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Standard Specification for ~~Medical-Grade~~ Beta-Tricalcium Phosphate ~~for Surgical Implantation~~Raw Material for Implantable Medical Devices[1]

This standard is issued under the fixed designation F1088; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This specification covers chemical and crystallographic requirements for beta-tricalcium phosphate (β-TCP) ~~for surgical implant~~ raw materials intended for use in medical device applications. For a material to be identified as medical-grade beta-tricalcium phosphate, it must conform to this specification (see Appendix X1).

1.2 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.3 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

F748 Practice for Selecting Generic Biological Test Methods for Materials and Devices

F981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Insertion into Bone

~~2.2 *American Society for Quality (ASQ) Document:*[3]~~

~~C1 Specification of General Requirements for a Quality Program~~

2.2 *International Organization for Standardization ~~Document:~~Documents:*[3]

ANSI/ISO/ASQ 9000 Quality Management Systems—Fundamentals and Vocabulary

ANSI/ISO/ASQ 9001 Quality Management Systems—Requirements

~~ISO~~ANSI/ISO 10993-1 Biological Evaluation of Medical ~~Devices — Part~~ Devices—Part 1: Evaluation Within a Risk Management System

ANSI/ISO/ASQ 13485 Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes

2.3 *United States Pharmacopeia (USP) Documents:*[4]

USP <191> Identification Tests for Calcium and Phosphate

USP <232> ~~United States Pharmacopeia: Elemental Impurities – Limits~~Elemental Impurities—Limits

USP <233> ~~United States Pharmacopeia: Elemental Impurities – Procedure~~Elemental Impurities—Procedure

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[1] This specification is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.13 on Ceramic Materials.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

[4] Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

2.4 *ICH Document:*[5]

ICH Q3D International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guideline for Elemental Impurities

2.5 *U.S. Code of Federal Regulations:*[6]

21 CFR 820 Food and Drugs Services, Part 820—Quality System Regulation

3. Chemical Requirements

3.1 Elemental analysis for calcium and phosphorus will be consistent with the expected stoichiometry of beta-tricalcium phosphate ($Ca_3(PO_4)_2$. The calcium and phosphorus content shall be determined using a suitable method such as USP <191> (see ~~2.4~~2.3) or X-ray fluorescence.

3.2 A quantitative X-ray diffraction analysis shall indicate a minimum beta-tricalcium phosphate content of 95 % as determined using Powder Diffraction File ~~#550898~~No. 550898[7] and a method equivalent to Forman[8] or Rietveld.[9,10]

3.3 *Elemental Impurities:*

3.3.1 The significance of elemental impurities within an absorbable material is ultimately dependent on the dimensional characteristics of the final product and the rate of release of those initially interstitial elements into the surrounding tissue and extracelluar fluid. Thus, any risk assessment of such impurities will be dependent on the final product design and intended application. Consequently, this raw material (not final device) standard provides for appropriate reporting of elemental impurities values, but does not mandate any specific ~~performance requirements.~~ concentration requirements. Therefore, elemental impurity limits shall be as agreed upon between the purchaser and the supplier. More detailed and pharmaceutical-oriented guidance regarding the appropriate means for both monitoring and assessing relevant elemental impurities within a final product can be found in USP Chapters <232> and <233> and ICH Q3D.

3.3.2 ~~Determine~~ For each raw material lot, determine the concentration of the respective elemental impurities within the beta-TCP by utilizing inductively coupled plasma mass spectroscopy (ICP-MS) or inductively coupled plasma atomic or optical emission spectroscopy (ICP-AES or ICP-OES) or an equivalent alternative method as described in USP Chapter <233>. The specific 24 different elemental impurities of interest are outlined in both USP <232> and in Table A.2.2 of ICH Q3D. Both of these documents include risk-based approaches toward the assessment and control of elemental impurities.

3.3.3 Except for intentionally added elements, assess the obtained results for compliance with the Parenteral Concentration limits described within the Individual Component Option of USP <232>, Table 3 (derived from ICH Q3D Option 1, Table A.2.2). If all listed elements except for those that are intentionally added can be assured to be maintained within the Parenteral Concentration ~~–~~Individual Component Option limits, the material "conforms" to USP <232>. If any listed element (other than those intentionally added) cannot be controlled to be maintained within the prescribed USP <232> limits, the material does not conform with USP ~~<232> and the concentration (in ppm, per USP <233> or equivalent) of each uncontrolled element shall be both monitored and reported.~~<232>.

3.3.3.1 Report the concentration (in ppm, per USP <233> or equivalent) of each element.

3.3.4 For each intentionally added element, the concentration (in ppm, per USP <233> or equivalent) shall be both monitored and reported.

3.3.5 The elemental impurities thresholds for the Individual Component Option of USP <232>, Table 3, provide specific elemental daily dosage limits for parenteral drug products. These daily elemental impurity limits (including those applied to intentionally added elements) should be considered as conservative thresholds for informational purposes only when applied to

[5] Available from ICH Secretariat, c/o IFPMA, 30 rue de St-Jean, P.O. Box 758, 1211 Geneva 13, Switzerland. Available online at http://www.ich.org/LOB/media/MEDIA423.pdf.

[6] Available from U.S. Government Publishing Office (GPO), 732 N. Capitol St., NW, Washington, DC 20401, http://www.gpo.gov.

[7] International Centre for Diffraction Data, 12 Campus Blvd, Newtown Square, PA 19073-3273.

[8] Forman, D. W. and Metsger, D. S., ~~"The~~"The Determination of Phase Composition of Calcium Phosphate Ceramics by X-Ray Diffraction ~~Determination of Phase Composition of Calcium Phosphate Ceramics by X-Ray Diffraction,"~~," *Transactions of the Seventh Annual Meeting of the American Society for Bone and Mineral Research*, Kelseyville, CA, 1985 p. 391.

[9] Jackson, L. E., Barralet, J. E., and Wright, A. J., ~~"Rietveld~~"Rietveld Analysis in Sintering Studies of Ca-Deficient Hydrxyapatite ~~Analysis in Sintering Studies of Ca-Deficient Hydrxyapatite,"~~," *Bioceramics 16*, Key Engineering Materials, Vols ~~254-256~~254–256, 2004, pp.297–300.

[10] Rietveld, H. M., *Acta Crystallogr*., Vol 22, 1967, p. 151.

absorbable implants. Proper application of these limits in setting raw material specifications should consider the amount of β-TCP in the final implant product as well as its degradation and elemental elution rate into the surrounding tissue.

3.3.5.1 The elemental impurity content of β-TCP raw materials used in implants with a successful clinical history may also be considered in setting limits for raw material specifications. For such data to be relevant, analyses shall be consistent with the methods of USP <233> and shall be conducted on raw material lots used for clinically released product.

3.3.6 See X2.2 for additional information.

3.4 It is recommended that all metals or oxides present in concentrations equal or greater than 0.1 % be noted in material descriptions.

~~**4. Quality Program Requirements**~~

~~4.1 The producer shall maintain a quality program, such as the program defined in ASQ C1.~~

4. Guidance for Manufacturing Control and Quality Assurance

4.1 Acceptable levels of manufacturing control are highly desirable and apply to the manufacture of the β-TCP raw material. Good manufacturing practice guidelines for achieving acceptable levels of manufacturing quality control may be found in:

4.1.1 21 CFR 820—Identifies the requirements that govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use.

4.1.2 ANSI/ISO/ASQ 9000—Provides fundamentals for quality management systems as described in the ISO 9000 family (informative) and specifies quality management terms and their definitions (normative).

4.1.3 ANSI/ISO/ASQ 9001—Presents requirements for a quality management system. The application of this specification can be used by an organization to demonstrate its capability to meet customer requirements for products and/or services, and for assessment of that capability by internal and external parties.

4.1.4 ANSI/ISO/ASQ 13485—Presents requirements for a quality management system specific to medical device design and manufacturing. The application of this specification can be used by an organization to demonstrate its capability to meet customer requirements for products and/or services, and for assessment of that capability by internal and external parties.

5. Certification

5.1 A certificate of compliance or a certificate of analysis that, at minimum, contains the following information shall be supplied for each shipment:

5.1.1 Supplier identification (including address and phone contact numbers).

5.1.2 Lot number.

5.1.3 Date of certification (include purchaser specification, if applicable).

5.1.4 Chemical description and CAS registry number (the CAS number for beta-tricalcium phosphate is 7758-87-4)

5.1.5 Calcium and phosphorous content (and ratio) per 3.1.

5.1.6 Beta-tricalcium phosphate content (in mass %) per 3.2.

5.1.7 Elemental impurities per 3.3.

5.1.7.1 Report concentration (ppm) for each element and whether or not it conforms with USP <232>, Table 3.

5.1.8 Intentionally added elements (if applicable).