Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Dental Amalgam, Mercury, and Amalgam Alloy

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This guidance refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR Part 801 have been approved under OMB control number 09 10-0485, expiration date August 31, 2011. Persons are not required to respond to a collection without a valid OMB number.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Dental Devices Branch
Division of Anesthesiology, Infection Control,
General Hospital, and Dental Devices
Office of Device Evaluation

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.regulations.gov. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073311.htm. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-847-8149 to receive a hard copy. Please use the document number (**1192**) to identify the guidance you are requesting.

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Class II Special Controls Guidance Document: Dental Amalgam, Mercury, and Amalgam Alloy

1. Introduction

The Food and Drug Administration (FDA) has developed this guidance as the special control to support the classification of dental amalgam into Class II (special controls), the reclassification of dental mercury[1] from Class I to Class II, and the current classification of amalgam alloy in Class II. The three devices are now classified in a single regulation, Dental Amalgam, Mercury, and Amalgam Alloy, 21 CFR 872.3070. Mercury is elemental mercury, supplied as a liquid in bulk, sachet, or predosed capsule form, intended to be combined with amalgam alloy for the direct filling of carious lesions or structural defects in teeth. Amalgam alloy is composed primarily of silver, tin, and copper, supplied as a powder in bulk, tablet, or predosed capsule form, and is intended to be combined with mercury for the direct filling of carious lesions or structural defects in teeth. Dental amalgam consists of a combination of mercury and amalgam alloy, and is intended for the direct filling of carious lesions or structural defects in teeth. FDA is issuing this guidance in conjunction with a Federal Register (FR) notice announcing the final rule classifying dental amalgam, mercury, and amalgam alloy into Class II (special controls). The classification regulation designates this guidance document as the special control for these three devices.

Designation of this document as a special control means that any firm currently marketing, or intending to market, dental amalgam, mercury, or amalgam alloy will need to address the issues covered in this special controls guidance. The firm must show that its device addresses the issues of safety and effectiveness identified in this guidance, either by meeting the recommendations of this guidance or by some other means that provides equivalent assurances of safety and effectiveness.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should

[1] 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.

follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm

2. Background

A manufacturer who intends to market a device of this generic type must

- conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the act), including the premarket notification requirements described in 21 CFR 807 Subpart E,
- conform to the special control developed for this device by addressing the specific risks to health associated with dental amalgam devices identified in this guidance, and
- obtain a substantial equivalence determination from FDA prior to marketing the device. (See also 21 CFR 807.81 and 807.87).

FDA believes that special controls, when combined with the general controls of the act, are sufficient to provide reasonable assurance of the safety and effectiveness of these devices.

This special control guidance identifies the classification regulation and product codes for dental amalgam, mercury, and amalgam alloy (Please refer to Section 3. Scope). Other sections of this guidance document provide recommendations to manufacturers on addressing risks related to these devices.

This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87, the guidance entitled Format for Traditional and Abbreviated 510(k)s[2], and the Premarket Notification 510(k) section of CDRH's Device Advice web page.[3]

Under The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance,[4] a manufacturer may submit a Traditional 510(k), an Abbreviated 510(k), or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA issues a Class II special controls guidance document for the device. Manufacturers considering certain modifications to their own cleared devices may lessen their

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2 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm

3 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm

4 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm

regulatory burden by submitting a Special 510(k). For more information on types of Premarket Notification 510(k)s that may be submitted to FDA, see the Premarket Notification 510(k) of CDRH's Device Advice web page[5].

3. Scope

The scope of this guidance is limited to the devices described below that are classified in 21 CFR 872.3070 and include the product codes listed in the table.

> **§ 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.

This generic type of device includes encapsulated dental amalgam, as well as its individual components mercury and amalgam alloy, which may be marketed individually in bulk, sachet, or tablet form.

Firms intending to market mercury or amalgam alloy separately will need to address the specific risks to health identified in this guidance for those devices.

The relevant FDA product codes for this classification are as follows:

Product Code	Description
OIV	Dental Amalgam
ELY	Mercury
EJJ	Amalgam Alloy

This generic type of device does not include the following:

- dental amalgam capsule classified under 21 CFR.872.3110
- mercury and alloy dispenser classified under 21 CFR 872.3080
- dental amalgamator classified under 21 CFR 872.3100
- base metal alloys classified under 21 CFR 872.3710, and
- noble metal alloys classified under 21 CFR 872.3060.

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5 http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm

4. Describing Your Device in a 510(k) Premarket Notification

FDA recommends that, when submitting a 510(k) premarket notification, you identify your device by regulation and product code as described in Section 3 and include the information discussed below.

FDA recommends that you compare your device to a legally marketed predicate device and that you provide information to show how your device is both similar to, and different from, the predicate device. Side by side comparisons, whenever possible, are desirable; for example, using a tabular format as shown below. We also recommend that you describe how any differences may affect the comparative safety or effectiveness of your device.

Table 1: Comparison of Your Device and Predicate Device

Descriptive Information	Your Device	Predicate Device
Intended Use – including any specific indication for use		
Composition of Materials – the chemical composition of device		
Physical Properties – e.g., compressive strength, creep, dimensional change		
Differences –aspects of the device that are different from the predicate device		

5. Risks to Health[6]

In the table below, FDA has identified the potential risks to health generally associated with the use of dental amalgam devices that this special controls guidance is intended to address. The measures recommended to mitigate these risks are described in this guidance document, as shown in the table below. Before submitting your 510(k), you should conduct a risk analysis to identify any other risks specific to your device. You should describe the risk analysis method used and include the results of this analysis in your 510(k). If you elect to use an alternative approach to address a particular risk identified in this document, or have identified other risks in addition to those described in this document, you should provide sufficient detail to support the approach you have used to address those risks.

[6] The preamble to the final rule describes in detail the risks to health presented by this device that FDA has identified and explains how the recommendations in this guidance address those risks.

Table 2: Dental Amalgam Risks and Recommended Mitigation Measures

Risks	Recommended Mitigation Measures
Exposure to Mercury	Section 8. Labeling Section 6. Performance Data (mercury vapor release)
Allergic Response Including Adverse Tissue Reaction	Section 7. Biocompatibility Section 8. Labeling
Contamination	Section 6. Composition and Performance Data
Mechanical Failure	Section 6. Composition and Performance Data Section 8. Labeling
Corrosion	Section 6. Composition and Performance Data Section 8. Labeling
Improper Use	Section 8. Labeling

Table 3: Mercury Risks and Recommended Mitigation Measures

Risks	Recommended Mitigation Measures
Exposure to Mercury	Section 8. Labeling
Contamination	Section 6. Composition and Performance Data
Improper Use	Section 8. Labeling

Table 4: Amalgam Alloy Risks and Recommended Mitigation Measures

Risks	Recommended Mitigation Measures
Allergic Response Including Adverse Tissue Reaction	Section 7. Biocompatibility Section 8. Labeling
Mechanical Failure	Section 6. Composition and Performance Data Section 8. Labeling
Corrosion	Section 6. Composition and Performance Data Section 8. Labeling
Improper Use	Section 8. Labeling

6. Composition and Performance Data

FDA recommends that you evaluate your dental amalgam, mercury, and amalgam alloy devices using the relevant portions of the FDA-recognized standard listed below or an equivalent method:

ISO 24234:2004(E), Dentistry—Mercury and alloys for dental amalgam.

For amalgam alloy and dental amalgam, we recommend that the testing be performed on the finished form[7] of the device, i.e., dental amalgam, the combination of mercury and amalgam alloy.

For mercury and dental amalgam, we recommend that the composition be free from contamination as specified by ISO 24234:2004(E).

A. Chemical Composition

FDA recommends that you provide the complete chemical composition of your dental amalgam, mercury, and amalgam alloy devices, totaling 100 percent by mass, and the Chemical Abstracts Service[8] (CAS®) registry number of all constituents of the formulation.

[7] The finished form is to be tested because mercury and amalgam alloy are not used alone but must be combined to form dental amalgam.

[8] http://www.cas.org/EO/regsys.html

B. Performance Data

FDA recommends that you provide the following performance data for your mercury[9] device:

- visual assessment that mercury is free from contamination, as specified by ISO 24234:2004(E).

FDA recommends that you provide the following physical properties of your dental amalgam and amalgam alloy[10] devices:

- compressive strength (MPa) @ 1 hr
- compressive strength (MPa) @ 24 hrs
- maximum creep (%)
- dimensional change during hardening (%)
- particle size distribution (μ) and shape, i.e., spherical, irregular, etc.
- corrosion products[11] identifying the ions leached ($\mu g/cm^2$) and mercury vapor released during corrosion (ng/cm^2 in 4 hrs)
- trituration time (s)
- working time (min)

7. Biocompatibility

FDA recommends that you conduct biocompatibility testing for your dental amalgam device on the finished form[12], i.e., the combined product of mercury and amalgam alloy, as described in the following FDA-recognized standard, or by an equivalent method:

ISO 7405:1997(E), Dentistry - Preclinical evaluation of biocompatibility of medical devices used in dentistry—Test methods for dental materials.

If the composition of your dental amalgam device has already been demonstrated to be biocompatible for the same indication and the same type of tissue contact, either by a predicate device or in the literature, you may support the biocompatibility of your device by identifying the predicate or citing to the literature, in lieu of performing biocompatibility testing. However, if your device contains new chemical components or additives, or uses new technology, you should conduct biocompatibility testing, as described above.

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[9] This includes dental amalgam when provided in encapsulated form.

[10] The physical properties of amalgam alloy are to determined from those of dental amalgam, the finished form.

[11] See Annex A, Determination of Immersion Corrosion for Dental Amalgam, of ISO 24234:2004(E)

[12] Preclinical evaluation of the finished form is a useful measure of biocompatibility, whereas such testing of individual device components, mercury or amalgam alloy, is not.

8. Labeling for Dental Professionals[13]

FDA recommends that the labeling of your dental amalgam, mercury, and amalgam alloy devices include information sufficient to inform dental professionals of the properties and proper use of the devices. This information should include the device's composition, including its mercury content, physical properties, warnings, precautions, and information for use as described below.

A. Composition

FDA recommends that the labeling of your dental amalgam, mercury, and amalgam alloy devices identify and provide the mass fraction of every element of the device, including mercury, that is present in a concentration greater than 0.5%. The identity of other elements present in a concentration less than or equal to 0.5% may be disclosed without percentages. Disclosure of the mercury content should be stated clearly on the packaging of the device. The following statement is recommended:

- Contains [ ]% mercury by weight

B. Physical Properties

FDA recommends that the labeling of your dental amalgam and amalgam alloy devices disclose the following physical properties:

- compressive strength (MPa) @ 24 hrs
- dimensional change during hardening (%)
- trituration time (s)
- working time (min)

C. Warnings

FDA recommends that the labeling of your dental amalgam and mercury devices include the following warnings for health professionals about potential exposure to mercury:

- **WARNING -- CONTAINS MERCURY**
- may be harmful if vapors are inhaled

D. Contraindication

FDA recommends that the labeling of your dental amalgam and mercury devices include the following contraindication:

- do not use in persons with a known mercury allergy

[13] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR Part 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of Part 801.

E. Precautions

FDA recommends that the labeling of your dental amalgam, mercury, and amalgam alloy devices include the following precautions regarding use of the devices:

- do not place the device in direct contact with other types of metals
- use with adequate ventilation
- single-use only
- store in a cool, well ventilated place

F. Information for Use

Dental amalgam has been and remains one of the most commonly used restorative materials in dentistry. Although amalgam has been used successfully for many years, the risks associated with this device have been controversial. 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 that the labeling of your dental amalgam, mercury, and amalgam alloy devices include the following statement regarding use of the devices, and that dental professionals consider this information when developing individual treatment recommendations:

> "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.[14] 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.[15] 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.[16]

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[14] 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.

[15] 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.

[16] 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.

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.[17] 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.

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.

[17] 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."