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Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Dental Devices: Classification of Encapsulated Amalgam Alloy
[Docket Number FDA-2008-N-0163²]

The American Dental Association (ADA) is pleased to offer comments in response to the Food and Drug Administration's request, as set forth in 73 Fed.Reg. 22879 (April 28, 2008). The ADA is the world's largest and oldest dental association, representing more than 155,000 dentists nationwide. For nearly 150 years, the ADA has actively sought to promote the oral health of the public and promote the development of scientifically accurate information.

DISCUSSION

The ADA previously submitted comments in response to FDA's proposed reclassification of amalgam in 2002 and restates and reaffirms those comments now. The ADA supports reclassification of dental amalgam with special controls, as proposed by the FDA in 2002. But it is essential that the special controls be carefully chosen; based on actual, sound scientific studies, and not on fear or unsubstantiated theory. To do otherwise would be to undermine the FDA regulatory system and to drive people away from needed care.

For this reason, the ADA does not support warnings or limitations on use of amalgam directed at particular populations because (as will be reviewed below) current scientific evidence does not support such action. Rather, the best scientific evidence continues to support the safety of dental amalgam. This evidence simply does not support a link between dental amalgam and systemic diseases or risks to pregnant women or developing fetuses. Finally, the evidence does not support the existence of "sensitive populations" at risk from dental amalgam.¹

Moreover, were FDA to require a warning or limit the use of amalgam, the ADA is concerned that it would hurt efforts to address the oral health needs of both individuals and the entire population. Individually, it would deprive some patients of the freedom to choose the optimal treatment for them. In others, especially young children and those with special needs, where it may not be possible to create the dry environment required for placement of alternative restorative materials, the elimination of amalgam as a treatment option could require the use of general anesthetics. Unwarranted FDA action will also affect the entire population. As is discussed below, elimination of dental amalgam as an option, even for limited groups, will have a profound effect on the nation's public health system because of the added cost of alternative treatments. FDA also needs to be aware of the "halo effect"; how a contraindication for one population will deter others from the same treatment. These problems

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¹ The ADA does recognize, of course, that a very small segment of the population may experience localized allergic reactions to dental amalgam.

highlight the importance of FDA acting only on sound scientific evidence and not on generalized concerns.

Some who support an outright ban of dental amalgam ignore or fail to understand the science supporting the conclusion that it remains a safe treatment option. Typically, they rely on non-peer-reviewed articles, studies that do not comply with Good Clinical Practice (GCP), or on studies which focus solely on sub-clinical effects at the cellular level, ignoring the dearth of evidence that amalgam causes humans any harm. Finally, those seeking a ban or drastic restriction on use rely on a false reading of the precautionary principle. Under this reading, unless the negative is proven (i.e. unless there is a study which can “prove” that no one, anywhere, can ever be harmed), all uses of amalgam must be ended. The problem with this approach to the precautionary principle is that it would result in the ban on almost any substance. For it is simply not possible to prove that anything is always safe. Even water cannot be “proven” safe because, at the wrong amount (dose) or ingested in the wrong way, harm is possible. While these amalgam opponents are, of course, free to advocate this or any other approach, the FDA is more constrained. As a British editor commented under similar circumstances: “But while it is one thing to debate an issue such as this..., it is quite another when a government or regulatory authority abruptly decides that it is time to ban amalgam on an emotional, or at the very least, un-critically appraised level.” **Editorial, Stephen Hancocks, *British Dental Journal* 204, 593 (2008) Published online: 14 June 2008 | doi:10.1038/sj.bdj.2008.492.** The FDA must resist such an unscientific approach to amalgam regulation.

In these comments, the ADA will respond to the specific questions raised by FDA, but will first offer a review of the scientific literature published since the last comprehensive review in 2004 by Life Sciences Research Office. ADA will then review why any action by FDA should have preemptive effect over state law.²

DENTAL AMALGAM FILLINGS AND HEALTH EFFECTS—A LITERATURE REVIEW

The last extensive review of the published literature relevant to amalgam safety was conducted by the Life Science Research Office (LSRO) and published in 2004. The ADA agrees with the FDA’s characterization of that study in its Federal Register notice reopening the comment period. 73 Fed.Reg. at 22879. That review was a “systematic and comprehensive evaluation.” Id. For that reason, the LSRO review is a logical starting point for an update on the scientific literature.

The LSRO expert panel concluded that “the studies [reviewed] contained insufficient evidence to support a correlation or causal relationship between exposure to dental amalgam and kidney or cognitive dysfunction; neurodegenerative disease (specifically Alzheimer’s disease and Parkinson’s disease); autoimmune disease (including multiple sclerosis); or adverse pregnancy outcomes.” Id.

Since that publication, there have been a variety of studies published, which are reviewed below. Two key studies, the “Childrens Amalgam Trials”, and the publications resulting from them, merit special note. These rigorous clinical trials complied with GCP, were prospective, included a relatively large number of subjects (over 500 in each study), measured multiple outcomes related to renal and neurological function and were conducted in children – a population purportedly more sensitive to any health effects from low-level mercury exposure.

None of the studies published since the work of the LSRO expert panel changes the basic conclusions reached by the LSRO expert panel: There is still no scientifically sound evidence of harm caused by dental amalgam in general or for any so-called sensitive population in particular.

² The FDA has recognized the risk of over-warning. 71 Fed. Reg. 3922 at 3935, and *Statement by the FDA before the Committee on Oversight and Government Reform*

Methodology

ADA staff within the Division of Science searched the literature published between January 1, 2004 (the end point of the LSRO review) and May 2, 2008. A search of the MEDLINE database using PubMed identified 433 articles on the topic of dental amalgam. The search was limited to *in vivo* studies on humans and those published in English. The abstracts of the 433 articles were reviewed to identify all studies relevant to amalgam and biochemical, behavioral and/or toxicological effects. Studies were limited to human evaluations, because of the large number of clinical studies published during this period and the fact that health effects in laboratory animals do not reliably predict health effects in humans. Thirty-seven relevant articles were identified.

The relevant studies are summarized below. Because one focus of FDA's request for comments is on pregnant women, studies touching on that topic are discussed first.

Literature Summary

A. Studies investigating the *in utero* effects of low-level elemental mercury exposure.

Summary: Maternal amalgam fillings result in *in utero* exposure to low levels of elemental mercury. *There is no evidence that this exposure is associated with any adverse pregnancy outcomes or health effects in the newborns and infants.*

Luglie PF, Campus G, Chessa G, Spano G, Capobianco G, Fadda GM, Dessole S.
Effect of amalgam fillings on the mercury concentration in human amniotic fluid.
Arch Gynecol Obstet. 2005 Feb;271(2):138-42. Epub 2003 Dec 20.

Seventy-two pregnant women took part in the prospective study examining the effect of the number and surface areas of amalgam fillings on the mercury concentration in amniotic fluid. The investigators found that the number and surface areas of amalgam fillings positively influenced the mercury concentrations in amniotic fluid, *but not at a statistically significant level*. The authors concluded that mercury levels detected in amniotic fluid were low and they observed no adverse outcomes during the pregnancies (incidence of hypertension, premature rupture of membranes, caesarean section rate, postpartum hemorrhage) or in the newborns (Apgar scores, hypocalcemia, hypoglycemia, hyperbilirubinemia, sepsis, respiratory distress syndrome, asphyxia, seizures).

Palkovicova L, Ursinyova M, Masanova V, Yu Z, Hertz-Picciotto I
Maternal amalgam dental fillings as the source of mercury exposure in developing fetus and newborn.
J Expo Sci Environ Epidemiol. 2008 May;18(3):326-31. Epub 2007 Sep 12.

This study assessed the relationship between maternal dental amalgam fillings and exposure of the developing fetus to mercury. The study subjects were 99 mother-child pairs. Questionnaires were completed after delivery and mercury levels in maternal and cord blood were recorded. The authors report that none of the cord blood samples contained mercury at levels considered to be hazardous for neurodevelopmental effects in children exposed to mercury in utero using the EPA reference dose (5.8 µg/l in cord blood). Levels of mercury in cord blood were associated with the number of maternal amalgam fillings and with the number of years since the last filling. Although the authors concluded that dental amalgam fillings in girls and women of reproductive age should be used with caution to avoid prenatal mercury exposure, the study conclusion was not based on any finding of an adverse outcome.

Hujoel PP, Lydon-Rochelle M, Bollen AM, Woods JS, Geurtsen W, del Aguila MA. Mercury Exposure from Dental Filling Placement during Pregnancy and Low Birth Weight Risk. *Am J Epidemiol*. 2005 Apr 15;161(8):734-40.

This population-based, case-control study evaluated the risk of a low birth weight pregnancy outcome associated with placement of amalgam fillings. The study was conducted by linking dental utilization data from Washington Dental Service to Vital Records birth certificates from Washington State. The study included women between the ages of 12 and 45 years with a dental treatment between January 1, 1993, and December 31, 2000. 1,117 women with low birth weight infants were compared with a random sample of 4,468 women who gave birth to infants that were not low birth weight. 4.9% of the women had at least one amalgam filling placed during pregnancy. These women were not found to be at higher risk for a low birth weight infant and neither were women who had from 4 to 11 amalgam fillings placed.

Daniels JL, Rowland AS, Longnecker MP, Crawford P, Golding J; ALSPAC Study Team. Maternal dental history, child's birth outcome and early cognitive development. *Paediatr Perinat Epidemiol*. 2007 Sep;21(5):448-57.

This study evaluated prenatal exposure to mercury from amalgam fillings and adverse the reproductive outcomes: preterm delivery, low birth weight and delayed neurodevelopment. Maternal dental history prior to and during pregnancy was documented for 7375 offspring born in Britain between 1991 and 1992. Nearly 90% of the women in this study received dental care during pregnancy. Of these women 31% had amalgams placed or removed. 71% of the women had 4 or more amalgams in place prior to conception. Dental care was not associated with gestational age or birth weight. The odds of term low birth weight or preterm birth were not associated with maternal history of any dental care during pregnancy or with having an amalgam filling placed or removed. Having more fillings in place at time of conception did not negatively affect pregnancy or birth outcome. Early communicative development scores were not associated with receiving dental care or with placement or removal of amalgam fillings. In addition, the odds of scoring low were not associated with maternal dental history. Although low (0.01 µg/g wet weight) and not statistically significant, the mean umbilical cord mercury concentration was slightly higher in women who had dental care. However cord mercury concentrations did not differ significantly among mothers in relation to amalgam fillings during pregnancy or by the number of amalgams in place prior to pregnancy. The association between maternal dental history and offspring's communicative development was not affected when adjusted for mercury level among the subset of offspring with umbilical cord mercury data. Overall, dental amalgam fillings were not associated with negative birth outcomes or delayed language development.

B. Large occupational studies evaluating effects on reproduction and pregnancy outcomes.

Summary: Only one study was identified on this topic. No significant association was found between occupational exposure to dental amalgam and miscarriage.

Lindbohm ML, Ylöstalo P, Sallmén M, Henriks-Eckerman ML, Nurminen T, Forss H, Taskinen H. Occupational exposure in dentistry and miscarriage. *Occup Environ Med*. 2007 Feb;64(2):127-33. Epub 2006 Oct 19

This study evaluated occupational exposures in dentistry and the risk for miscarriage. The final study population included 222 cases of miscarriage and 498 controls. Data was collected using a questionnaire. The investigators found non-significant associations between exposure to some acrylate compounds, dental amalgam, solvents, disinfectants and radiation and miscarriage. There was no dose-response relationship.

C. Studies evaluating the amount of mercury absorbed from breast milk and the effect on the developing brain.

Summary: Only one study was identified on this topic. The study reported that the presence of maternal dental amalgam fillings may expose nursing infants to mercury levels that exceed WHO's intake limit. The reported results are not in agreement with previous results from similar studies (cited below) and the authors cited the incorrect WHO intake limit.

da Costa SL, Malm O, Dorea JG.
Breast-Milk Mercury Concentrations and Amalgam Surface in Mothers from Brasilia, Brazil.
Biol Trace Elem Res. 2005 Aug;106(2):145-51.

This study examined the mercury levels in human breast milk in 23 women in Brazil. The authors state that dental fillings were the primary source of inorganic mercury. The authors found a correlation between breast-milk mercury concentrations and amalgam surfaces. However, it is important to note that the correlation coefficient was low at 0.6. This means that approximately sixty percent of the variation in the response variable (mercury in milk) can be explained by the explanatory variable (amalgam surfaces). The remaining forty percent can be explained by inherent variability. The authors concluded that in 56.5% of low-fish-eating mothers, the amount of mercury likely ingested by breast-fed infants would exceed the WHO reference, which the authors state is 0.5µg/kg body weight/day. The tolerable daily intake set by the WHO is actually 2.0µg/kg body weight/day. Using this number 2 mothers (7%) had breast milk samples above WHO's intake limit. The mercury concentrations from the breast milk in this group of women are from 3 to 14 times higher than previously reported.¹⁻⁴ In addition, the other studies reported fish consumption as an additional source of mercury exposure. The women in this study reported eating fish on average once per month. The women in this study had on average 7 amalgam fillings. Other studies reported higher numbers of amalgam fillings. Therefore, the higher breast milk mercury concentrations in this group of women are not explained by frequent fish consumption or a greater number of amalgam fillings.

- 1 Oskarsson A, Schutz A, Skerfving S, Hallen IP, Ohlin B, Lagerkvist BJ. Total and inorganic mercury in breast milk and blood in relation to fish consumption and amalgam fillings in lactating women. Arch Environ Health 1996;51:234-241.
- 2 Drexler H, Schaller KH. The mercury concentration in breast milk resulting from amalgam fillings and dietary habits. Environ Res. 1998;77:124-91.
- 3 Drasch G, Aigner S, Roeder G, Staiger F, Lipowsky G. Mercury in human colostrum and early breast milk. Its dependence on dental amalgam and other factors. J Trace Elem Med Biol. 1998;12:23-7.
- 4 Ursinyova M, Masanova V. Cadmium, lead and mercury in human milk from Slovakia. Food Addit Contam. 2005 Jun;22(6):579-89.

D. Well-controlled studies that use standardized measures of exposure and evaluate neurotoxic and/or neuropsychological effects and, if any, dose-response relationships.

Summary: A number of well-controlled studies that evaluated neuropsychological and neurobehavioral function and exposure to amalgam fillings in children and adults are described below. Many of the studies used data generated from the Children's Amalgam Trials that evaluated exposure in hundreds of school children between the ages of 6 and 10 over a five or seven year period. *These studies found no evidence that exposure to amalgam causes adverse health outcomes using a number of neurological endpoints.*

Kingman A, Albers JW, Arezzo JC, Garabrant DH, Michalek JE.

Amalgam exposure and neurological function.
Neurotoxicology. 2005 Mar;26(2):241-55.

This study examined 1663 dentate Vietnam era veterans participating in the Air Force Health Study. Study outcomes included clinical neurological signs, vibrotactile thresholds and summary variables for different levels of peripheral neuropathy. No significant associations were found between amalgam exposure and clinical neurological signs of abnormal tremor, coordination, station or gait, strength, sensation, or muscle stretch reflexes or for any level of peripheral neuropathy in the subjects. A significant association was detected between amalgam exposure and the continuous vibrotactile sensation response. The authors reported that this association was a sub-clinical finding that was not associated with symptoms, clinically evident signs of neuropathy, or any functional impairment. The authors concluded that overall, there was no association between amalgam exposure and neurological signs or clinically evident peripheral neuropathy.

DeRouen TA, Martin MD, Leroux BG, Townes BD, Woods JS, Leitão J, Castro-Caldas A, Luis H, Bernardo M, Rosenbaum G, Martins IP.
Neurobehavioral effects of dental amalgam in children: a randomized clinical trial.
JAMA. 2006 Apr 19;295(15):1784-92.

This article is the first published report examining the safety of amalgam in children who participated in a randomized controlled trial over a seven-year period. A total of 507 children in Lisbon, Portugal aged 8 to 10 years received either dental amalgam or composite restorations. During the seven-year trial period children were assessed for effects on memory, attention, visuomotor function, and nerve conduction velocities. The authors concluded that children who received dental restorative treatment with amalgam did not show statistically significant differences in neurobehavioral assessments or in nerve conduction velocity compared to children who received composite fillings. The authors also reported a higher re-treatment need among the children who received composite fillings.

Bellinger DC, Trachtenberg F, Barregard L, Tavares M, Cernichiari E, Daniel D, McKinlay S.
Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial.
JAMA. 2006 Apr 19;295(15):1775-83.

This article is the first published report of the findings from the New England Children's Amalgam Trial that randomized 534 children ages 6 to 10 to two groups that either received dental amalgam or composite restorations. In the five-year study investigators conducted multiple assessments of IQ score, memory index, visuomotor composite and urinary albumin. The authors reported no statistically significant differences in neuropsychological or renal effects observed in children who had amalgam fillings placed compared to those that had composite fillings placed. The authors stated that although very small IQ effects cannot be ruled out, these findings suggest that the health effects of amalgam restorations in children need not be the basis of treatment decisions when choosing restorative dental materials.

Bellinger DC, Daniel D, Trachtenberg F, Tavares M, McKinlay S.
Dental amalgam restorations and children's neuropsychological function: the New England Children's Amalgam Trial.
Environ Health Perspect. 2007 Mar;115(3):440-6. Epub 2006 Oct 30.

This randomized controlled clinical trial included 534 children (6- to 10-years old at baseline) and evaluated the effect of exposure to mercury from dental amalgam on neuropsychological function over a five-year period. Children who received dental amalgam restorations were compared to those who received composite restorations. The children had on average approximately 9 carious

surfaces restored. The authors concluded that there was no difference in the neuropsychological function of the children who received dental amalgam fillings compared to the children who received composite fillings.

Bellinger DC, Trachtenberg F, Daniel D, Zhang A, Tavares MA, McKinlay S.
A dose-effect analysis of children's exposure to dental amalgam and neuropsychological function: the New England Children's Amalgam Trial.
J Am Dent Assoc. 2007 Sep;138(9):1210-6.

This study describes a more sensitive analysis of the data described in the previous study. The authors examined a sample of children with substantial unmet dental needs using a dose-effect analysis. There was no significant association between neuropsychological outcomes and mercury exposure. The authors concluded that there appeared to be no detectable adverse neuropsychological outcomes in children attributable to the use of amalgam restorations.

Lauterbach M, Martins IP, Castro-Caldas A, Bernardo M, Luis H, Amaral H, Leitão J, Martin MD, Townes B, Rosenbaum G, Woods JS, Derouen T.
Neurological outcomes in children with and without amalgam-related mercury exposure: seven years of longitudinal observations in a randomized trial.
J Am Dent Assoc. 2008 Feb;139(2):138-45. Erratum in: J Am Dent Assoc. 2008 Apr;139(4):404.

This randomized, prospective controlled trial examined the safety of dental amalgam. Data was collected over a seven year period of the Children's Amalgam Trial, which included 507 children from the ages of 8 through 12 years. Children received either amalgam or composite fillings and received a mean of 7.7 to 10.7 amalgam surfaces per subject over the seven years of follow-up. The investigators performed annual clinical neurological examinations to assess neurobehavioral and neurological effects. The authors concluded that amalgam exposure had no adverse neurological outcomes.

Bellinger DC, Trachtenberg F, Zhang A, Tavares M, Daniel D, McKinlay S.
Dental Amalgam and Psychosocial Status: The New England Children's Amalgam Trial.
J Dent Res. 2008 May;87(5):470-474.

This study was part of the New England Children's Amalgam Trial that randomized 534 children ages 6 to 10 to two groups that either received dental amalgam or composite restorations. The investigators examined psychosocial outcomes using both a parent-completed Child Behavior Checklist and children's self-reports. The authors concluded that there was no evidence that exposure to mercury from dental amalgam fillings was associated with adverse psychosocial outcomes in the five-year period following amalgam placement.

E. Studies examining the effects of co-exposure to organic and elemental mercury.

Summary: These studies did not evaluate adverse health effects, but attempted to identify relevant biomarkers and indicators of exposure.

Levy M, Schwartz S, Dijk M, Weber JP, Tardif R, Rouah F.
Childhood urine mercury excretion: dental amalgam and fish consumption as exposure factors.
Environ Res. 2004 Mar;94(3):283-90.

Sixty children were studied to assess urinary mercury excretion and its relation to dental amalgam and fish consumption. Children with amalgam fillings had significantly higher urinary mercury levels compared to children with non-amalgam fillings. The authors reported that the

urinary mercury levels were also associated with fish consumption. The urinary mercury levels in the amalgam group were well below levels that are known to cause adverse health effects.

Björkman L, Lundekvam BF, Laegreid T, Bertelsen BI, Morild I, Lilleng P, Lind B, Palm B, Vahter M.
Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study. *Environ Health*. 2007 Oct 11;6:30.

The study evaluated methyl and inorganic mercury in different regions of the brain, blood, muscle and toenails in an effort to determine useful biomarkers for mercury exposure. The authors concluded that methyl mercury in blood was a useful biomarker for methyl mercury concentrations in the brain. They found no useful biomarkers for inorganic mercury in the brain. For non-occupationally exposed individuals the study found that the number of dental amalgam surfaces was an indicator of the concentration of inorganic mercury in the brain.

F. Well-controlled studies using standardized measures that investigate the incidences of kidney disease, emotional instability, erethrism, pulmonary dysfunction or other characteristics of occupational mercury exposure in dental professionals.

Summary: The two small studies on this topic were conducted via questionnaires.

Ritchie KA, Burke FJ, Gilmour WH, Macdonald EB, Dale IM, Hamilton RM, McGowan DA, Binnie V, Collington D, Hammersley R.
Mercury vapour levels in dental practices and body mercury levels of dentists and controls. *Br Dent J*. 2004 Nov 27;197(10):625-32; discussion 621.

This study evaluated 180 dentists in West Scotland for mercury exposure and effects on their health and cognitive function. Dentists were found to have, on average, over 4 times the level of urinary mercury compared to age- and education-matched control subjects. The authors reported that, based on their questionnaire, dentists were more likely than control subjects to report having a disorder of the kidney, although this effect was not significantly associated with their urinary mercury level. An age effect was found for memory disturbances in dentists but not in the control subjects. There was no significant association between urinary mercury concentrations and self-reported memory disturbance. See Note, below, for information on U.S. dental professionals.

Jones L, Bunnell J, Stillman J.
A 30-year follow-up of residual effects on New Zealand School Dental Nurses, from occupational mercury exposure. *Hum Exp Toxicol*. 2007 Apr;26(4):367-74.

This study compared the general health, reproductive health, cognition and mood of 43 ex-School Dental Service employees exposed to copper amalgam with 32 matched controls. The authors concluded that the dental nurses (average age of 52) did not appear to be neurobehaviorally compromised. The exposed group reported that they were in very good health, which was the same as the control group. The authors reported that there were seven symptoms from a list of 33 that were selected from a medical definition of mercury poisoning that were reported at a higher rate by exposed group than by the control group (arthritis, bloating, dry skin, headache, metallic taste, sleep disturbances and unsteadiness). It did not appear that the investigators performed post-hoc testing to compensate for multiple comparisons.

Note: Each year the ADA conducts a Health Screening Program for dental professionals at the annual meeting. Exposure to elemental mercury is assessed through testing urine samples for mercury. Since testing was instituted in 1976, there has been a steady decline in mercury exposure in

the thousands of dental professionals that have been tested. Over the past two decades, the urinary mercury levels have dropped to within the range found in non-occupationally exposed females 19 to 49 years in the U.S as reported by the CDC NHANES data from 1999-2002.

G. Studies evaluating any genetic basis for sensitivity to mercury exposure.

Summary: Studies evaluating exposure effects in individuals that are reportedly sensitive to mercury did not show consistent evidence that a sensitive group exists. In addition, no specific genotoxic effects were found associated with exposure to amalgam.

Prochazkova J, Sterzl I, Kucerova H, Bartova J, Stejskal VD.
The beneficial effect of amalgam replacement on health in patients with autoimmunity.
Neuro Endocrinol Lett. 2004 Jun;25(3):211-8.

This uncontrolled study evaluated thirty-five patients described as mercury-allergic with autoimmunity that had their amalgam fillings replaced with composite fillings and ceramic materials. The authors evaluated self-reported health status and lymphocyte reactivity. The authors reported that 71% of patients experienced health improvements and that the patients who improved were the ones with the highest lymphocyte reactivity before amalgam removal. The conclusion was that mercury-containing amalgam may be an important risk factor for patients with autoimmune diseases and that lymphocyte reactivity is a valuable tool for selection of patients for amalgam replacement. The study did not include a control group.

Melchart D, Vogt S, Köhler W, Streng A, Weidenhammer W, Kremers L, Hickel R, Felgenhauer N, Zilker T, Wühr E, Halbach S.
Treatment of health complaints attributed to amalgam.
J Dent Res. 2008 Apr;87(4):349-53.

This randomized and controlled study compared the reduction of subjective complaints in 90 "amalgam patients" using three treatment strategies. Individuals were randomly assigned to have their amalgams removed only, to have their amalgams removed with "biological detoxification" therapy or to participate in a health promotion program without dental amalgam removal. Observations were made for 18 months. Mercury in erythrocytes, blood and urine were evaluated. Mercury concentrations in the removal groups were significantly different from the non-removal group in blood and urine, but not in erythrocytes. An improvement in subjective health complaints was found in all three groups.

Melchart D, Köhler W, Linde K, Zilker T, Kremers L, Saller R, Halbach S.
Biomonitoring of mercury in patients with complaints attributed to dental amalgam, healthy amalgam bearers, and amalgam-free subjects: a diagnostic study.
Clin Toxicol (Phila). 2008 Feb;46(2):133-40.

This report describes an investigation into the suitability of using mercury levels as a means of identifying patients with health complaints attributed to dental amalgam. Mercury levels in erythrocytes, plasma, urine, and saliva were determined in 27 patients complaining about health problems attributed to amalgam, 27 healthy volunteers with amalgam fillings, and 27 healthy amalgam-free volunteers. The investigators found that concentrations of inorganic mercury in blood and of total mercury in urine and saliva differed significantly between individuals with amalgam fillings and amalgam-free volunteers, but not between symptomatic patients and healthy volunteers with amalgam fillings. Levels of organic mercury were equal in all groups. The authors concluded that concentrations of total and inorganic mercury in body fluids do not distinguish between asymptomatic amalgam bearers and those who suffer from a poorly defined syndrome of multiple nonspecific symptoms.

Vamnes JS, Lygre GB, Grønningsaeter AG, Gjerdet NR.
Four years of clinical experience with an adverse reaction unit for dental biomaterials.
Community Dent Oral Epidemiol. 2004 Apr;32(2):150-7.

This study describes the findings from 296 patients examined at the Norwegian National Dental Biomaterials Adverse Reaction Unit from 1993 to 1997. Dental amalgam was the primary reason for referral. Patients reported general subjective symptoms, such as muscle and joint pain, fatigue, memory problems and orofacial symptoms. The investigators found no significant correlation between mercury concentrations in blood and urine and the number of subjective symptoms or objective findings.

Nerdrum P, Malt UF, Høglend P, Oppedal B, Gundersen R, Holte M, Löne J.
A 7-year prospective quasi-experimental study of the effects of removing dental amalgam in 76 self-referred patients compared with 146 controls.
J Psychosom Res. 2004 Jul;57(1):103-11.

This quasi experimental study evaluated changes in mental and physical symptoms in 76 patients who had their dental amalgam removed seven years prior to the evaluation. These individuals were compared with patients with known chronic medical disorders seen in alternative (n=51) and ordinary (n=51) medical family practices and non symptomatic patients with dental amalgam fillings (control group, n=44). Removal of amalgam reduced the reported physical and mental symptoms to the level of the group with known chronic medical disorders. The control group consistently reported fewer symptoms. The authors concluded that their findings did not support the hypothesis that removal of amalgam will reduce health complaints to normal levels.

Frisk P, Danersund A, Hudecek R.
Changed Clinical Chemistry Pattern in Blood After Removal of Dental Amalgam and other Metal Alloys Supported by Antioxidant Therapy.
Biol Trace Elem Res. 2007 120:163-70.

This study examined clinical chemistry patterns in patients with complaints related to amalgam restorations. All 24 patients with complaints had their amalgams removed and were treated with antioxidants at unspecified doses (vitamin B-complex, vitamin C, vitamin E, and sodium selenite). The authors reported that the clinical chemistry patterns before and after amalgam removal were significantly different. The authors also reported that individuals' clinical chemistry patterns before amalgam removal were significantly different from an age- and sex-matched control group. The authors concluded that the individuals clinical chemistry patterns could be used to identify individuals based on amalgam removal. However, the lack of proper controls makes it impossible to determine the reason for the change in clinical chemistry patterns. The authors did not report on any associated health effects.

Wojcik DP, Godfrey ME, Christie D, Haley BE.
Mercury toxicity presenting as chronic fatigue, memory impairment and depression: diagnosis, treatment, susceptibility, and outcomes in a New Zealand general practice setting (1994-2006).
Neuro Endocrinol Lett. 2006 Aug;27(4):415-23.

This study describes a group of 465 patients who were given a diagnosis of chronic mercury toxicity (CMT) based on chronic physical and mental symptoms that were previously undiagnosed. The investigators found a correlation between CMT and the Apo-lipoprotein E4 genotype, which they suggest identifies a significant risk for developing Alzheimer's disease in these individuals. The individuals diagnosed with CMT had their amalgams removed and underwent chelation therapy. The authors

reported that treated individuals had significant reductions in symptoms to the level reported by healthy individuals. The study design did not include randomization or blinding.

Lygre GB, Gjerdet NR, Björkman L.

A follow-up study of patients with subjective symptoms related to dental materials.
Community Dent Oral Epidemiol. 2005 Jun;33(3):227-34.

This study evaluated changes in the intensity of subjective symptoms after replacement of dental materials in patients referred to the Dental Biomaterials Adverse Reaction Unit in Norway for adverse reactions to dental materials. Of 142 patients, follow-up questionnaires were completed by 84 patients (3 were not included because the questionnaire was incomplete) and compared to 442 individuals in the general population (control group). Patients who had replaced dental materials (n=35) continued to report higher symptom indices than individuals in the control group. Patients who had not replaced dental materials (n=46) did not report any reduction in intensity of symptom indices. The authors concluded that the intensity of local (in the mouth) and some general subjective symptoms was reduced after dental materials were replaced, but not to the level reported by the general population.

Di Pietro A, Visalli G, La Maestra S, Micale R, Baluce B, Matarese G, Cingano L, Scoglio ME.

Biomonitoring of DNA damage in peripheral blood lymphocytes of subjects with dental restorative fillings.

This study evaluated the genotoxicity of dental restorative materials. The investigators evaluated blood specimens from 68 subjects (44 exposed to either or both dental amalgam and composites). DNA damage was assessed using the comet assay and the investigators concluded that both amalgam and methacrylates trigger the generation of cellular reactive oxygen species that cause oxidative DNA lesions.

Atesagaoglu A, Omurlu H, Ozcagli E, Sardas S, Ertas N.

Mercury exposure in dental practice.
Oper Dent. 2006 Nov-Dec;31(6):666-9.

This study evaluated the genotoxicity of occupational exposure to mercury in 10 dentists. The authors concluded that blood samples taken from dentists exposed to mercury vapor concentrations below $0.1\text{mg}/\text{m}^3$ did not exhibit cytogenetic damage to leukocytes.

H. Gender differences in the pharmacokinetics and toxicity of mercury.

Summary: One study reported a possible gender difference related to mercury excretion. However, there were no adverse health effects associated with this gender difference. More studies are needed to determine if a gender difference exists.

Woods JS, Martin MD, Leroux BG, DeRouen TA, Leitão JG, Bernardo MF, Luis HS, Simmonds PL, Kushleika JV, Huang Y.

The contribution of dental amalgam to urinary mercury excretion in children.
Environ Health Perspect. 2007 Oct;115(10):1527-31.

This randomized controlled clinical trial included 507 children (8- to 10-years old at baseline) and evaluated the effect of exposure to mercury from dental amalgam on urinary mercury excretion. The authors report that urinary mercury concentrations were highly correlated with both the number of amalgam fillings and the time since placement in children. The authors also found that girls excrete significantly higher concentrations of mercury in urine than boys with comparable treatment. This finding suggests that there may be sex-related differences in mercury excretion.

I. Study evaluating the influence of amalgam fillings on antibiotic-resistant bacteria in the gut and the mouth.

Summary: No evidence was found to support the hypothesis that amalgam fillings are associated with antibiotic-resistant bacteria in the gut or mouth.

Roberts MC, Leroux BG, Sampson J, Luis HS, Bernardo M, Leitão J.
Dental Amalgam and Antibiotic- and/or Mercury-resistant Bacteria.
J Dent Res. 2008 May;87(5):475-9.

This study examined the association between the presence of amalgam fillings and antibiotic- or mercury-resistant bacteria in the mouth. Participants of the study were a subset of the children who participated in the randomized controlled trial designed to assess the safety of amalgam (Children's Amalgam Trial). 150 children were included in the study designed to detect a half log change in bacteria levels with 15% drop out. The authors concluded that there was no evidence that amalgam fillings influenced the level of antibiotic- or mercury-resistant bacteria in the mouth or urine.

J. Kidney function and exposure to amalgam fillings.

Summary: Amalgam exposure had no effect on a number of markers of glomerular and tubular kidney function in over 500 children over a five-year period, except for microalbuminuria (the incidence of which was higher in the amalgam group). More studies are needed to determine if this is a consistent finding.

Barregard L, Trachtenberg F, McKinlay S.
Renal effects of dental amalgam in children: the New England children's amalgam trial.
Environ Health Perspect. 2008 Mar;116(3):394-9.

This randomized, prospective controlled trial examined the safety of dental amalgam in children who received either amalgam or composite fillings. Data was collected over a five year follow-up period of the Children's Amalgam Trial, which included 534 children from the age of 6 through 10 years. The investigators assessed changes on markers of glomerular and tubular kidney function and urinary mercury levels. The authors found no significant differences between the treatment groups and no significant effects related to the number of dental amalgam fillings on the markers. Children in both treatment groups experienced microalbuminuria, but the prevalence was higher in the amalgam group. The authors concluded that the increase in microalbuminuria may be random, but should be further evaluated.

K. Two systematic reviews (one with meta-analysis) examining the association between dental amalgam and health effects.

Summary: Two systematic reviews evaluated neurological outcomes and exposure to amalgam fillings. No statistically significant associations were found for amalgam exposure and multiple sclerosis in adults and neurobehavioral and neuropsychological scores in children.

Aminzadeh KK, Etminan M.
Dental amalgam and multiple sclerosis: a systematic review and meta-analysis.
J Public Health Dent. 2007 Winter;67(1):64-6. Review.

This meta-analysis evaluated the association between dental amalgam restorations and multiple sclerosis. A systematic search for data published between 1966 to April 2006 was conducted

using Medline, EMBASE and the Cochrane library. The authors report finding four observational studies (three case control studies and one cohort study) that met their inclusion criteria. A meta-analysis revealed a slight nonstatistically significant increase between the presence of amalgam fillings and MS. The study does not provide evidence for or against an association.

Rasines G.

Mercury released from amalgam restorations does not give rise to toxic effects on the nervous system of children.

Evid Based Dent. 2008;9(1):25-7.

This systematic review examined whether or not placement of amalgam restorations increase the risk of neuropsychological disorders compared to composite restorations in children between the ages of 6 and 10. The author included 3 clinical studies and concluded that there is no significant statistical association between the neurobehavioral and neuropsychological scores of children with amalgam versus composite fillings.

L. Studies evaluating the mercury dose absorbed from amalgam fillings.

Summary: Studies consistently demonstrated that exposure to amalgam fillings results in absorption of elemental mercury by the body. Overall, the results are similar to previous reports considered during the LSRO review.

Halbach S, Vogt S, Köhler W, Felgenhauer N, Welzl G, Kremers L, Zilker T, Melchart D.
Blood and urine mercury levels in adult amalgam patients of a randomized controlled trial:
Interaction of Hg species in erythrocytes.

Environ Res. 2008 May;107(1):69-78. Epub 2007 Sep 4.

This study evaluated the internal exposure to amalgam-related mercury and estimated the amalgam-related absorbed dose of mercury. The integrated mercury dose absorbed from amalgam fillings was estimated at up to 3 µg per day for an average number of fillings and 7.4 µg per day for a high amalgam load. The authors concluded that these estimates are well below the tolerable dose of 30 µg per day established by WHO.

Maserejian NN, Trachtenberg FL, Assmann SF, Barregard L.

Dental amalgam exposure and urinary mercury levels in children: the New England Children's Amalgam Trial.

Environ Health Perspect. 2008 Feb;116(2):256-62.

This study examined the associations between various detailed amalgam exposure measures and urinary mercury in 267 children participating in the Children's Amalgam Trial. The authors reported that the current total of amalgam surfaces was the most robust predictor of current urinary mercury concentration. The study was not designed to examine amalgam safety.

Dunn JE, Trachtenberg FL, Barregard L, Bellinger D, McKinlay S.

Scalp hair and urine mercury content of children in the Northeast United States: The New England Children's Amalgam Trial.

Environ Res. 2008 May;107(1):79-88. Epub 2007 Oct 24.

This analysis of data collected over the five year period of the Children's Amalgam Trial, which included 507 children from the ages of 8 through 12 years, reports mean hair mercury levels of 0.3-0.4 µg/g and mean urinary mercury levels of 0.7-0.9 µg/g creatinine. The authors report that the use of chewing gum in the presence of amalgam fillings was a predictor of higher urinary

mercury levels. The urinary mercury levels in these children are similar to the mean urinary mercury levels in adult females in the U.S. according to the CDC's NHANES data.

Guzzi G, Grandi M, Cattaneo C, Calza S, Minoia C, Ronchi A, Gatti A, Severi G.
Dental amalgam and mercury levels in autopsy tissues: food for thought.
Am J Forensic Med Pathol. 2006 Mar;27(1):42-5.

This study examined the association between mercury levels in brain tissue from 18 cadavers and the number of occlusal dental amalgam fillings. The authors report that mercury levels increased with the number of dental amalgam fillings for all tissues and that mercury levels were significantly higher in brain tissues compared with thyroid and kidney tissues in subjects with more than 12 occlusal amalgam fillings, but not in subjects with 0 to 3 occlusal amalgam fillings. The authors also stated that the levels of mercury were higher in all tissues in cases of suicide compared to non-suicides. The authors did not have accurate information on fish consumption. Individual data was not presented and the data on the association between higher mercury levels and suicide was not presented. The study did not use controls

M. A large retrospective study evaluating neurological effects of amalgam fillings.

Summary: This large retrospective cohort study found no association between amalgam fillings and chronic fatigue syndrome or kidney disease. A slightly elevated risk for multiple sclerosis was reported, but may have been due to confounding variables.

Bates MN, Fawcett J, Garrett N, Cutress T, Kjellstrom T.
Health effects of dental amalgam exposure: a retrospective cohort study.
Int J Epidemiol. 2004 Aug;33(4):894-902. Epub 2004 May 20.

A retrospective cohort study that included 20,000 people in the New Zealand Defense Force between 1977 and 1997. The authors investigated the association of amalgam fillings and disorders of the nervous system and kidneys. Multiple sclerosis had an adjusted hazard ratio of 1.24, but there was no association with chronic fatigue syndrome or kidney disease. There were insufficient cases for investigation of Alzheimer's or Parkinson's diseases. The authors concluded that their results provided only limited evidence of an association between amalgam and disease.

COMMENTS IN RESPONSE TO SPECIFIC FDA QUESTIONS

(1) *How many annual procedures use mercury amalgams? What are the trends?*

A study published in 2007 reviews current data on amalgam usage in the United States. Beazoglou T, Eklund S, Heffley D, Meiers J, Brown LJ, Bailit H, Economic Impact of Regulating the Use of Amalgam Restorations, Public Health Reports 2007 September-October; vol. 122, 657. That study estimates total amalgam placements in 2005 as being approximately 31% of the total of restorations. (46% were composites.) The study also reviewed trends for amalgam placements. The mean percentage of decline in amalgam placements per year for the preceding twelve years was 3.7%. It is expected that this trend will continue into the foreseeable future.

This is an important point because the trend away from amalgam usage (due primarily to the availability of alternatives in many clinical situations and the desire for more aesthetically pleasing white fillings) lessens the need for draconian regulatory action.

(2) *What are the differences in cost between amalgams and alternative materials (e.g., composite, other metals, ceramics, etc.)? Are there differences in replacement lives?*

This is a significant issue, and one which bears directly on the public health issues of any potential FDA action. Even a partial ban on dental amalgam would have a profound effect on the costs of oral health care and, perhaps, even a greater impact on the public health system. Beazoglou, et al. estimate, for example, that a ban on just children aged 0 to 9 “will increase dental expenditures about \$1.1 billion per year and \$13 billion from 2005 through 2020.” *Id.* at 660. Just as troubling, the economic analysis associated with such a price increase concludes that the increase will result in 15.4 million cases of untreated dental disease. *Id.* If a broader ban—including children plus women of child-bearing age—were imposed, the costs per year would jump to approximately \$3 billion.

There are several reasons for these harmful consequences. First, the primary substitutes for amalgam, composites and cast restorations, are 46% more expensive. *Id.* at 661-62. Second, composite restorations, on average, are less durable than amalgam and require more frequent replacement. *Id.* See, also, DeRouen TA, Martin MD, Leroux BG, Townes BD, Woods JS, Leitão J, Castro-Caldas A, Luis H, Bernardo M, Rosenbaum G, Martins IP. Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. *JAMA.* 2006 Apr 19;295(15):1784-92.

In summary, even a partial limitation on the placement of amalgam will have profound effects, resulting in significant costs and untreated disease. Clearly, such a cost must not be imposed based on speculative concerns unsupported by the best scientific studies.

(3) What are reimbursement rates for dental amalgam and the alternative materials?

Information about the cost of amalgams and alternatives is set forth above. Often, insurance will not even cover composite restorations in posterior teeth. Or, if such restorations are covered, many insurance plans only pay at the rate for amalgam fillings. This highlights the importance of FDA considering all the ramifications of its action. Restrictions on amalgam placements will come at a cost and that cost will largely be borne by the patient and the public health systems in the states.

(4) How would labeling describing the risks of amalgam for certain subpopulations (e.g., children under age 6, pregnant and lactating women, hypersensitive or immunocompromised individuals) affect the demand for, and use of, mercury amalgam? How would the risks included in the labeling be communicated to those subpopulations?

FDA mandated labeling must be supported by science. The sort of labeling asked about here is not, as is clear from a review of the recent science, set forth above. Obviously, if such an unsupported warning were mandated, those to whom the warning were given would be deterred from having amalgam restorations placed. But at what costs? Clearly, there is a monetary cost which is significant, both individually and in the aggregate. Beazoglou T, Eklund S, Heffley D, Meiers J, Brown LJ, Bailit H, Economic Impact of regulating the Use of Amalgam Restorations, *Public Health Reports* 2007 September-October; vol. 122, 657. But there is also a health cost. As prices rise, some will forego treatment. *Id.*

The ADA supports full and open communication between dentists and their patients. To facilitate that, the ADA had developed a comprehensive and accurate patient information brochure dealing with restorative options. See http://www.ada.org/prof/resources/topics/materials/dental_fillings_facts_full.pdf. The ADA encourages its members to use this brochure as part of the dentist-patient discussion surrounding treatment options. Additional information regarding the pros and cons of various treatment options is not needed. However, if the FDA were to mandate some form of brochure or warning, it is essential that dentists and their patients are not bombarded with conflicting and additional warning requirements. As is discussed below, any disclosure requirement imposed by FDA should be accompanied by an explicit statement that FDA intends to preempt state law in this regard.

(5) What is the current exposure to mercury for patients? For professionals? What would be the reduction in exposure associated with the alternatives described previously in this section of this document?

For Patients: The New England Childrens Amalgam Trial (Bellinger DC, Trachtenberg F, Barregard L, Tavares M, Cernichiari E, Daniel D, McKinlay S. Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. JAMA. 2006 Apr 19;295(15):1775-83) found that the average urinary mercury levels in children with amalgam fillings was higher at 0.9 (range of 0.1 to 5.7) micrograms per gram creatinine compared to children with composite fillings at 0.6 (range of 0.1 to 2.9) micrograms per gram creatinine. Mercury levels in the amalgam group were still within established background population levels and levels that are considered safe. Hair mercury levels were similar in both groups. Therefore, a small reduction in mercury exposure would be expected if amalgam restorations were replaced with composite restorations. However, this reduction in exposure would not be expected to result in any health benefit. Just because a substance can be measured in the body does not mean that the substance causes harm.

For Professionals: ADA Health Screening data evaluating mercury exposure in female U.S. dental professionals from 1997 to 2007 found an average urinary mercury level of approximately 2.5 micrograms/L. This level is within the range found in non-occupationally exposed females 19 to 49 years in the U.S as reported by the CDC NHANES data from 1999-2002. Therefore, the reduction in mercury exposure for professionals may be negligible.

SCENIHR REPORT

A recent review of the evidence conducted by a Scientific Committee of the European Commission addressed safety concerns for patients, professionals and the use of alternative restorative materials. See http://ec.europa.eu/health/ph_risk/committees/04_scenihhr/docs/scenihhr_o_016.pdf.

The committee concluded that dental amalgams are effective and safe, both for patients and dental personnel. The Committee's report states, "SCENIHR concluded that dental amalgams are an effective restorative material and may be considered the material of choice for some restorations. While some local adverse effects are seen, the incidence is low and usually readily managed. The current use of dental amalgams does not pose a risk to health apart from allergic reactions. The main exposure to mercury in individuals with amalgam restorations occurs during the placement or removal of fillings. **There is no clinical justification for removing clinically satisfactory amalgam restorations, except in patients allergic to amalgam constituents.** The mercury released during placement and removal also results in exposure of the dental personnel. However, this may be minimized by the use of appropriate clinical techniques.

According to SCENIHR, alternative materials are not without clinical limitations and toxicological hazards. Allergies to some of these substances have been reported, both in patients and in dental personnel. Available scientific data concerning exposure to these substances are limited. The use of these substances has revealed little evidence of clinically significant adverse events.

Environmental and Indirect health effects

The Scientific Committee on Health and Environmental Risks (SCHER) adopted a report on the environmental risks and indirect health effects of mercury in dental amalgam.

SCHER concluded that environmental risks and indirect exposure of humans to methylmercury (from emissions due to use of dental amalgam) are much lower than tolerable limits, indicating a low risk of serious health effects. With regard to environmental risks of amalgam alternatives, the available information is too limited to conduct a proper comparative assessment."

IF FDA MANDATES DISCLOSURE OR WARNING, FDA MUST EXPLICITLY STATE ITS INTENT TO PREEMPT STATE LAW

If the FDA mandates certain warnings or information be provided to patients, the ADA believes it is imperative for the FDA to indicate clearly that the Agency's regulatory approach preempts conflicting state and local laws, and state-law product liability actions, against dentists who use dental amalgam products in their practices. As FDA has repeatedly stressed in Congressional testimony, Federal Register preambles, and amicus briefs filed in product liability court cases, the Agency's deliberate, nuanced decisions regarding product risks, warnings, and specifications should not be countered by conflicting state laws or by courts in product liability actions. Otherwise, such state laws and court decisions may undermine the safe and beneficial use of these essential medical devices, to the detriment of millions of patients.

In the instant case, FDA has spent years evaluating the benefits and safety profile of dental mercury amalgam products. Based upon this review, FDA will issue some form of final regulation, perhaps in the form of special controls. Conflicting state laws, including product liability lawsuits brought under state law, should be subject to preemption. As explained below, express medical device preemption should apply due to the comprehensive nature of the FDA regulatory process and any resulting guidance document – which makes the FDA regulatory regime applicable to dental mercury amalgam products more akin to FDA's Premarket Approval ("PMA") process than the 510(k) clearance process.

This is important because conflicting state laws and product liability actions undermine the Agency's expertise and directly threaten the Agency's ability to regulate the dissemination of risk and benefit information. In addition, such state law requirements may lead to risk exaggeration or "over-warning," the risks of which are just as significant and detrimental as the risks associated with under-warning.³ Additionally, state lawsuits and conflicting laws may have the unintended consequence of decreasing or eliminating access to dental amalgam products due to the cost and complexity of complying with conflicting legal regimes.⁴

Based upon the concerns expressed above, we request that FDA make clear, as it did in the 2006 preamble, that federal preemption applies to dental amalgam products and to legal actions brought against dentists and other health care practitioners.⁵

FDA's Comprehensive Regulatory Regime for Dental Amalgam Products

The FDA has been studying the use of dental mercury amalgam for many years leading up to the issuance of the proposed rule establishing "Special Controls" for dental amalgam products (hereafter "Proposed Rule"). Beginning in the early 1990s, in response to public concern about the safety of dental amalgam, FDA began to review scientific information from varied government, private, and international health organizations regarding the risks and benefits of dental amalgam products.⁶ After considering the scientific information it had received, along with the recommendations of the various reporting parties, FDA issued the Proposed Rule addressing dental mercury amalgam.

³ See 71 Fed. Reg. 3922 at 3935; see also *Statement by the FDA before the Committee on Oversight and Government Reform*, supra at note 3. Over-warning can cause medical professionals and patients to avoid using beneficial medical products, and the use of unsubstantiated warnings may cause confusion or even diminish the impact of valid warnings by limiting appreciation of more significant contraindications and side effects. See *Statement by the FDA before the Committee on Oversight and Government Reform* supra at note 3; see also 71 Fed. Reg. 3922, at 3935.

⁴ See *Statement by the FDA before the Committee on Oversight and Government Reform* supra at note 3.

⁵ See 71 Fed. Reg. 3922, at 3933-3936.

⁶ See generally, 67 Fed. Reg. 7620 (Feb. 20, 2002).

Any FDA regulation will be intended to achieve the uniform regulation of all dental amalgam products, perhaps by classifying them as class II devices and by imposing uniform “Special Controls” on the production and use of such products.⁷ Such a regulatory approach would provide a comprehensive set of labeling, specifications, and handling requirements for dental amalgam products; address the risks presented by such products; and provide a reasonable assurance of the safety and effectiveness of such products.⁸

Express Preemption

Section 521 of the FFDCFA expressly preempts state-law requirements that are different from, or in addition to, the FFDCFA’s device requirements.⁹ The Supreme Court, in *Riegel v. Medtronic*, recently ruled that this provision preempts state-law tort claims premised on allegations that a medical device that has received FDA PMA approval is unsafe or ineffective.¹⁰

The Supreme Court held that devices that are approved by FDA through the PMA process are subject to device-specific requirements that qualify for preemption under the Medical Device Amendments of the FFDCFA.¹¹ The court also established that common-law causes of action for negligence and strict liability impose “requirements” that are preempted by federal medical device requirements.¹² Additionally, the court identified several considerations for determining whether regulatory obligations may be considered affirmative, device-specific requirements that would preempt conflicting state requirements under the FFDCFA’s device preemption provision.

The Supreme Court held that to preempt state requirements, federal requirements must be device specific rather than applicable “across the board to almost all medical devices.”¹³ The Supreme Court also held that to preempt state requirements, federal requirements must constitute specifications or affirmative obligations that FDA mandates as a means to assure safety and effectiveness.¹⁴

A “Special Controls” guidance document in the instant case would satisfy these criteria. The requirements established by the “Special Controls” guidance would not be requirements of general applicability but would be specific to dental amalgam products. Additionally, the primary purpose of the “Special Controls” guidance would be to assure that dental amalgam products are manufactured and used in a manner that is safe and effective. Accordingly, the “Special Controls” guidance document would establish device-specific requirements that would trigger express preemption in accordance with the Supreme Court’s Riegel decision.¹⁵

⁷ See *id.* at 7625. Specifically, FDA has suggested the following actions in the Proposed Rule: (1) encapsulated alloy/mercury would be classified separately into device class II with “Special Controls” consisting of conformance to voluntary consensus standards and FDA’s “Special Controls” guidance document, (2) dental mercury would be reclassified from class I to class II with “Special Controls,” and (3) “Special Controls” would be added to the existing class II device, amalgam alloy.

⁸ See *id.* at 7627.

⁹ See 21 U.S.C. §360k(a).

¹⁰ See generally, *Riegel v. Medtronic*, 128 S. Ct. 999 (2008).

¹¹ See *id.* at 1007.

¹² See *id.* at 1007-08 (stating that “[a]bsent other indication, reference to a State’s “requirements” includes its common-law duties).

¹³ See *id.* at 1006-07.

¹⁴ See *id.* at 1007.

¹⁵ The ADA recognizes that express device preemption was supported by the Supreme Court in *Riegel* only for devices approved via the PMA process rather than cleared via the 510(k) process. In the instant case, however, even though the amalgam products would be cleared via the 510(k) process, the specific requirements imposed

Further, due to the comprehensive regulatory regime established by the FDA for dental amalgam products, it would be unfair, inappropriate, and contrary to preemption principles for dentists who use such products in their practices to be subject to conflicting state laws, regulations, and potential tort actions alleging, for example, a failure to warn. Dentists must be protected against state regulations and tort actions that usurp the Agency's expert role in evaluating the safety and efficacy of medical devices.

The Agency has repeatedly stressed that state product liability lawsuits, and state laws and regulations that challenge or conflict with FDA's careful determination of safety, efficacy, and appropriate labeling, routinely have detrimental public health effects.¹⁶ Such state laws, regulations, and product liability actions may prompt over-warning and the exaggeration of product risks.

In fact, FDA has stated, in both Congressional testimony and the 2006 preamble, that over-warning can impede the appropriate use of beneficial therapies.¹⁷ Patients may refrain from using, and doctors and dentists may refrain from prescribing, beneficial products based on unnecessarily heightened concerns regarding a product's risks.¹⁸ Additionally, warnings that conflict with FDA requirements are unlikely to be scientifically substantiated. This may lead to consumer confusion regarding the validity of such warnings or, worse, a tendency to distrust or downplay all warnings – even valid substantiated warnings.¹⁹ Furthermore, if multiple product liability lawsuits result in contrary rulings, it would no longer be feasible for dentists to use certain medical products.²⁰ In recognition of these problems, the Agency asserted in the 2006 preamble that such conflicting laws, regulations, and product liability actions should be preempted.²¹

In consideration of these problems²² and other public health concerns, FDA appropriately interprets and implements its responsibility under the FFDCA as establishing both a floor and a ceiling for risk information.²³ In the instant case, any FDA regulation would establish a measured approach – a floor and a ceiling – for labeling and risk communication for dental amalgam products.

Based upon the above precedent and FDA policy statements, product liability lawsuits or state laws regarding dental amalgam products that impose requirements that are different from or in addition to the federal requirements that would be established by the Proposed Rule's "Special Controls" guidance should be preempted. The FDA has previously preempted state law requirements in

by the "Special Controls" guidance document in the instant case create the type of device-specific requirements that implicate express preemption.

¹⁶ See *id.*; see also the 2006 preamble, 71 Fed. Reg. 3922, and the Letter to California Attorney General, *supra* note 5.

¹⁷ See 71 Fed. Reg. 3922 at 3935, and *Statement by the FDA before the Committee on Oversight and Government Reform* *supra* at note 3.

¹⁸ *Id.*

¹⁹ See 71 Fed. Reg. 3922 at 3935, and *Statement by the FDA before the Committee on Oversight and Government Reform* *supra* at note 3.

²⁰ See *Statement by the FDA before the Committee on Oversight and Government Reform* *supra* at note 3.

²¹ See 71 Fed. Reg. 3922 at 3936.

²² In the 2005 'Proposition 65' letter, FDA also addressed the negative impact of, and asserted preemption over, warnings required by a state statute, where the state-required warnings conflict with the Agency's regulatory approach. FDA's 'Proposition 65' letter warned that excessive label warning statements may have the unintended consequence of suppressing the appropriate use of beneficial products. In addition, FDA indicated that state warning requirements may not be scientifically substantiated or supported to the same degree as the Agency's regulatory requirements, and may therefore be misleading.

²³ See 71 Fed. Reg. 3922 at 3935.

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rulemaking proceedings,²⁴ and the ADA respectfully requests that the FDA clarify that the provisions of the Proposed Rule and “Special Controls” guidance document preempt state laws, regulations, or tort causes of action that are different from, or in addition to, FDA requirements.

CONCLUSION

The ADA supports reclassification of amalgam, but any special controls or other steps must be scientifically based. Warnings and restrictions for dental amalgam would run counter to the best available science and the consequence of any such action would be great.

Sincerely,

/s/

Mark J. Feldman, D.M.D.
President

MJF:jkb

²⁴ *Id.*