the intended use of the devices or their substitutes.

Further, FDA has determined that testing recommendations would not result in increases in the existing levels of use of the devices or changes in the intended use of the devices or their

substitutes. (Ref. 77) None of the tests require additional specimens of dental amalgam, amalgam alloy, or mercury. The test for mercury requires only visual inspection, which can be performed using current inventory, i.e., without the need for any additional mercury for the test. The tests for dental amalgam and amalgam alloy, required by the final rule and that were not routinely performed prior to the final rule, would require approximately 2.2 grams per product, which can be obtained from material used for a previous non-destructive test already routinely performed or from inventory needed for all testing. To the extent a manufacturer elects to procure additional product for the test, the amount is not significant. (Ref. 77) Moreover, the possibility a manufacturer would even elect to procure additional material for such tests is speculative. FDA found that its action in this final rule to classify dental amalgam into class II, reclassify mercury from class I to class II, and to establish a special control for dental amalgam, mercury, and amalgam alloy does not significantly affect the quality of the human environment and that there are no extraordinary circumstances (Ref. 77). (See also, Utah Env'tl. Cong. v. Bosworth, 443 F.3d 732 (10th Cir. 2006) (stating an extraordinary circumstance exists "only where a proposed action 'may have a significant environmental effect.'") (citations omitted)). Based on FDA's review, it concludes that this final rule is appropriately categorically excluded under 21 CFR 25.34(b), and therefore, does not require an environmental assessment or an environmental impact statement.

(Comment) Some comments suggested that dental amalgam manufacturers should provide an environmental impact statement to prove that dental amalgams are environmentally safe.

(Response) Under 21 CFR 25.40, FDA generally requires an applicant to prepare an environmental assessment for any action that is not categorically excluded. FDA would

determine, for each 510(k) submission the agency may receive, what environmental documents may be necessary to comply with the agency's obligations under NEPA.

#### IV. ENVIRONMENTAL IMPACT

The agency has considered the environmental effects of this final rule and has determined under categorical exclusion 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required (Ref. 77).

#### V. ANALYSIS OF IMPACTS

##### A. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes this final rule is a not an economically significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because of the relatively minor direct costs to entities attributable to this final rule, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandates that may result in the expenditure

by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$133 million, using the most current (2008) Implicit Price Deflator of the Gross Domestic Product. FDA does not expect this final rule to result in a 1-year expenditure that could exceed this amount.

#### B. Summary of Economic Impacts

The final rule classifies dental amalgam into class II, reclassifies mercury from class I to class II, and designates a special control to support the class II classifications of these two devices, as well as the current class II classification of amalgam alloy. Today’s action classifies the three devices in a single regulation. The special control for the devices is a guidance document entitled “Class II Special Controls Guidance Document: Dental Amalgam, Mercury, and Amalgam Alloy,” which includes labeling recommendations as well as quality control procedures.

Conforming to the special control will require few additional resources at the manufacturing stage as well as costs to FDA for administering the final regulation. Some dentists may consider the information-for-use statement, along with many other factors, when making treatment decisions for their patients. A small number of dentists may use dental amalgam for some patients for whom they may not have used the device previously, and decide not to use the device for other patients for whom they may have used the device. However, any change away from use of dental amalgam is likely to result in negative public health outcomes (delayed dental treatments or increased costs of treatment). While there would be a decrease in mercury exposure, there is no evidence that there would be any reduction in adverse affects associated



with mercury. Conversely, any change towards use of dental amalgam is likely to result in positive public health outcomes or decreased costs of treatment.

### C. Objective and Need of the Final Rule

The purpose of this final rule is to classify dental amalgam, reclassify mercury, and designate a special control to support the class II classification of dental amalgam, mercury, and amalgam alloy as required by section 513 of the act. The special control for the device is a guidance document with composition and performance data, biocompatibility, and labeling recommendations. One of the labeling recommendations is the following information for use:

“Dental amalgam has been demonstrated to be an effective restorative material that has benefits in terms of strength, marginal integrity, suitability for large occlusal surfaces, and durability.<sup>33</sup> Dental amalgam also releases low levels of mercury vapor, a chemical that at high exposure levels is well-documented to cause neurological and renal adverse health effects.<sup>34</sup> Mercury vapor concentrations are highest immediately after placement and removal of dental amalgam but decline thereafter.

Clinical studies have not established a causal link between dental amalgam and adverse health effects in adults and children age six and older. In addition, two

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<sup>33</sup> 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.

<sup>34</sup> Liu, J. et al., “Toxic effects of metals,” Casarett & Doull’s Toxicology: The Basic Science of Poisons, Chapter 23, pp. 931-979, McGraw-Hill Medical, New York, New York, 2008.  
Clarkson, T.W. et al., “The Toxicology of Mercury and Its Chemical Compounds,” Critical Reviews in Toxicology, Vol. 36, pp. 609-662, 2006.

clinical trials in children aged six and older did not find neurological or renal injury associated with amalgam use.<sup>35</sup>

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.

The Agency for Toxic Substances and Disease Registry's (ATSDR) and the Environmental Protection Agency (EPA) have established levels of exposure for mercury vapor that are intended to be highly protective against adverse health effects, including for sensitive subpopulations such as pregnant women and their developing fetuses, breastfed infants, and children under age six.<sup>36</sup> Exceeding these levels does not necessarily mean that any adverse effects will occur.

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<sup>35</sup> 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, No. 15, April, 19, 2006.  
Bellinger, D.C. et al., "Neuropsychological and Renal Effects of Dental Amalgam in Children: A Randomized Clinical Trial," Journal of the American Medical Association, Vol. 295, No. 15, April 19, 2006, 1775-1783, 2006.  
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, No. 3, March 2008.  
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.  
Lauterbach, M. et al., "Neurological Outcomes in Children with and Without Amalgam-Related Mercury Exposure: Seven Years of Longitudinal Observations in a Randomized Trial," Journal of the American Dental Association, Vol. 139, 138-145, February 2008.

<sup>36</sup> Agency for Toxic Substances and Disease Registry (ATSDR) and Research Triangle Institute, Toxicological profile for mercury, U.S. Dept. of Health and Human Services, Public Health Service, Atlanta, Georgia, 1999.  
United States Environmental Protection Agency (EPA), "Integrated Risk Information System (IRIS) Screening-Level literature Review" – Mercury, elemental, 2002.

FDA has found that scientific studies using the most reliable methods have shown that dental amalgam exposes adults to amounts of elemental mercury vapor below or approximately equivalent to the protective levels of exposure identified by ATSDR and EPA. Based on these findings and the clinical data, FDA has concluded that exposures to mercury vapor from dental amalgam do not put individuals age six and older at risk for mercury-associated adverse health effects.

Taking into account factors such as the number and size of teeth and respiratory volumes and rates, FDA estimates that the estimated daily dose of mercury in children under age six with dental amalgams is lower than the estimated daily adult dose. The exposures to children would therefore be lower than the protective levels of exposure identified by ATSDR and EPA.

In addition, the estimated concentration of mercury in breast milk attributable to dental amalgam is an order of magnitude below the EPA protective reference dose for oral exposure to inorganic mercury. FDA has 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.”

The guidance also recommends that the labeling of dental amalgam and mercury devices include warnings about potential exposure to mercury, including: “WARNING: CONTAINS MERCURY” and “harmful if vapors are inhaled.” The labeling recommendations also include the following contraindication: “Do not use in persons with a known mercury allergy.” In

addition, the special controls guidance document includes recommendations regarding composition and performance data, and biocompatibility testing.

The need for this regulation stems from the current poor distribution of accurate information about exposure to mercury (Hg) through dental amalgam. The special control imposed by this final rule will ensure that dentists are reminded that dental amalgam contains mercury, and will provide them with FDA's assessment of the most current, best available information regarding use of the device in various patient groups.

#### D. Risk

Mercury poisoning is a disease caused by exposure to mercury or its compounds. The most common exposure is to organic mercury through fish consumption. Elemental mercury may be inhaled or absorbed through the skin and is used for dental restorations as amalgam. Toxic effects of mercury, depending on the level of exposure, include damage to the brain, kidneys, and lungs, with symptoms that include sensory impairment, disturbed sensation, and lack of coordination. Elemental mercury is primarily associated with neurologic toxicity (Ref. 78), although most cases do not have any noticeable physiological effects. Table 2 of this document shows reported elemental mercury exposures and treatments for 2005-2007.

TABLE 1.--ELEMENTAL MERCURY EXPOSURES AND TREATMENT OUTCOMES

Year	Number of Reported Exposures	Number Seeking Treatment	No Adverse Outcome	Minor Adverse Outcome	Moderate Adverse Outcome	Major Adverse Outcome	Death
2005	2,786	909	747	99	55	6	2
2006	2,336	854	767	66	20	1	0
2007	2,319	672	576	55	38	3	0
Total	7,441	2,435	2,090	220	113	10	2
Percentage		100.0	85.83	9.03	4.64	0.41	0.08

Source: American Association of Poison Control Centers (Refs. 79, 80, and 81).

Dental amalgam has not been shown to cause mercury poisoning and no data show a causal effect of dental amalgam for any adverse health effects (except in a small number of patients with a known allergy to mercury). Dental amalgam does contain mercury, although in quantities much smaller than those associated with the adverse outcomes summarized in table 2 of this document.

Dental amalgam has been used to restore decayed teeth since the 1890s in the United States, although early prototypes were available from the 1830s. Amalgam is an alloy that is about 50% mercury (usually combined with silver, tin, or copper) and is one of several potential materials used to treat dental caries. Over the last 15 years (1993-2008), we estimate that approximately 900 million restorations have been performed using dental amalgam, although the annual number of all restorations, as well as amalgam restorations, has been decreasing (see Section V.E). According to Delta Dental Insurance (Ref. 82), the typical amalgam restoration has 1.8 surfaces (a “surface” is a measure of exposed surface of the restoration). Research has indicated that each surface of an amalgam restoration releases approximately 0.534  $\mu\text{g}$  Hg/day (Ref. 83). With a baseline of 900 million amalgams and 1.8 surfaces per amalgam, we estimate 865 million  $\mu\text{g}$  Hg/day were released by amalgams (900 million amalgams x 1.8 surfaces per amalgam x 0.534  $\mu\text{g}$  Hg/day per surface) during 2008.

We are unable to estimate possible changes in exposure to mercury that may result from this rule. Dentists may use dental amalgam for some patients for whom they may not have used the device previously, and decide not to use the device for other patients for whom they may have used the device. However, any change away from use of dental amalgam is likely to result in negative public health outcomes (delayed dental treatments or increased costs of treatment); while there would be a decrease in mercury exposure, there is no evidence that there would be

any reduction in adverse affects associated with mercury. Conversely, any change toward use of dental amalgam is likely to result in positive public health outcomes (fewer delayed dental treatments or decreased costs of treatment).

#### E. Baseline in the Absence of the Final Rule

During 2008, there were an estimated 154.1 million dental restorations in the United States (Ref. 84). This number represents a decrease of almost 12 million restorations from 2005, with the decrease associated with better dental care. We assume that recent 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. Table 2 of this document shows projected annual restorations and annual amalgam restorations expected for the 15-year evaluation period.

TABLE 2.--PROJECTED ANNUAL DENTAL RESTORATIONS (IN MILLIONS)

Evaluation Year	Total U.S. Population	Total Restoration	Amalgam Restorations	Other Restorations
2009	307.2	149.0	50.5	98.5
2010	310.2	145.0	49.0	96.0
2011	313.2	141.0	47.6	93.5
2012	316.3	137.2	46.2	91.0
2013	319.3	133.4	44.8	88.5
2014	322.4	129.7	43.5	86.2
2015	325.5	126.1	42.2	83.9
2016	328.7	122.6	41.0	81.6
2017	331.8	119.1	39.8	79.4
2018	335.0	115.8	38.6	77.2
2019	338.2	112.5	37.5	75.0
2020	341.4	109.4	36.4	72.9
2021	344.6	106.3	35.4	70.9
2022	347.8	103.3	34.4	68.9
2023	351.0	100.3	33.4	67.0

The population of the United States is projected to increase at an annual rate of about 0.9 percent over this period and dental restorations as a whole, as well as amalgam restorations, are

expected to decrease by about 1.9 percent per year. This projection is based on the expected age distribution of the population as reported by the Census Bureau and historical rates of restorations by age-cohort. For example, the population between the ages of 0-4 was about 20.3 million in 2005, during which year 3,339,000 restorations were conducted for this age cohort, for an average of 0.16 restorations per capita. The Census Bureau projected that there will be about 20.9 million in the population aged 0-4 in 2009. Using the per capita rate of restorations, we expect there to be 3,344,000 restorations for this age group. The distributions of restoration by material and by age groups were summed for each year to result in the estimates shown in table 2 of this document.

As an approximation of the total number of patients in specific populations who might be expected to be more vulnerable to mercury (pregnant women and their fetuses, children under the age of six, including those who are breastfed), we use the total number of pregnant and lactating women and children under six as the targeted or special populations in this analysis. According to the Agency for Toxic Substances and Disease Registry (Ref. 85), very young children are more sensitive to mercury than adults. Mercury in a mother's body can pass to the fetus and may accumulate there (Ref. 85), and a nursing infant may be exposed to inorganic mercury through breast milk. Because of these sensitivities, we projected dental amalgam restorations for children under the age of 6, as well as for pregnant and lactating females ages 15-44 based on reporting from the American Dental Association (ADA) and projections from the Bureau of Census. The number of pregnant women was obtained from the National Center of Health Statistics for 2004 (Ref. 86). The rate of pregnancy among women between the ages of 15 and 44 for 2004 (0.1036) was used to project future annual pregnancies. Approximately two-thirds of all live births breast feed at least once (Ref. 87). Therefore, we have estimated that two-

thirds of the previous years' live births account for lactating women. The number of children under the age of 6 was obtained from Census projections. We could not obtain information on the potential number of other affected sub-populations but believe they could reasonably be accounted for in these projections, which include practically all the affected persons. Table 3 of this document shows these projections.

TABLE 3.--PROJECTED AMALGAM RESTORATIONS FOR SPECIFIC POPULATIONS (IN MILLIONS)

Evaluation Year	Number of Pregnant and Lactating Women	Total Children Under the age of 6	Total Amalgam Restorations	Total Amalgam in Pregnant and Lactating Women	Total Amalgam in Children Under 6	Total Amalgam Restorations in Sensitive Sub-Populations
2009	9.22	25.1	50.5	1.8	2.6	4.4
2010	9.23	25.3	49.0	1.8	2.5	4.3
2011	9.27	25.5	47.6	1.7	2.5	4.2
2012	9.29	25.7	46.2	1.6	2.4	4.0
2013	9.32	26.0	44.8	1.6	2.3	3.9
2014	9.37	26.2	43.5	1.5	2.3	3.8
2015	9.41	26.4	42.2	1.5	2.2	3.7
2016	9.44	26.7	41.0	1.4	2.1	3.5
2017	9.49	26.9	39.8	1.4	2.1	3.5
2018	9.55	27.1	38.6	1.3	2.0	3.3
2019	9.62	27.2	37.5	1.3	2.0	3.3
2020	9.70	27.4	36.4	1.3	1.9	3.2
2021	9.78	27.6	35.4	1.2	1.8	3.0
2022	9.93	27.7	34.4	1.2	1.8	3.0
2023	10.04	27.9	33.4	1.2	1.7	2.9

Because the annual use of dental amalgam for restorations is expected to continue to decrease, the exposures of these sub-populations to amalgam are also expected to decrease along with exposures in the population age six and older. We model the expected contribution per day of amalgam for the evaluation period in table 4 of this document. These projections are based on the decreasing number of amalgam restorations expected as replacements. During the period 1993-2008, according to data supplied by the ADA, approximately 60 million annual restorations used amalgam for a total of 900 million current amalgam restorations in place. In the absence of



the final rule, we project only 50.5 million new amalgam restorations during 2009, down from 60 million from 1993, resulting in only 890.5 million amalgam restorations for the entire population (900 million restorations in place + 50.5 new restorations during year 1 – 60 million restorations from 1993). Therefore, the daily potential exposure to mercury vapor originating from dental amalgam is expected to decrease gradually in the absence of the final rule.

TABLE4.--PROJECTED TOTAL UG HG PER DAY FROM DENTAL AMALGAM IN THE ABSENCE OF THE FINAL RULE (IN MILLIONS)

Evaluation Year	Number of Amalgam Restorations in Place	Number of Annual Amalgam Restorations	Micrograms ( $\mu$ g) of Mercury (Hg) Per Day
2009	890.5	50.5	856
2010	879.5	49.0	845
2011	867.1	47.6	833
2012	853.3	46.2	820
2013	838.1	44.8	806
2014	821.6	43.5	790
2015	803.8	42.2	772
2016	784.8	41.0	754
2017	764.6	39.8	735
2018	743.2	38.6	714
2019	720.7	37.5	693
2020	697.1	36.4	670
2021	672.5	35.4	646
2022	646.9	34.4	622
2023	620.3	33.4	596

Table 4 of this document includes estimates of projected levels of mercury per day associated with the expected number of amalgams in place. Each amalgam is assumed to have 1.8 surfaces and release 0.534  $\mu$ g Hg per day per surface.

#### F. The Final Rule

This final rule will classify dental amalgam as class II, reclassify mercury from class I to class II, and designate a special control to support the class II classifications of these class II devices, as well as the current class II classification of amalgam alloy. All three devices will now be classified in a single regulation. Under Class II, these devices will be subject to a special

control. In this case, we are designating as the special control a guidance document (with composition and performance data, biocompatibility testing, and labeling recommendations). The guidance document provides for some increased testing requirements that will ensure the composition of the amalgam as well as labeling recommendations. Specific additional tests in the guidance document include particle size distribution assays and corrosion testing that are not typically currently conducted by manufacturers. The labeling recommendations include a warning that dental amalgam contains mercury and provide information for use explaining that, although there are 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, the estimated concentration of mercury in breastmilk attributable to dental amalgam exposure is low and is an order of magnitude below the EPA protective reference dose for oral exposure to inorganic mercury. The estimated daily dose of mercury in children under age 6 with dental amalgams is also low and at or below the ATSDR and EPA protective reference levels.

#### G. Costs of the Final Rule

FDA is required by statute to classify devices (21 USC 360c). This final rule classifies dental amalgam into Class II and reclassifies dental mercury (hereinafter “mercury”) from Class I to Class II. Importantly, the rule also establishes special controls for dental amalgam, mercury, and amalgam alloy (mercury and amalgam alloy are combined to form dental amalgam).

The costs of the final rule are the costs of complying with and administrating the special control (including testing and labeling costs, and FDA administration costs).

The special controls guidance referenced in this final rule recommends that dental amalgam, mercury, and amalgam alloy be subject to periodic assays to demonstrate physical

properties. Two of these assays are not routinely conducted and, consequently, would constitute additional expenses. In addition, the special controls guidance recommends labeling that the labeling state that the device contains mercury, that it should not be used in persons with a known allergy to mercury, and that data are limited regarding long term outcomes in certain populations. These labeling revisions are also additional requirements for manufacturers.

## 1. Manufacturing Costs

### a. Testing Costs

FDA records indicate the final rule will affect 50 separate products manufactured by 16 companies. These companies are classified in the Dental Equipment and Supplies Industry (NAICS 339114) by the Census of Manufacturers (NAICS is the North American Industry Classification System).

The special controls guidance document that is part of this final rule includes two recommended quality control assays that are not routinely conducted by manufacturers. These assays are particle size distribution testing and corrosion products identification. While some of the 16 manufacturers may use in-house laboratories to conduct these tests, if additional equipment is needed they are more likely to use contract laboratories. Discussions with contract laboratories showed that estimated costs for conducting assays of these types ranged between \$35 and \$150 per test with a typical test costing approximately \$75.

It is unclear how frequently these tests would be conducted. The current guidance recommends that tests be conducted once before marketing. However, we expect manufacturers to test each of their 50 marketed products at least once per year to ensure product quality. Therefore, the expected annual cost of conducting these additional tests equals \$7,500 per year (50 products times 2 tests times \$75).

### b. Labeling Costs Associated With the Final Rule

The recommended labeling controls included in this final rule will result in enhanced labeling for dental amalgam devices. Specifically, the guidance recommends that the labeling for this product state that the device contains mercury, that it should not be used in persons with a known allergy to mercury, and that current scientific evidence indicates there is no connection between the device and adverse events in the population age six and older. The label also informs dentists that the clinical data are limited regarding long term outcomes in certain patients who might be expected to be more sensitive to the effects of mercury.

We expect that each of the 50 products currently marketed will develop a new label that includes this information. The cost of developing new artwork, label design, regulatory review, production, and application was estimated based on a labeling cost model developed by the Eastern Research Group (Ref. 88) and updated to 2008. Overall, the cost of developing a new label using these guidelines is estimated to be approximately \$2,000 per label. Each of the 50 products marketed by 16 manufacturers is expected to have a revised label due to this requirement and result in a total one-time labeling cost of \$100,000 (50 products times \$2,000).

### c. Increased Manufacturing Costs

The total increased manufacturing costs of this final rule are \$107,500 in the first evaluation year and \$7,500 per year thereafter. The present value over 15 years is \$186,600 (3 percent discount rate) or \$161,800 (7 percent discount rate).

## 2. Costs of FDA Regulatory Oversight

Although FDA currently regulates dental amalgam, the reclassification from this final rule is likely to increase oversight. Label review will likely be more rigorous and inspections will entail review of more testing data. Any reviews of marketing applications will be more rigorous

and there are likely to be increases in the number of marketing applications submitted for review (although we have not estimated any such increase). In addition, FDA can anticipate additional interest in these products, which will probably require resources to respond to consumer and media requests for information. These activities are not likely to consume more than 30 minutes of full-time equivalent (FTEs) per product per year, or approximately 26 hours of resources. The estimated cost of an FDA FTE is approximately \$130,000 per year, or about \$64.75 per hour. (This estimate includes salary, benefits, overhead, and support). Therefore, the increased use of FDA resources due to the final rule is only approximately \$1,700 per year (26 hours times \$64.75). The present values of 15 years of this cost equal \$20,300 (using 3 percent annual discount rate) and \$15,500 (using 7 percent annual discount rate).

### 3. Total Costs

Table 5 of this document shows the estimated present value of costs and the annualized costs of the final rule by type. Testing costs and the costs of FDA administration are annual recurring costs. While the present values of these costs differ by discount rate, the annualized costs are not affected by discount rates.

TABLE 5.--PRESENT VALUE AND ANNUALIZED COSTS OF FINAL RULE

	Present Value at 3 Percent	Present Value at 7 Percent	Annualized Value at 3%	Annualized Value at 7%
Labeling Cost	\$100,000	\$100,000	\$8,400	\$10,100
Testing Cost	\$89,500	\$68,300	\$7,500	\$7,500
Cost of FDA Administration	\$20,300	\$15,500	\$1,700	\$1,700
Total Cost	\$209,800	\$183,800	\$17,600	\$19,300

### H. Potential Public Health Effects of the Final Rule

The recommended information for use statement will provide dentists with current information to help them make treatment decisions for their patients. We expect that dentists will consider

that information, along with other factors, when making treatment decisions for their patients. Dentists may use dental amalgam for some patients for whom they may not have used the device previously, and decide not to use the device for other patients for whom they may have used the device. However, any change away from use of dental amalgam is likely to result in negative public health outcomes (delayed dental treatments or increased costs of treatment); while there would be a decrease in mercury exposure, there is no evidence that there would be any reduction in adverse affects associated with mercury. Conversely, any change toward use of dental amalgam is likely to result in positive public health outcomes (fewer delayed dental treatments or decreased costs of treatment).

### I. Alternatives to the Final Rule

The principal regulatory alternatives considered were as follows: (1) No new regulatory action, (2) Class II but with other special controls, (3) reclassification to Class III, and (4) ban the use of mercury in dental restorations.

#### 1. No New Regulatory Action

No new regulatory action is the projected baseline we use to estimate the effects of the other options. By definition, there are no costs or public health effects associated with the baseline.

#### 2. Class II but with Other Special Controls

This alternative would retain class II but calls for different special controls. While deciding the type of special controls best suited for this device, we considered many different options. For example, we considered a labeling requirement that would require dentists to inform patients of the presence of mercury in dental amalgam and discuss treatment options and a special controls guidance document with labeling recommendations. Whatever the special

controls in this alternative, the result would be that patients would get direct information that would include the presence of mercury in amalgam. The costs of this alternative would include the opportunity costs both dentists and patients of discussing treatment options, costs of alternative restorative materials, potentially delayed or deferred treatments, the cost of periodic testing by manufacturers, and the cost of FDA administration. There would be an expected reduction in mercury exposure and some potential reduction in anxiety for patients who would choose alternative materials with this information and after consultation with dentists. The costs and effects of this alternative are shown in table 6 of this document.

TABLE 6.--PRESENT VALUE AND ANNUALIZED EFFECTS OF ALTERNATIVE LABELING

	Present Value – 3%	Present Value – 7%	Annualized Value – 3%	Annualized Value – 7%
Costs (in millions)	\$2,433 to \$6,563	\$1,932 to \$4,948	\$208 to \$550	\$212 to \$543
Reduced Mercury Exposures (in million of $\mu\text{g}$ Hg per day)	0 to 153.2	0 to 109.5	0 to 12.8	0 to 12.0
Delayed Dental Treatments	0 to 990,000	0 to 813,000	0 to 83,000	0 to 89,000

The ranges shown in Table 6 show the uncertainty of how patients and dentists may be expected to react to information and differences in the durability of alternative materials. The estimates and ranges shown in table 6 include the effects of the higher costs of alternative materials, ranges of expected useful life of alternative materials, opportunity costs of dentists providing counseling, opportunity costs of patients, different durations of counseling, different expected reactions by patients to the information that amalgam contains mercury (based on market response of tuna consumers), and ranges of estimates of price elasticities of demand for dental services. The ranges are shown to address a wide range of potential alternative special controls that we did not select.

### 3. Reclassification to Class III

Class III classification of these products would require that manufacturers obtain premarket approval for dental amalgam, mercury, and amalgam alloy. The most likely effect of this alternative would be that marketers would choose to withdraw their products from the market rather than incur the costs and resources necessary to collect safety and effectiveness data to support premarket approval applications. The effects of this regulatory alternative are probably equivalent to a ban on the use of mercury in restorations and should be equal to the estimated impacts discussed for Alternative 4.

#### 4. Ban the Use of Mercury in Dental Restorations

Another alternative is to ban dental amalgam. The ban would not give consumers a choice with respect to the use of dental amalgam. All consumers would be forced to use alternative materials or defer treatment for dental caries. The costs and effects of a ban are shown in tables 7 and 8 of this document. While the estimated number of delayed dental caries treatments that may result from a ban are not included in table 7, we consider them to represent negative public health effects. Any delay in dental treatment would likely lead to further deterioration and patient discomfort. However, there are no empirical data to suggest how long a delay in treatment would typify the response to a ban or what the social costs of delayed (or avoided) dental treatment would be. This negative public health outcome should be considered an additional non-quantified cost. The annualized public health effects appear equal for both discount rates due to rounding to the nearest hundred thousand. The difference in annualized treatment delays shown in Table 6 is a reflection of the differing responses to prices and alternative special controls. The totality of a potential ban removes most of the variability of response to regulation and reduces differences arising from different discount rates.



TABLE 7 – COSTS OF A BAN

(In millions)

	PRESENT VALUE— 3%	PRESENT VALUE— 7%	ANNUALIZED VALUE—3%	ANNUALIZED VALUE—7%
TOTAL COSTS ASSUMING DURABLE ALTERNATIVE MATERIAL	\$33,224.0	\$25,867.0	\$3,784.2	\$2,840.2
TOTAL COSTS ASSUMING ALTERNATIVE MATERIALS HAVE TEN-YEAR REPLACEMENT LIFE	\$63,953.8	\$44,714.7	\$5,359.3	\$4,909.7

TABLE 8.--POTENTIAL PUBLIC  
HEALTH EFFECTS OF A BAN

	Present Value— 3%	Present Value— 7%	Annualized Value---3%	Annualized Value—7%
Reduced Mercury Exposure	688.6 million µg Hg per day	525.5 million µg Hg per day	57.7 million µg Hg per day	57.7 million µg Hg per day
Delayed Caries Treatments (in millions)	27.1	21.0	2.3	2.3

### J. Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because of the relatively minor costs to manufacturing entities attributable to this final rule, the agency believes that the final rule will not have a significant economic impact on a substantial number of small manufacturing entities.

FDA records indicate the final rule will affect 50 separate products manufactured by 16 domestic companies. These companies are classified in the Dental Equipment and Supplies Industry (NAICS 339114) by the Census of Manufacturers. The affected industry (NAICS 339114; Dental Equipment and Supplies) is typified by small entities. Only about 35 of the approximately 875 establishments in the entire industry employ more than 100 workers. According to the Small Business Administration Size Standards, any entity with fewer than 500 employees is considered small in this industry. We therefore conclude that the manufacturing 16 companies affected by this final rule will be small businesses. The formal costs per company, however, are relatively small. The annualized costs of developing new required and recommended labeling and conducting additional assays to ensure product quality are not significant for a substantial number of small entities. The annualized costs per firm, \$750 using a 3-percent discount rate or \$865 using a 7-percent discount rate, are not significant. (These annualized costs are based on an average of 3.125 products per company). The average value of shipments for establishments in this industry with fewer than five employees was \$244,100 according the Census of Manufacturers. The annualized costs of the final rule represent less than 0.5% of the annual value of shipments. We certify that there will not be a significant economic impact on a substantial number of small entities.

## VI. FEDERALISM

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to “construe \* \* \* a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute.” Federal law includes an express preemption provision that preempts certain state requirements "different from or in addition to" certain federal requirements applicable to devices. 21 U.S.C. 360k; Medtronic v. Lohr, 518 U.S. 470 (1996); Riegel v. Medtronic, 128 S. Ct. 999 (2008).

In this rulemaking, FDA has determined that general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of these devices, and that there is sufficient information to establish special controls to provide such assurance. FDA has therefore imposed special controls to address the risks of exposure to mercury, allergic reaction including adverse tissue reaction, contamination, mechanical failure, corrosion, and improper use. These special controls create "requirements" for specific medical devices under 21 U.S.C. 360k, even though product sponsors have some flexibility in how they meet those requirements. Papike v. Tambrands, Inc., 107 F.3d 737, 740-42 (9<sup>th</sup> Cir. 1997).

The preemptive effects are the result of existing law set forth in the statute as interpreted in decisions of the United States Supreme Court. FDA therefore has not sought separate comment on the preemptive effect of this action because it is not seeking independently to preempt state law beyond the effects of 21 U.S.C. 360k or existing case law.

## VII. THE PAPERWORK REDUCTION ACT OF 1995

This final rule refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 801 have been approved under control number 0910-0485; the collections of information in 21 CFR part 807 subpart E have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 50 have been approved under OMB control number 0910-0130; and the collections of information in 21 CFR 820 have been approved under OMB control number 0910-0073.

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#### List of Subjects in 21 CFR Part 872

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 872 is amended as follows:

#### PART 872--DENTAL DEVICES

1. The authority citation for 21 CFR Part 872 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

§ 872.3050 [Removed]

2. Remove § 872.3050.

3. Add § 872.3070 to subpart D to read as follows:

§ 872.3070 Dental amalgam, mercury, and amalgam alloy.

(a) Identification. Dental amalgam is a device that consists of a combination of elemental mercury, supplied as a liquid in bulk, sachet, or predosed capsule form, and amalgam alloy composed primarily of silver, tin, and copper, supplied as a powder in bulk, tablet, or predosed capsule form, for the direct filling of carious lesions or structural defects in teeth. This device

also includes the individual component devices, mercury and amalgam alloy, when intended to be combined with each other to form dental amalgam.

(b) Classification. Class II (special controls). The special control for this device is FDA's "Class II Special Controls Guidance Document: Dental Amalgam, Mercury, and Amalgam Alloy." See § 872.1(e) for the availability of this guidance document.

Dated: \_\_\_\_\_.

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