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Standard Specification for Beta-Tricalcium Phosphate for Surgical Implantation¹

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1. Scope

1.1 This specification covers chemical and crystallographic requirements for beta-tricalcium phosphate (β-TCP) for surgical implant 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 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](#)

2.3 *International Organization for Standardization Document:*⁴

[ISO 10993-1 Biological Evaluation of Medical Devices — Part 1: Evaluation Within a Risk Management System](#)

2.4 *United States Pharmacopeia (USP) Documents:*⁵

[USP <191> Identification Tests for Calcium and Phosphate](#)

[USP <232> United States Pharmacopeia: Elemental Impurities – Limits](#)

[USP <233> United States Pharmacopeia: Elemental Impurities – Procedure](#)

2.5 *ICH Document:*⁶

[ICH Q3D International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guideline for Elemental Impurities](#)

3. Chemical Requirements

3.1 Elemental analysis for calcium and phosphorus will be consistent with the expected stoichiometry of beta-tricalcium phosphate (Ca₃(PO₄)₂). The calcium and phosphorus content shall be determined using a suitable method such as USP <191> (see [2.4](#)) 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 #550898⁷ and a method equivalent to Forman⁸ 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 extracellular 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. More detailed and pharmaceutical-oriented guidance regarding the appropriate means for both

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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 Society for Quality (ASQ), 600 N. Plankinton Ave., Milwaukee, WI 53203, <http://www.asq.org>.

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

⁵ Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, <http://www.usp.org>.

⁶ 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>.

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

⁸ Forman, D. W. and Metsger, D. S., "The 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 Analysis in Sintering Studies of Ca-Deficient Hydroxyapatite," *Bioceramics 16*, Key Engineering Materials, Vols 254-256, 2004, pp.297–300.

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

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 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.

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 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.

5. Keywords

5.1 advanced ceramics; β -TCP; beta-tricalcium phosphate; calcium phosphate material; ceramic; surgical implant

APPENDIXES

(Nonmandatory Information)

X1. RATIONALE

X1.1 This specification is needed to ensure a high quality material for use in medical device applications. The chemical, crystallographic, and phase requirements serve as criteria for a high-purity, consistent product that can be implanted in the body. These requirements provide specifications for biocompatible grades of beta-tricalcium phosphate for use in the physiological environments.

X1.2 It is recognized that a separate performance standard may be necessary for each end-use product. For this reason, physical and mechanical properties were not specified. A source of general test methods for ceramics may be found in Vol 15.02 of the *Annual Book of ASTM Standards*.

X2. BIOCOMPATIBILITY

X2.1 This specification is needed to ensure a high quality material for use in biological applications. Beta-tricalcium phosphate has been demonstrated to exhibit a well characterized biological response equivalent to or better than that exhibited by reference materials cited and tested in Practices **F981** and **F748** or equivalent. The chemical, crystallographic, and phase requirements contained in this specification serve as criteria for a high-purity, consistent product that can be implanted in the body. The suitability of the material from a human implant perspective is dependent on the specific application. The biological tests appropriate for the specific site, such as recommended in Practice **F748** or ISO 10993-1 should be used as a guideline. Further testing of specific properties may be required for specific applications.

X2.2 *Elemental Impurities Limits*—The USP <231> Heavy Metals Test was obsoleted on December 1, 2017 and has been replaced with USP <233>, which outlines acceptable analytical methods for determining the concentrations of individual elemental impurities. USP <232> describes a risk-based approach to setting limits on elemental impurities for pharmaceuticals. While medical devices are not within the scope of USP <232>, the limits set for parenteral drugs can be applied to absorbable materials by estimating the release rate of elemental impurities based on their concentrations and the degradation rate of the device. If the concentration of an elemental impurity within the material conforms to the Paren-

teral Concentration – Individual Component Option limits of USP <232> then no risk analysis is needed. The term *heavy metals* has been dropped in favor of *elemental impurities* in keeping with ICH Q3D. The term *heavy metals* is imprecise and there is confusion as to exactly which elements are included. Furthermore, the USP <231> Heavy Metals Test is based on the reaction of various metal cations with sulfide and, therefore, cannot distinguish between those elements. It is also a limit test, meaning that it can only determine whether the total concentration of metals is less than or greater than a pre-set value, which is assumed to be lead. In contrast, ICH Q3D lists 24 elements of interest, which are categorized according to their toxicities, with individual limit values varying accordingly. The methods outlined in USP <233> are quantitative and highly sensitive, so the concentration of each element of interest can be determined. This provides more detailed information that allows a more robust risk analysis with fewer conservative assumptions. Previous versions of this specification allowed up to 30 ppm lead, 5 ppm mercury, 5 ppm cadmium, 3 ppm arsenic, and 50 ppm total heavy metals (as determined by USP <231>). No rationale for those requirements was given and they were not consistent with the requirements of other standards for absorbable materials. Furthermore, the release rate of an impurity will be dependent upon a number of factors including phase chemistry, physical exposure of the impurity to the environment, and implant location.

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