Draft Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Dental Bone Grafting Material

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on: June 30, 2004

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Center for Devices and Radiological Health

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Food and Drug Administration
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Preface

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 (the applicant) 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 dental bone grafting material devices into class II. The device, as proposed, is a naturally or synthetically derived material that is intended to fill, augment, or reconstruct periodontal or bony defects of the oral and maxillofacial region. This guidance will be issued in conjunction with a Federal Register (FR) notice announcing the proposal to establish the Class II (special controls) classification of this device type. This guidance is issued for comment purposes only. If a final rule for this device is not issued, this guidance will not be issued as a special control.

Following the effective date of a final rule for the device, any firm submitting a 510(k) for a bone grafting material device will need to address the issues covered in this special controls 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 marketing the device.

This special controls guidance document identifies the proposed 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

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 types 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

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

clear and concise form, such as a table, **or** (2) describe the acceptance criteria that 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(l), 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.

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[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 devices described below.

As defined in 21 CFR 872.3930, tricalcium phosphate (TCP) is a bone void filler material that is currently regulated as a Class III device[6], under the product code LPK. Other bone grafting materials are currently regulated as unclassified devices under the product codes, LYC and NPM.

FDA is proposing that TCP and other bone grafting materials, except those with drug or biologic components, be classified into Class II and identified as follows:

> **§ 872.3930 Bone Grafting Material.**
>
> Identification. Bone grafting material is a naturally or synthetically derived material, such as hydroxyapatite, tricalcium phosphate, demineralized bone additives, collagen, or polylactic acids, that is intended to fill, augment, or reconstruct periodontal or bony defects of the oral and maxillofacial region.

The natural sources may be human or animal. Synthetic sources may be either resorbable or non-resorbable.

The scope of this guidance does not include the following:

- bone grafting materials for non-oral/maxillofacial indications, e.g., for spinal, orthopedic, or general restorative use. These indications are addressed in the guidance entitled, **"Class II Special Controls Guidance Document: Resorbable Calcium Salt Bone Void Filler Device[7]."**

- bone grafting materials with drug or biologic components, e.g., bone morphogenic proteins (BMPs), under the product codes NPZ and NQA. Jurisdiction of these products will be determined by FDA's Office of Combination Products[8]. Such products within the jurisdiction of CDRH have been regulated as Class III devices, requiring a premarket approval application (PMA).

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:

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[6] The definition of device includes certain articles that were once regulated as drugs, which are referred to as "transitional devices." See Section 520(l)(1) of the Act.

[7] http://www.fda.gov/cdrh/ode/guidance/855.html

[8] http://www.fda.gov/oc/combination/

- a description of the components, e.g., powder and liquid, of the device and its assembly
- a description of any accessories used with the device
- the range of dimensions, shapes, and device designs
- engineering drawings
- 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)

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 below.

- **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 or contains animal-source material we recommend that you follow the recommendations in the FDA guidance below.

- **Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices)**[9]

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

A. Chemical Composition of the Device

- The complete chemical composition, summing to 100% by mass, including all additives (include the Chemical Abstracts Service[10] (CAS®) registry number of all components).
- Description of the composition, including an elemental analysis, identifying the trace impurities.

B. Physical Properties of the Device

- Magnified photograph(s) (e.g., SEM micrographs) of the device showing particle shape and porosity.
- The following physical properties, as applicable:
    - Resorption period range (weeks)
    - Relative mass percentages of crystalline and amorphous phases (%)
    - Calcium to phosphorous ratio (Ca/P)
    - Volumetric porosity (% void space)
    - Particle size range (µ)
    - Sintering temperature (°C)
    - Compressive strength (MPa)
    - Elastic modulus (GPa)
    - Shear modulus (GPa)
    - pH
    - Water solubility @ 20°C ($\mu g/mm^3$).

[9] http://www.fda.gov/cdrh/ode/88.html

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

C. 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 specific 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:

- formulation or design dissimilar from formulation or design previously cleared under a premarket notification
- new technology, i.e., technology different from that used in legally marketed bone grafting material devices
- indications for use dissimilar from bone grafting material devices of the same type.

FDA will always 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 bone grafting material devices addressed by this guidance document are non-significant risk devices and, therefore, the study is subject to the abbreviated requirements of 21 CFR 812.2(b). In addition to the requirements of section 21 CFR 812.2(b), sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

After FDA determines that the device is substantially equivalent, clinical studies conducted in accordance with the indications reviewed in the 510(k), including clinical design validation studies conducted in accordance with the quality systems regulation, are exempt from the investigational device exemptions (IDE) requirements. However, such studies must be performed in conformance with 21 CFR Part 56 and 21 CFR Part 50**.**

8. Biocompatibility

FDA recommends that you conduct biocompatibility testing for permanent implant devices in contact with bone, as is described in the FDA guidance:

- **Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices (G95-1)**[11].

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. If, however, the composition of your bone grafting material device has already been demonstrated as biocompatible in a predicate device or in the literature, biocompatibility testing may not be necessary. In this instance, you should identify the reference(s) to support the biocompatibility of your device.

9. Sterilization

FDA recommends that you provide sterilization information in accordance with the FDA guidance:

- **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**[12].

In particular, your bone grafting material device should be sterile and achieve a sterility assurance level (SAL) of $1x10^{-6}$.

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[13].

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

[11] http://www.fda.gov/cdrh/g951.html

[12] http://www.fda.gov/cdrh/ode/guidance/361.html

[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.

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

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:

- not intended for immediate load-bearing
- 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
- 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.