Designation: F1581 – 08 (Reapproved 2020)

Standard Specification for Composition of Anorganic Bone for Surgical Implants[1]

This standard is issued under the fixed designation F1581; 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 material requirements for anorganic xenogeneic or allogeneic bone (apatite) intended for surgical implants. For a material to be called anorganic or deorganified bone, it must conform to this specification (see Appendix X1).

1.2 The biological response to apatite in soft tissue and bone has been characterized by a history of clinical use and by laboratory studies (**1**, **2**, **3**).[2] Xenogeneic bone, with organic components present, has been shown to be antigenic in the human host (**4**) whereas the same material that has been completely deorganified has been shown to elicit no inflammatory or foreign body reactions in human clinical use (**5**, **6**, **7**).

1.3 This specification specifically excludes synthetic hydroxylapatite, hydroxylapatite coatings, ceramic glasses, tribasic calcium phosphate, whitlockite, and alpha- and beta-tricalcium phosphate.

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

1.5 **Warning—**Mercury has been designated by many regulatory agencies as a hazardous substance that can cause serious medical issues. Mercury, or its vapor, has been demonstrated to be hazardous to health and corrosive to materials. Use caution when handling mercury and mercury-containing products. See the applicable product Safety Data Sheet (SDS) for additional information. The potential exists that selling mercury or mercury-containing products, or both, is prohibited by local or national law. Users must determine legality of sales in their location.

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.* (See Appendix X2).

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]

D513 Test Methods for Total and Dissolved Carbon Dioxide in Water

D1688 Test Methods for Copper in Water

D2972 Test Methods for Arsenic in Water

D3557 Test Methods for Cadmium in Water

D3559 Test Methods for Lead in Water

D3919 Practice for Measuring Trace Elements in Water by Graphite Furnace Atomic Absorption Spectrophotometry

D4129 Test Method for Total and Organic Carbon in Water by High Temperature Oxidation and by Coulometric Detection

E1184 Practice for Determination of Elements by Graphite Furnace Atomic Absorption Spectrometry

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

F1185 Specification for Composition of Hydroxylapatite for Surgical Implants

2.2 *Code of Federal Regulations:*[4]

Title 21, Part 820

2.3 *National Formulary:*[5]

Tribasic Calcium Phosphate

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

Current edition approved Aug. 1, 2020. Published August 2020. Originally approved in 1995. Last previous edition approved in 2016 as F1581 – 08 (2016). DOI: 10.1520/F1581-08R20.

[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 Superintendent of Documents, 732 N. Capitol St., NW, Mail Stop: SDE, Washington, DC 20401, http://www.access.gpo.gov.

[5] National Formulary 25. Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org. Succeeding USP editions may alternatively be referenced.

2.4 *United States Pharmocopeia:*[6]
Identification Tests for Calcium and Phosphate <191>
Lead <251>
Mercury <261>
Cadmium <461>
Arsenic <211>
Heavy Metals <231> Method 1
Nitrogen Determination <4617>

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

3. Terminology

3.1 *Definitions:*

3.1.1 *allogeneic, adj*—derived from different individuals of the same species.

3.1.2 *anorganic, adj*—denoting tissue (for example, bone) from which the organic material has been totally removed. Also referred to as *deorganified, deproteinized* or *deproteinated.*

3.1.3 *apatite, n*—the mineral substance having the molecular formula $Ca_{10}(X)_2(PO_4)_6$ where X = OH (hydroxyapatite or hydroxylapatite), CO_3 (carbonated apatite), F (fluorine), or Cl (chlorine) (**8**).

3.1.4 *xenogeneic, adj*—derived from individuals of a different, specified species. For example, bovine bone, when used as an implant material in humans, is xenogeneic.

4. Chemical Requirements

4.1 Elemental analysis for calcium and phosphorus shall be consistent with the expected composition of the source of the biologically-derived bone mineral (**9**).

4.2 An X-ray diffraction analysis of the material shall be consistent with PDF card #9-432 for hydroxyapatite (**10**) or PDF card #35-180 for calcium phosphate carbonate (carbonated apatite). Analysis of relative peak intensities shall be consistent with published data.[8]

4.3 The crystal size of the anorganic bone shall be determined from the X-ray diffraction data using the well-known Scherrer formula (**11**).

4.4 The concentration of trace elements in the anorganic bone shall be limited as follows:

Element	ppm, max
arsenic	3
cadmium	5
mercury	5
lead	30
total heavy metals (as lead)	50

For referee purposes, use either inductively coupled plasma/mass spectroscopy (ICP/MS) (**12**) or the USP methods <191>, <251>, <261>, <211>, <231> Method 1, <4617>; and for cadmium, use either <461> or the U.S. Geological Survey Method on cadmium. (See 2.4 and 2.5.) Graphite furnace atomic absorption spectrophotometry may also be used for analysis of trace elements using for arsenic (Test Methods D2972), copper (Test Methods D1688), cadmium (Test Methods D3557), lead (Test Methods D3559) with 1 g anorganic bone/100mL water samples. General guides for the application of the graphite furnace are given in Practices D3919 and E1184.

4.5 The maximum allowable limit of all heavy metals determined as lead shall be 50 ppm as described in 2.4 or equivalent. Sample preparation shall be identical to that for tribasic calcium phosphate as specified in the National Formulary (see 2.3), except that approximately 1 g of material shall be dissolved in approximately 30 mL of 5 % HCl and boiled.

4.6 It is recommended that all minor constituents such as metals or oxides not detected as lead and present in concentrations equal to or greater than 0.1 % be identified and quantified.

4.7 Organic content shall be measured either as total carbon or nitrogen (see Note 1) or total protein by amino acid analyses (**13**). For all methods, a synthetic hydroxylapatite control that conforms to Specification F1185 or an established National Institute of Standards and Technology (NIST) standard shall be used. The maximum allowable limit of either nitrogen, carbon, or protein shall be within two standard deviations of the mean value established for the control.

NOTE 1—The Kjeldahl process for nitrogen determination (USP <461>) is set forth by the Association of Official Analytical Chemists (**14**) as an appropriate measure of proteins. Alternatively, organic material (carbon) can be measured by the coulometric method (Test Method D4129). Subtract from this value the carbonate content, which can be determined by Test Methods D513.

4.8 The carbonate content of the anorganic bone shall be determined. Carbonate content is typically 5 to 6 % in bone mineral prior to removal of the organic phase. Residual carbonate content remaining after processing is one means of distinguishing between the various processing methods utilized to process bone powder into anorganic bone. Carbonate content is linked to dissolution and resorbability characteristics of anorganic bone products and should be kept within 1 % of previous lots in order to assure consistent performance. Low carbonate content anorganic bone mineral (2 % or less) is barely soluble in dilute acids as compared to anorganic bone containing 5 to 6 % carbonate.

4.9 Functional groups will be identified by infrared analysis. Typical functional groups of apatites have been described by Elliott (**8**), LeGeros et al (**15**), and Rey (**16**, **17**, **18**).

[6] United States Pharmacopeia 30. Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org. Succeeding USP editions may alternatively be referenced.

[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] 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. 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 19801.

4.10 Analysis of additional elements or ionic species associated with the source or with processing conditions should be specified for this material.

5. Test Specimen Fabrication

5.1 Prepare test specimens from the same batch of material and by the same processes as those employed in fabricating the implant device.

6. Quality Program Requirements

6.1 The manufacturer shall conform to Quality Systems Regulations (see Title 21, Part 820, of the Code of Federal Regulations[4]) or its equivalent.

7. Biocompatibility

7.1 The biocompatibility of anorganic bone may depend upon processing conditions or source material history, or both, which may not be identified by the compositional requirements of this specification. The biocompatibility of these products should be ensured by a combination of preclinical testing and process controls. Material derived under the desired process conditions should be tested in accordance with the recommendations of Practice F748 and manufacturing controls put in place to ensure that process variations outside of acceptable tolerances do not occur. Substantial changes in process conditions or source control parameters shall necessitate additional biocompatibility testing to ensure maintenance of an acceptable tissue response.

8. Sterilization

8.1 Anorganic bone may be supplied presterilized in accordance with current procedures set forth by the Association for the Advancement of Medical Instrumentation (AAMI) and Quality Systems Regulations established by the Food and Drug Administration (FDA).[9]

8.2 If user sterilization or resterilization is intended, validated instructions for sterilization shall be supplied with the package insert.

9. Keywords

9.1 allogeneic; anorganic; apatite; bone; hydroxyapatite; hydroxylapatite; implant; xenogeneic

[9] Federal Register, Vol 43, No. 141, 21 July 1978.

APPENDIXES

(Nonmandatory Information)

X1. RATIONALE

X1.1 Xenogeneic and allograft bone is commercially available as grafting material. To eliminate concerns about possible immunogenicity effects or partially purified bone, anorganic or deorganified bone has been developed. To achieve reliable biocompatibility as an implant material, this material must be characterized for its hydroxylapatite mineral component and trace element content as well as for the absence of organic material. At the current time, sufficient data do not exist to provide specific limits for carbon and nitrogen values. Individual laboratories must apply statistical analysis to show equivalence with the negative control. Test results that might provide data to assign specific limits for carbon and nitrogen are hereby solicited.

X2. BIOCOMPATIBILITY

X2.1 No known surgical implant material has ever been shown to be completely free of adverse reactions in the human body. However, long-term clinical experience of the use of the material referred to in this standard has shown that an acceptable level of biological response can be expected, if the material is used in appropriate applications.