

Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Dental Bone Grafting Material Devices

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Division of Anesthesiology, Infection Control,
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Preface

Public Comment

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance document was developed as a special controls guidance to support the classification and reclassification of certain dental bone grafting material devices into class II. The device is a material that is intended to fill, augment, or reconstruct periodontal or bony defects of the oral and maxillofacial region. FDA is issuing this guidance in conjunction with a Federal Register (FR) notice announcing the final rule.

Designation of this document as a special control means that any firm submitting a 510(k) for a bone grafting material device will need to address the issues covered in this guidance. However, the firm need only show that its device meets the recommendations of this guidance or, in some other way, provides equivalent assurances of safety and effectiveness.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of bone grafting material devices. Thus, a manufacturer who intends to market a device of this generic type should (1) 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, (2) address the specific risks to health associated with bone grafting material identified in this guidance, and (3) obtain a substantial equivalence determination from FDA prior to

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marketing the device.

This special controls guidance document identifies the regulation and product codes for bone grafting material devices (refer to **Section 4 - Scope**). In addition, other sections of this special controls guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these devices and lead to a timely 510(k) review and clearance. This document supplements other FDA documents regarding the content requirements of a 510(k) submission. You should also refer to 21 CFR 807.87 and "**How to Prepare a 510(k) Submission**" on FDA Device Advice at <http://www.fda.gov/cdrh/devadvice/314.html>.

Under "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**¹," a manufacturer may submit a Traditional 510(k) or an Abbreviated 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once a class II special controls guidance document has been issued. Additionally, manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this special controls guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of section 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this special controls guidance document.

¹ <http://www.fda.gov/cdrh/ode/parad510.html>

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Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to **Section 10 - Labeling** for specific information that should be included in the labeling for devices of the type covered by this guidance document.)

Summary report

We recommend that the summary report contain a:

- **Description of the device and its intended use**

We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. (Refer to **Section 5 - Device Description** for specific information that we recommend you include in the device description for devices of the type covered by this guidance document.) You should also submit an "indications for use" enclosure.²

- **Description of device design**

We recommend that you include a brief description of the device design requirements.

- **Identification of the risk analysis method**

We recommend that you identify the risk analysis method(s) used to assess the risk profile in general as well as the specific device's design and the results of this analysis. (Refer to **Section 6 - Risks to Health** for the risks to health generally associated with the use of this device that FDA has identified.)

- **Discussion of the device characteristics**

We recommend that you discuss the device characteristics that address the risks identified in this class II special controls guidance document, as well as any additional risks identified in your risk analysis.

- **Description of performance aspects**

We recommend that you include a brief description of the test method(s) you have used or intend to use to address each performance aspect identified in **Sections 7 through 10** of this Class II special controls guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that

² Refer to <http://www.fda.gov/cdrh/ode/indicate.html> for the recommended format.

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you will apply to your test results.³ (See also 21 CFR 820.30, Subpart C - Design Controls under the Quality System Regulation.)

Reliance on standards

If you choose to rely on a recognized standard for any part of the device design or testing, you may include either a:

- statement that testing will be conducted and meet specified acceptance criteria before the product is marketed; or
- declaration of conformity to the standard.⁴

Because a declaration of conformity is based on results from testing, we believe you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, please refer to section 514(c)(1)(B) of the Act and the FDA guidance, *Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA*.⁵

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(1), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a 510(k) submission for a bone grafting material device.

³ If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

⁴ See **Required Elements for a Declaration of Conformity to a Recognized Standard** (Screening Checklist for All Premarket Notification [510(K)] Submissions), <http://www.fda.gov/cdrh/ode/reqrecstand.html>.

⁵ <http://www.fda.gov/cdrh/ode/guidance/1131.html>

4. Scope

The scope of this guidance is limited to the type of device described below under the product codes LYC and NPM:

Section 872.3930 Bone grafting material.

(a) Identification. Bone grafting material is a material, such as hydroxyapatite, tricalcium phosphate, polylactic and polyglycolic acids, or collagen, that is intended to fill, augment, or reconstruct periodontal or bony defects of the oral and maxillofacial region.

(b) Classification. (1) Class II (special controls) for bone grafting materials that do not contain a drug that is a therapeutic biologic. The special control is FDA's "Class II Special Controls Guidance Document: Dental Bone Grafting Material Devices."

The scope of this guidance does not include the following:

- bone grafting materials that contain a drug that is a therapeutic biologic, such as bone morphogenic proteins (BMPs) and other biological response modifiers, under the product codes NPZ and NQA. Jurisdiction of these products is determined by FDA's Office of Combination Products⁶. Such products within the jurisdiction of CDRH are regulated as Class III devices, requiring a premarket approval application (PMA) (see 21 CFR 872.3930(b)(2)).
- human demineralized bone, whether minimally manipulated⁷ or modified with additives. Minimally manipulated demineralized bone is regulated as a human cell, tissue, and cellular and tissue-based product (HCT/P) under Section 361 of the Public Health Service Act (21 CFR 1271.10). Human demineralized bone with additives is regulated as a medical device and is subject to premarket notification (510(k)) procedures⁸. FDA intends to publish a separate rule for human demineralized bone with additives to classify the device into class II and establish a special control.
- bone grafting materials for non-oral/maxillofacial indications, e.g., for spinal and other orthopedic applications. Manufacturers of these devices should refer to 21 CFR 888.3045 and the recommendations provided in the guidance entitled, "**Class II Special Controls Guidance Document: Resorbable Calcium Salt Bone Void Filler Device**"⁹.

⁶ <http://www.fda.gov/oc/combination/>

⁷ See 21 CFR 1271.3(f).

⁸ Federal Register, January 19, 2001 (66 FR 5447)

⁹ <http://www.fda.gov/cdrh/ode/guidance/855.html>

5. Device Description

We recommend that you identify your device by regulation number and product code identified in **Section 4 - Scope** and include the following information:

- a description of the principle of operation (i.e., the scientific principles behind how the device achieves its intended use)
- a description of how the device will be marketed, e.g., sterile, assembled, single use, powder.

We recommend that you provide information to show how the new device is both similar to and different from the legally marketed 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 and effectiveness of the new device.

Device and Predicate Comparison Table

Descriptive Information	Device	Predicate
Intended Use - including the indications for use, when applicable		
Device Design – i.e., components, dimensions, or form		
Composition of Materials - chemical composition of your device and patient-contacting accessories		
Physical Properties , e.g., resorption time, phase purity, particle size range, porosity, strength		
FDA-Recognized Standards list of those you have followed, e.g., material characterization, biocompatibility, sterilization standards ¹⁰		

¹⁰ For the list of FDA-Recognized Standards, see <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>

6. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the bone grafting material device addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. You should also conduct a risk analysis, before submitting your 510(k), to identify any other risks specific to your device. The 510(k) should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified Risks	Recommended Mitigation Measures
Ineffective Bone Formation	Section 7 - Material Characterization
Adverse Tissue Reaction	Section 8 - Biocompatibility
Infection	Section 9 - Sterilization
Improper Use	Section 10 - Labeling

7. Material Characterization

We recommend that you evaluate your bone grafting material device using the relevant FDA-recognized standards listed below or equivalent methods.

- **American Society for Testing and Materials (ASTM) F 1185-88(1993), “Standard Specification for Composition of Ceramic Hydroxylapatite for Surgical Implants,” 1988.**
- **American Society for Testing and Materials (ASTM) F 1581-99, “Standard Specification for Composition of Anorganic Bone for Surgical Implants,” 1999.**
- **American Society for Testing and Materials (ASTM) F 1088, “Standard Specification for Beta-Tricalcium Phosphate for Surgical Implantation,” 1992.**

If your device is derived from natural sources, we recommend that you follow the FDA guidances listed below.

- **Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices)¹¹.**
- **Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin¹².**

¹¹ <http://www.fda.gov/cdrh/ode/88.html>

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In addition, we recommend that you include the information described below regarding composition, physical property, and *in vivo* performance.

A. Chemical Composition

- complete chemical composition, summing to 100% by mass, including all additives and the Chemical Abstracts Service¹³ (CAS®) registry number of all components.
- description of the composition, including an elemental analysis, identifying the trace impurities.

B. Physical Properties

- magnified photographs, e.g., SEM micrographs, of the device showing particle size, shape, and porosity
- a plot of the resorption of your device versus time showing the time for total clearance or integration under a representative model
- healing time, i.e., the earliest time at which implant loading may be successfully attempted
- phase purity, i.e., the relative mass percentages of crystalline and amorphous phases (%)
- calcium to phosphorous ratio (Ca/P)
- volumetric porosity (% void space)
- particle size distribution plot (μ)
- sintering temperature(s) ($^{\circ}\text{C}$)
- compressive strength (MPa)
- elastic modulus (GPa)
- shear modulus (GPa)
- pH
- water solubility @ 20°C ($\mu\text{g}/\text{mm}^3$).

Performance In Vivo

In accordance with the least burdensome provisions of the Act, the Agency will rely upon well-designed bench and/or animal testing rather than requiring clinical studies for new devices unless there is a justification for asking for clinical information to support a determination of substantial equivalence. While, in general, clinical studies will not be needed for most bone grafting material devices, FDA may recommend that you collect clinical data for a bone grafting material device for any of the following:

¹² <http://www.fda.gov/cder/guidance/q5a-fnl.pdf>

¹³ <http://www.cas.org/EO/regsys.html>

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- formulation or design dissimilar from a formulation or design previously cleared under a premarket notification
- technology different from that used in other legally marketed bone grafting material devices
- indications for use dissimilar from other bone grafting material devices.

FDA will consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale.

If animal testing is performed, we recommend that your study include the following:

- an animal model that is representative of the indications for use and that involves the anatomical sites proposed for use
- use of skeletally mature animals and a critical size defect
- use of the predicate device or autogenous bone graft as the positive control and an empty defect as the negative control
- radiography, histology, and histomorphometry to assess bone formation, device resorption, and residual material generation, if present, at relevant intervals over the duration of healing
- supportive biomechanical testing to demonstrate the quality of the newly formed bone.

If a clinical study is needed to demonstrate substantial equivalence, i.e., conducted prior to obtaining 510(k) clearance of the device, the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812. FDA believes that the bone grafting material devices addressed by this guidance document are significant risk devices.¹⁴ Sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

8. Biocompatibility

FDA recommends that you conduct biocompatibility testing for your bone grafting device as a permanent implant device in contact with tissue/bone, as described in the FDA guidance:

- **Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices (G95-1)**¹⁵.

We recommend that you select biocompatibility tests (Parts 5 and 10 of ISO-10993) appropriate for the duration and level of contact with your device. Testing may include, but is not limited to cytotoxicity, sensitization, genotoxicity, implantation, chronic toxicity, and carcinogenicity. Note that if the composition of your bone grafting material device has already been demonstrated

¹⁴ See **Significant Risk and Nonsignificant Risk Medical Device Studies**, <http://www.fda.gov/oc/ohrt/irbs/devices.html#risk>.

¹⁵ <http://www.fda.gov/cdrh/g951.html>

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to be biocompatible for the same indication and type of tissue contact in a predicate device or in the literature, biocompatibility testing may not be necessary. In this instance, you should identify references to support the biocompatibility of your device.

9. Sterilization

FDA recommends that you provide sterilization information in accordance with the **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**.¹⁶ You should sterilize the device to a sterility assurance level (SAL) of 1×10^{-6} using a sterilization cycle that has been validated in accordance with the QSR.

10. Labeling

Your 510(k) submission should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR Part 801.¹⁷

Instructions for Use

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, under 21 CFR 807.87(e), we recommend submitting clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients. Instructions should encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

We also recommend that the instructions for use of your bone grafting material device be written in sufficient detail to enable a practitioner with minimal experience to achieve the desired results. This should include instructions for:

- site preparation
- proper placement and containment of the device
- site closure
- patient care following treatment.

Indications and Contraindications

We recommend that the labeling of your bone grafting material device include both the specific indications and contraindications of the device.

Precautions

¹⁶ <http://www.fda.gov/cdrh/ode/guidance/361.html>.

¹⁷ 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.

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We recommend that the labeling of your bone grafting material device include precautions about the limitations of the device. For example, such precautions may include the following:

- effect on pediatric patients is not known
- effect on patients with a preexisting disease condition (specify) is not known.

Warnings

We recommend that the labeling of your bone grafting material device include warnings against misuse of the device. For example, such warnings may include the following:

- single-use only, do not resterilize or reuse
- not intended for immediate load-bearing (specify the time when loading is advisable)
- do not overfill defects
- do not leave defect open
- do not compromise blood supply to the defect area
- the device should be secured to prevent motion and migration, use in areas where the graft can be adequately contained
- do not use if package is opened or damaged or if expiration date has been exceeded.