Designation: F1185 – 23

Standard Specification for Composition of Medical-Grade Hydroxylapatite for Surgical Implants[1]

This standard is issued under the fixed designation F1185; 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 hydroxylapatite intended for surgical implants. For a material to be called medical-grade hydroxylapatite, it must conform to this specification. (See Appendix X1.)

1.2 The biological response to hydroxylapatite in soft tissue and bone has been characterized by a history of clinical use (**1-3**)[2] and by laboratory studies (**4-6**).

1.3 This specification includes powder, particulate, and forms intended for use as surgical implants, components of surgical implants, or as raw materials for manufacturing processes such as thermal spray coating, electrophoretic deposition, physical vapor deposition, and so forth.

1.4 This specification specifically excludes hydroxylapatite coatings, amorphous calcium phosphate, ceramic-glasses, tribasic calcium phosphate, whitlockite, and alpha- and beta-tricalcium phosphate (see Specification F1088).

1.5 The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.6 *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.*

1.7 *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:*[3]

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

F1088 Specification for Medical-Grade Beta-Tricalcium Phosphate Raw Material for Implantable Medical Devices

F2024 Practice for X-ray Diffraction Determination of Phase Content of Plasma-Sprayed Hydroxyapatite Coatings

2.2 *Code of Federal Regulations:*[4]

Title 21 Part 820 Quality System Regulation

2.3 *National Formulary:*[5]

Tribasic Calcium Phosphate

2.4 *United States Pharmacopeia (USP) Documents:*[6]

USP <191> Identification Tests for Calcium and Phosphate

USP <232> Elemental Impurities—Limits

USP <233> Elemental Impurities—Procedure

2.5 *U.S. Geological Survey Method:*[7]

Cadmium

2.6 *ANSI/ISO Standards:*[8]

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

ANSI/ISO/ASQ 9001 Quality Management Systems—Requirements

[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] The boldface numbers in parentheses refer to the list of references at the end of this specification.

[3] 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.

[4] Available from U.S. Government Printing Office, N. Capitol and H St., NW, Washington, DC 20402.

[5] National Formulary XVI. Available from U.S. Pharmacopeia Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852.

[6] United States Pharmacopeia XXI. Available from U.S. Pharmacopeia Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852.

[7] Crock, J. G., Felichte, F. E., and Briggs, P. H., "Determination of Elements in National Bureau of Standards Geological Reference Materials SRM 278 Obsidian and SRM 688 Basalt by Inductively Coupled Argon Plasma—Atomic Emission Spectrometry," *Geostandards Newsletter*, Vol 7, 1983, pp. 335–340.

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

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

3. Terminology

3.1 *Definitions of Terms Specific to This Standard:*

3.1.1 *hydroxylapatite*—the chemical substance having the empirical formula $Ca_5(PO_4)_3OH$.[9]

4. Chemical Requirements

4.1 Elemental analysis for calcium and phosphorus shall be consistent with the expected stoichiometry of hydroxylapatite. The calcium and phosphorus contents, or alternatively, the ratio of calcium to phosphorous, shall be determined using suitable methods such as ion chromatography, X-ray fluorescence, or X-ray diffraction (see USP <191>).

4.2 A quantitative X-ray diffraction analysis shall indicate a minimum hydroxylapatite content of 95 % as determined in accordance with Practice F2024. Analysis of relative peak intensities shall be consistent with published data.[10]

4.3 *Elemental Impurities:*

4.3.1 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 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.

4.3.2 For each raw material lot, determine the concentrations of the respective elemental impurities within the hydroxylapatite 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. Per Section 4 of ICH Q3D, ten of the 24 elements of interest (Class 2B elements, Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, and Tl) may be excluded from the risk analysis due to their low abundance and low potential for being co-isolated with other materials.

4.3.2.1 Hydroxylapatite materials that are produced synthetically from purified compounds should have significantly lower and more consistent concentrations of elemental impurities compared to materials derived from natural sources. If the manufacturer can demonstrate adequate process control, sampling frequency for elemental impurities may be reduced.

4.3.3 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>.

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

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

4.3.5 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 hydroxylapatite in the final implant product as well as its degradation and elemental elution rate into the surrounding tissue.

4.3.5.1 The elemental impurity content of hydroxylapatite 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.

4.3.6 See X2.2 for additional information.

4.3.7 The analysis of other trace elements may be required based on the conditions, apparatus, or environments specific to the manufacturing techniques and raw materials.

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

5. Biocompatibility

5.1 Before any new device is used clinically, the biological response should be characterized by the methods recommended in ANSI/ISO 10993-1 or Practices F748 and F981 as appropriate. See X2.2 for additional information.

[9] Chemical Abstracts Service Registry Number [1306-06-5].

[10] The Joint Committee on Powdered Diffraction Standards has established a Powder Diffraction File. The Committee operates on an international basis and cooperates closely with the Data Commission of the International Union of Crystallography and ASTM (American Society for Testing and Materials). Hydroxylapatite data can be found on file card number 9-432 and is available from the Joint Committee on Powder Diffraction Standards, 1600 Park Lane, Swarthmore, PA 19081.

6. Test Specimen Fabrication

6.1 Prepare test specimens using the same raw materials and processes as those employed in fabricating the medical-grade hydroxylapatite raw material or finished medical device.

7. Guidance for Manufacturing Control and Quality Assurance

7.1 Acceptable levels of manufacturing control are highly desirable and apply to the manufacture of hydroxylapatite raw materials and finished devices. Good manufacturing practice guidelines for achieving acceptable levels of manufacturing quality control may be found in:

7.1.1 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.

7.1.2 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).

7.1.3 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.

7.1.4 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.

8. Certification of Hydroxylapatite Raw Materials

8.1 For hydroxylapatite supplied as a raw material, a certificate of compliance or a certificate of analysis that, at minimum, contains the following information shall accompany each shipment:

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

8.1.2 Lot number.

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

8.1.4 Chemical description and CAS registry number (the CAS number for hydroxylapatite is 1306-06-5).

8.1.5 Calcium and phosphorous content (and/or ratio) per 4.1.

8.1.6 Hydroxylapatite content (in mass %) per 4.2.

8.1.7 Elemental impurities per 4.3.

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

8.1.8 Intentionally added elements (if applicable).

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

9. Keywords

9.1 bioceramic; bone graft; hydroxylapatite (HA); hydroxyapatite; tricalcium phosphate (TCP); whitlockite

APPENDIXES

(Nonmandatory Information)

X1. RATIONALE

X1.1 Hydroxylapatite is commercially available as a synthetic bone-grafting material and is used as a raw material for coatings applied to the bone interface of many orthopedic implants. As with any implant material, the bioresponse is critically dependent upon the material properties. To achieve reliable biocompatibility, these must be known and consistent. This material standard provides specifications for a biocompatible grade of hydroxylapatite. Trace element content and physical form must be within established biocompatibility standards.

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 Ref (**7**).