Designation: F 1581 – 99

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

This standard is issued under the fixed designation F 1581; 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 [2] and by laboratory studies **(1,2,3)**. 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 *This standard does not pruport to address all of the safety concerns, such as health concerns due to the presence of transmissible disease, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*(See Appendix X2).

2. Referenced Documents

2.1 *ASTM Standards:*

D 513 Test Methods for Total and Dissolved Carbon Dioxide in Water[3]

D 1688 Test Methods for Copper in Water[3]

D 2972 Test Methods for Arsenic in Water[3]

D 3557 Test Methods for Cadmium in Water[3]

D 3559 Test Methods for Lead in Water[3]

D 3919 Practice for Measuring Trace Elements in Water by Graphite Furnace Atomic Absorption Spectrophotometry[3]

D 4129 Test Method for Total and Organic Carbon in Water High Temperature Oxidation and Coulometric Detection[4]

E 1184 Practice for Electrothermal (Graphite Furnace) Atomic Absorption Analysis[5]

F 748 Practice For Selecting Generic Biological Test Methods for Materials and Devices[6]

F 1185 Specification for Composition of Ceramic Hydroxylapatite for Surgical Implants[6]

2.2 *Code of Federal Regulations:*[7]

Title 21, Part 820

2.3 *National Formulary:*[8]

Tribasic Calcium Phosphate

2.4 *United States Pharmocopeia:*[9]

Identification Tests for Calcium and Phosphate <191>

Lead <251>

Mercury <261>

Cadmium <461>

Arnsenic <211>

Heavy Metals <231> Method 1

Nitrogen Determination <4617>

2.5 *U.S. Geological Survey Method:*[10]

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 or C1 (**8**).

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[1] This specification is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Devices and is under 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] *Annual Book of ASTM Standards*, Vol. 11.01.

[4] *Annual Book of ASTM Standards*, Vol. 11.02.

[5] *Annual Book of ASTM Standards*, Vol. 03.06.

[6] *Annual Book of ASTM Standards*, Vol. 13.01.

[7] Available from Standardization Documents Order Desk, Bldg. 4 Section D, 700 Robbins Ave., Philadelphia, PA 19111-5094, Attn: NPODS.

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

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

[10] 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.

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 will 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.[11]

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

Element	ppm, max
As	3
Cd	5
Hg	5
Pb	30
total heavy metals (as lead)	50

For referee purposes, use either inductively coupled plasma/mass spectroscopy (ICP/MS) (**11**) or the United States Pharmocopeia (USP) methods <191>, <251>, <261>, <211>, <231> Method 1, < 4617> and for cadmium 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 ananlysis of trace elements using (Test Methods D 2972), Cd (Test Method D 1688), Pb (Test Methods D 3559) with 1 g anorganic bone/100mL H_2O samples. G eneral guides for the application of the graphite furnace are given in Practices D 3919 and E 1184.

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

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

4.6 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 F 1185 or an established NIST standard must be used. The maximum allowable limit of either nitrogen, carbon, or protein will 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 **(12)** as an appropriate measure of proteins. Alternatively, organic material (carbon) can be measured by the coulometric method (Test Method D 4129). Subtract from this value the carbonate content, which can be determined by Test Methods D 513.

4.7 Functional groups will be identified by infrared analysis. Typical functional groups of apatites have been described by Elliott **(8)**, LeGeros et al **(14)**, and Rey **(15,16,17)**.

4.8 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 Good Manufacturing Practices (see Title 21, Part 820, of the Code of Federal Regulations[7]) 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 F 748 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 will 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 Good Manufacturing Practices (GMP) established by the Food and Drug Administration (FDA).[12]

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

[11] 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.

[12] Federal Register, Vol. 43, No. 141, Friday, July 21, 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.

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