A portion of this guidance has been replaced by a new guidance located at: http://www.fda.gov/cdrh/ode/guidance/1389.html . For questions, please contact Angela Blackwell at (301) 827-5283 ext 119 or by email at AEB@cdrh.fda.gov

CALCIUM PHOSPHATE (Ca-P) COATING DRAFT GUIDANCE FOR PREPARATION OF FDA SUBMISSIONS FOR ORTHOPEDIC AND DENTAL ENDOSSEOUS IMPLANTS

Division of General and Restorative Devices

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* Final comments have not been received from FDA Orthopaedic and Restorative Devices and Dental Products Advisory Panels, and contents of this document are subject to change.

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I. PREFACE

The development of this guidance document for the preparation of FDA submissions as they pertain to calcium phosphate (Ca-P) coatings of orthopedic and dental endosseous implants is based on the evaluation of both published and unpublished studies. Several values for the various chemical, physical, and mechanical parameters listed in this document (Appendix B) are based on previous Ca-P coated devices that have been found substantially equivalent to legally marketed predicates. The guidance also provides a list of standards, methods, and publications (Appendix A) that may be used in characterizing the Ca-P powder and coating. The chemical, physical and mechanical parameters of this guidance document parallel the "ASTM Draft Specification for Calcium Phosphate Coatings for Implantable Materials," F4.2.3.5. and are in accordance with Ca-P issues discussed at a workshop on characterization of calcium phosphate materials sponsored by the Society for Biomaterials held at the National Institutes of Health in 1989. It is the purpose of this document to aid in the preparation of submissions (e.g., premarket notifications (510(k)), Investigational Device Exemption (IDE) applications, Premarket Approval (PMA) applications, reclassification petitions, and master files) for Ca-P coated nonporous total hip and dental endosseous implants for prosthetic attachment. Specifically, this document is intended to inform the device manufacturer of important information that should be submitted to either demonstrate equivalence (e.g., 510(k)), safety (e.g., IDE) or provide reasonable assurance of the safety and effectiveness of these devices (PMA or reclassification petition) for their intended use. Additions and changes to the document may be incorporated with time as science changes and scientific techniques are improved. This guidance is for both **synthetic and natural sources** of calcium phosphates.

II. GENERAL REQUIREMENTS OF PREMARKET NOTIFICATIONS (510(k)) FOR Ca-P COATING CHARACTERIZATION

A 510(k) must be submitted by all distributors of calcium phosphate coated orthopedic and dental endosseous implants. All requirements of the Federal Food, Drug and Cosmetic Act and 21 CFR 807 subpart E concerning 510(k)'s must be provided including proprietary and common names, proposed labeling and advertisements, directions for use, drawings of the device, characterization of the device and its materials, the establishment registration number, intended use, a summary of information concerning the safety and effectiveness of this device, proof that predicate devices were either marketed prior to May 28, 1976, found to be substantially equivalent or were reclassified. In addition, the names, material composition, 510(k) numbers (if applicable), drawings/photographs and documentation of the substantial equivalence of each stem or dental device to be used with a Ca-P coating shall be included.

If the calcium phosphate coating is not similar in chemical, crystallographic, physical and mechanical properties to those previously found to be substantially equivalent, then the submission of at least two year clinical follow-up data for nonporous coated total hips and three year data for dental endosseous implants for prosthetic attachment, is necessary

before further consideration. This clinical data must be collected under an approved IDE application. Such studies are considered to involve significant risk devices. Therefore, an IDE must be granted by FDA before the study may begin. Section III of this document incorporates ranges that have been defined by devices previously found substantially equivalent and are being provided for information purposes only.

The following claims either implied, promoted, or indicated in labeling raise new issues of safety and effectiveness. These claims place the device into class III and are not permitted without PMA approval.

A. The Ca-P coating permits bone to actually bond with implant surface.

B. Superiority of Ca-P coated implants on both degree and rate of fixation in bone.

C. Presence of more supporting bone on the Ca-P coated implant surfaces versus uncoated implants contributing to implant success.

D. Rapid bone growth on Ca-P coated implants.

E. Better performance of Ca-P coated implants than uncoated implants.

F. Bone-bonding phenomenon mirrors the bone-bonding associated with Ca-P.

G. Ca-P coating avoids resorption (either of itself or surrounding bone).

III. COATING APPLICATION AND CHARACTERIZATION

Coating characterization can be derived from either finished devices or coated coupon samples that are subject to identical manufacturing and processing procedures, including sterilization.

A. Method of Coating Application

Manufacturing details must include the following:

1. the type of deposition process;

2. what, if any, post-deposition heat treatment is employed;

3. all critical control process parameters; and

4. the sterilization process utilized.

B. Chemical and Crystallographic Analysis of the Ca-P Powder and Coating

The following test data should be supplied:

1. Elemental Analysis

An elemental analysis for the powder and coating forms should be supplied, noting any impurities including, but not limited to, the heavy metals identified in ASTM F1185, i.e., As, Cd, Hg, Pb. Most calcium phosphate sources are variations of phosphate rocks in which heavy metal impurities such as those mentioned in ASTM F1185 are generally insignificant. Yet, naturally occurring sources such as coralline may have some heavy metal content.

Characterization of the protein present in the powder or coating should also be included.

2. Calcium to Phosphorous (Ca/P) Ratio

The Ca/P ratios in atomic percent for the powder and the coating should be reported. It is recognized that the Ca/P ratio of the coating may deviate from the ideal stoichiometric ratio. Therefore, a sufficient number of samples should be analyzed to produce a statistically meaningful mean and variance (i.e., 95% confidence interval).

Examples of stoichiometric ratios are as follows:

Hydroxylapatite = 1.67
Tricalcium Phosphate = 1.5
Calcium pyrophosphate = 1.0

(SEE APPENDIX B FOR RANGES THAT HAVE PREVIOUSLY BEEN FOUND ACCEPTABLE)

3. X-ray Diffraction (XRD)

The spectra should be included for both the powder and coating forms. Individually superimpose the standards that are given for the relevant calcium phosphate compound in the powder diffraction files of the JCPDS (Joint Committee on Powder Diffraction Standards). Spectra must be plotted as relative intensity vs. diffraction angle, with a table identifying all peaks by intensity, d-spacing and 2theta.

In addition to the XRD spectra for the Ca-P coating (including the superposition of the standards in the powder diffraction files of the JCPDS), supply the following:

a. an indication as to whether the coating is scraped from a coupon or if the coating was analyzed as a thin film on a substrate.

b. the XRD parameters (e.g. scans were run between 10 and 60 degrees at rate of 0.02 deg/sec).

c. the percentage of crystalline material (total crystallinity) and the percentage of individual crystalline compounds present in the coating.

d. a description of the methods and materials used in calculating the percentage of the crystalline material in the coating (both total crystallinity of coating and individual crystalline compounds) as compared to the amorphous component of the total coating. These methods should be referenced and the accuracy and precision should be stated.

e. the stoichiometric formulas of each crystalline compound present and the percentage of each compound present based on XRD scan, (i.e., % of alpha-TCP, beta-TCP, CaO, and HA). The percent of total crystalline material in the coating should also be identified.

4. Infrared Spectrometry (IR)

The IR spectra of both the powder and coating forms should be supplied. Spectra must be plotted as percent transmittance vs. wavenumber.

Identify the characteristic absorption bands and their radical groups for Ca-P compound . For example, the characteristic absorption bands for hydroxylapatite are as follows:

$PO_4$3-: 570cm^{-1}, 962cm^{-1}, 1050cm^{-1}
OH^-: 630cm^{-1}, 3540cm^{-1}

5. Solubility of Ca-P compound

A complete report on the solubility testing of the coated samples should be provided. This testing should be conducted in a physiologically similar solution such as tris - HCl buffered solution at 37^oC. Implants should be tested at a pH of 3.0 and 7.3. Measurements should include dissolved Ca

and P. Weight loss should also be measured. If compound contains other elements such as fluorine, these elements should also be measured.

C. Physical Properties

Information provided should include the following:

1. Coverage of Substrate/Surface Topography

   a. The location of all coating on the device should be described.

   b. Photomicrographs of the coating at 100X should be supplied.

2. Thickness

   The thickness of the coating, including the tolerance should be reported, along with a description of any intended variations of the thickness with respect to implant geometry.

3. Density

   The density (g/cm^3) for both the powder and coating should be reported.

4. Surface Roughness

   The surface roughness (Ra) and the tolerances of the substrate and coating should be supplied.

D. Mechanical Requirements

A minimum sample size as given ASTM (unless specified otherwise) and a copy of the complete test report are required for all the following tests. All samples should be soaked in a physiological equivalent (excluding protein substances) solution A complete report includes methods/materials, raw data, photo/drawing of set-up and complete failure report including SEMs of failure regions and failure types (e.g., coating/epoxy, with coating, or coating/substrate). SEMs at 100X magnification of the epoxy/coating/substrate prior to testing should be provided to demonstrate any potential penetration of the epoxy.

1. Tensile Strength

   The static tensile strength of the coating is required.

2. Shear Strength

   The static shear strength of the coating is required.

3. Fatigue Testing

Fatigue characteristics of the coating/substrate interface should be supplied for a coupon that has undergone the same manufacturing process as the finished device or for the finished device. Testing should be performed on the worst case scenorio. An S/N curve should be provided. For femoral stems, the S/N curve may be substituted with testing of the stem at a load of 3-4 times body weight and R = 0.1 for 10 million cycles. A sample size of five is required.

4. Abrasion Resistance

The abrasion characteristics of the coated device should be provided. To date, FDA is not aware of any standards for an abrasion test of Ca-P coatings, however the abrasion characteristics of the coating must be characterized to determine if the coating will spall. Quantitative methods with sppropriate rationale and validation are preferred.

IV. Animal Studies

The results produced in the preclinical studies (Section III), the intended use of the device, implied or explicit claims, along with the basic design of the prosthesis, will determine whether or not animal studies are required. For additional guidance on animals studies for dental endosseous implants refer to the "Guidance for the Arrangement and Content of a Premarket Approval (PMA) Application for an Endosseous Implant for Prosthetic Attachment".

V. Clinical Studies

The results produced in the preclinical and animal studies (Sections III and IV), the intended use of the device, implied or explicit claims, along with the basic design of the prosthesis, will determine whether clinical studies are required. The clinical trials must be randomized, controlled, prospective studies comparing the coated device to an uncoated device. For additional guidance on clinical studies for dental endosseous implants refer to the "Guidance for the Arrangement and Content of a Premarket Approval (PMA) Application for an Endosseous Implant for Prosthetic Attachment".

VI. Reporting

Refer to Appendix C for a report form that should be utilized in expediting the review of the calcium phosphate data. All of the information supplied in this form should have references to the location of the methods and materials, data, and analysis contained elsewhere in the application.

APPENDIX A

RELEVANT STANDARDS, METHODS, OR PUBLICATIONS

GUIDANCE SECTION	*STANDARDS*	*METHODS*	*PUBLICATIONS*	*COMMENTS*
III.A.4 (Sterilization Process)			ODE Blue Book #K90-1	
III.B.1 (Elemental Analysis)	ASTM F1185 ASTM F1088 ASTM F2.3.3	Atomic Absorption		
III.B.3 (X-ray Diffraction)	JCPDS 9-348 JCPDS 9-169 JCPDS 9-432 JCPDS 9-346 JCPDS 11-177 JCPDS 37-1497 ASTM F4.2.3.8	Hanawalt Method for Powder External and Internal Methods for Coating Calculation of total area under curve (% amorphous material)	Cullinity, B.D., Elements of X-Ray Diffraction, 2nd Ed., Addison-Wesley, Reading, Mass., 1978	Methods are dependent on starting material
III.B.5 (Solubility)			Ducheyne, P., et.al., "Calcium Phosphate Ceramic Coatings on Porous Titanium: Effect of Structure and Composition on Electrophoretic Deposition, Vacuum Sintering and in vitro Dissolution", Biomaterials, Vol. 11, No. 4, May 1990.	

GUIDANCE SECTION	*STANDARDS*	*METHODS*	*PUBLICATIONS*	*COMMENTS*
III.C.2 (Coating Thickness)	ASTM E376 ASTM C747 ASTM C769			
III.C.3 (Density)		Helium Pycnometer		
III.C.4 (Surface Roughness)	ANSI/ASME B46.1			
III.D.1 (Tensile Strength)	- ASTM C633 - ASTM F4.2.3.11A			
III.D.2 (Shear Strength)	- ASTM C633 - ASTM F4.2.3.11B			
III.D.3 (Fatigue Testing for dental implants)		- Three Point Bending - Rotating Beam - Modified Static Test Mthds		
III.D.3 (Fatigue Testing for hip prostheses)	ASTM F4.2.5.10 ISO 7206			
IV & V (Animal and Clinical Studies)			"Guidance for the Arrangement and Content of a Premarket Approval (PMA) Application for an Endosseous Implant for Prosthetic Attachment", FDA Publication	

APPENDIX B

CALCIUM PHOSPHATE POWDER AND COATING CHARACTERISTICS OF LEGALLY MARKETED DEVICES

GUIDANCE SECTION	***MAXIMUM OR MINIMUM CLEARED***	***RANGE***	**COMMENTS**
III.B.1 (Elemental Analysis)	50 ppm heavy metals (MAX)		
III.B.2 (Ca/P Ratio)		- Powder: 1.66-1.67 - Coating: 1.67-1.76	
III.B.3.c (Crystallinity)	62% Total Crystallinity (MIN) Powder form: minimum of 95% purity for single compound powders		Coating form: if coating is described as a single compound (e.g., hydroxylapatite), the coating must be manufactured using a powder conforming to the minimum purity. If the purity of the powder is less than 95% or if the coating contains less than 90% of the labeled compound, the labeling for the implant should identify all major compounds present in the coating.
III.C.3 (Density)	- Powder: 3.05 g/cm^3 - Coating: 2.98 g/cm^3		
III.D.1 (Tensile Strength)	7.4 ksi (50.8 MPa) (MIN)		
III.D.2 (Shear Strength)	3.198 ksi (22.0 MPa)		

APPENDIX C

CALCIUM PHOSPHATE COATING CHARACTERIZATION FORM

Device Trade Name: _____

Manufacturer: _____

Substrate Material: _____ Standard (e.g., ASTM): _____

Calcium Phosphate Coating Tradename: _____

A. Method of application and sterilization

Method of Application of coating: _____

Post deposition heating: _____

Sterilization Method: _____

B. Chemical/Crystallographic Requirements

1. Powder Form:

Trace Element Analysis Method _____

Chemical Composition: _____
_____
_____
_____
_____

Heavy Metals present (ppm) _____

Coating Form:

Trace Element Analysis Method _____

Chemical Composition: _____
_____
_____
_____
_____

Heavy Metals present (ppm) _____

2. Powder Form:

Ca/P ratio _____ Mean and S.D.)
Method _____

Coating Form:

Ca/P ratio _____ Mean and S.D.)
Method _____

3. X-ray Diffraction Pattern

Powder:

% Crystallinity _____ mean and S.D.)
% Amorphous _____

Method: _____

Compounds and their % present in coating: _____

Total Coating:

% Crystallinity _____
% Amorphous _____

Method: _____
_____

Compounds and their % present in coating: _____

4. Infrared Spectroscopy ? _____

Description: _____

5. Solubility:

Electrolyte: _____ Temp: _____ pH: _____

Dissolution Rate: _____ (Ca)
_____ (P)
Weight Loss: _____

Method: _____

C. Physical Requirements

1. Coverage of Substrate ? _____
Surface incongruities ? _____

2. Thickness _____ Method _____

3. Density _____ Method _____

4. Surface Roughness of Substrate _____
Method: _____

Surface Roughness of Coating _____
Method: _____

D. Mechanical Requirements

1. Static Tensile Strength _____ Method _____
   Failure Areas _____
   _____

2. Static Shear Strength _____ Method _____

   Failure Areas _____
   _____

3. Fatigue Strength _____ Method _____
   (Coated device or coupon)

   Fatigue Strength once exposed to saline or similar condition
   _____

   Method: _____

5. Abrasion Resistance _____
   Method: _____
   _____

E Animal Data? (if applicable) _____

F. Clinical Data ? (if applicable) _____