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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.

ε[1] NOTE—Mercury warning was editorially added in April 2008.

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*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.*~~

1.4 **Warning—**Mercury has been designated by EPA and many state agencies as a hazardous material that can cause central nervous system, kidney, and liver damage. Mercury, or its vapor, may be hazardous to health and corrosive to materials. Caution should be taken when handling mercury and mercury-containing products. See the applicable product Material Safety Data Sheet (MSDS) for details and EPA's website (http://www.epa.gov/mercury/faq.htm) for additional information. Users should be aware that selling mercury or mercury-containing products, or both, in your state may be prohibited by state law.

1.5 *This standard does not purport 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:* [3]

D 513 Test Methods for Total and Dissolved Carbon Dioxide in Water
D 1688 Test Methods for Copper in Water
D 2972 Test Methods for Arsenic in Water
D 3557 Test Methods for Cadmium in Water
D 3559 Test Methods for Lead in Water
D 3919~~Practice for Measuring Trace Elements in Water by Graphite Furnace Atomic Absorption Spectrophotometry~~[3]
~~D4129Test Method for Total and Organic Carbon in Water High Temperature Oxidation and Coulometric Detection~~ Practice for Measuring Trace Elements in Water by Graphite Furnace Atomic Absorption Spectrophotometry
D 4129 Test Method for Total and Organic Carbon in Water by High Temperature Oxidation and by Coulometric Detection
E 1184 Practice for Electrothermal (Graphite Furnace) Atomic Absorption Analysis
~~F748Practice For Selecting Generic Biological Test Methods for Materials and Devices~~
F 748 Practice for Selecting Generic Biological Test Methods for Materials and Devices
F 1185 Specification for Composition of ~~Ceramic~~ Hydroxylapatite for Surgical Implants

[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 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* ~~, Vol. 11.01.~~ volume information, refer to the standard's Document Summary page on the ASTM website.

2.2 *Code of Federal Regulations:*[4]
Title 21, Part 820
2.3 *National Formulary:*
~~Tribasic Calcium Phosphate~~
~~2.4~~ [5]
Tribasic Calcium Phosphate
2.4 *United States Pharmocopeia:*[6]
Identification Tests for Calcium and Phosphate <191>
Lead < 251>
Mercury <261>
Cadmium <461>
~~Arnsenic <211>~~
Arsenic <211>
Heavy Metals <231> Method 1
Nitrogen Determination <4617>
2.5 *U.S. Geological Survey Method:*
~~Cadmium~~ [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.*~~ 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 Cl (8).~~ (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 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.~~

~~4.3~~The concentration of trace elements in the anorganic bone shall be limited as follows: 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
~~As~~	~~3~~
arsenic	3
~~Cd~~	~~5~~
cadmium	5

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

[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] Annual Book of ASTM Standards, Vol. 03.06.~~

[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.

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

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

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

[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.

~~Hg~~	~~5~~
mercury	5
~~Pb~~	~~30~~
lead	30
total heavy metals (as lead)	50

For referee purposes, use either inductively coupled plasma/mass spectroscopy (ICP/MS) (~~11~~12) or the ~~United States Pharmocopeia (USP)~~ 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.~~cadmium. (See 2.4 and 2.5). Graphite furnace atomic absorption spectrophotometry may also be used for ~~ananlysis~~analysis of trace elements using for arsenic (Test Methods D 2972), ~~Cd~~copper (Test Methods D 1688), ~~Pb~~cadmium (Test Methods ~~D3559~~D 3557), lead (Test Methods D 3559) with 1 g anorganic bone/100mL ~~H_2O~~water samples. General guides for the application of the graphite furnace are given in Practices D 3919 and E 1184~~E1184~~.

~~4.4The~~4.5 The maximum allowable limit of all heavy metals determined as lead ~~will~~shall be 50 ppm as described in 2.4 or equivalent. Sample preparation ~~will~~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 ~~will~~shall be dissolved in approximately 30 mL of 5 % HCl and boiled.

~~4.5It~~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.~~6~~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 F 1185 or an established National Institute of Standards and Technology (NIST) standard ~~must~~shall be used. The maximum allowable limit of either nitrogen, carbon, or protein ~~will~~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 ~~(12~~**(14)** 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.

~~4.7Functional groups will be identified by infrared analysis. Typical functional groups of apatites have been described by Elliott (~~

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 **(~~14~~(15)**, and Rey **(~~15,~~(16,17, 18)**.

4.8~~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 ~~Good Manufacturing Practices~~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 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~~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 ~~Good Manufacturing Practices (GMP)~~ Quality Systems Regulations established by the Food and Drug Administration (FDA).[9]

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