Designation: F1088 – 23

Standard Specification for Medical-Grade Beta-Tricalcium Phosphate 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) 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 *International Organization for Standardization Documents:*[3]

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

ANSI/ISO/ASQ 9001 Quality Management Systems—Requirements

ANSI/ISO 10993-1 Biological Evaluation of Medical 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> Elemental Impurities—Limits

USP <233> Elemental Impurities—Procedure

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 2.3) 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 No. 550898[7] and a method equivalent to Forman[8] or Rietveld.[9,10]

3.3 *Elemental Impurities:*

[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.

Current edition approved April 15, 2023. Published April 2023. Originally approved in 1987. Last previous edition approved in 2018 as F1088 – 18. DOI: 10.1520/F1088-23.

[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.

[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 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.

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 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 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>.

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 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. 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).

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

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

5.1.8.1 Report the concentration of each intentionally added element (mass percent or ppm).

6. Keywords

6.1 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 are 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 guidelines. 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 Parenteral 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 preset 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.