

Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement; Guidance for Industry and FDA

Document issued on: July 17, 2002

**This document supersedes “Class II Special Controls Guidance Document:
Polymethylmethacrylate (PMMA) Bone Cement 510(k)s; Final Guidance for
Industry” dated August 2, 2001.**



**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health**

**Orthopedic Devices Branch
Division of General, Restorative, and Neurological Devices
Office of Device Evaluation**

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Hany W. Demian at (240) 276-3676 or by electronic mail at hany.demian@fda.hhs.gov.

Additional Copies

Additional copies are available from the Internet at: <http://www.fda.gov/cdrh/ode/guidance/668.pdf>, or CDRH Facts-On-Demand. In order to receive this document via your fax machine, call the CDRH Facts-On-Demand system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system. At the second voice prompt, press 1 to order a document. Enter the document number (668) followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

TABLE OF CONTENTS

1.	INTRODUCTION	4
2.	BACKGROUND	4
3.	THE CONTENT AND FORMAT OF AN ABBREVIATED 510(K) SUBMISSION	5
4.	SCOPE	7
5.	RISKS TO HEALTH	8
6.	BIOCOMPATIBILITY	8
7.	MATERIAL AND PERFORMANCE CHARACTERIZATION	9
8.	STERILITY	11
9.	LABELING	12
10.	CLINICAL STUDIES	14
	APPENDIX 1	15
	APPENDIX 2	17

Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement; Guidance for Industry and FDA

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

1. Introduction

On October 14, 1999, FDA issued an order reclassifying the polymethylmethacrylate (PMMA) bone cement from class III (premarket approval) into class II (special controls). This guidance document was developed as a special control guidance to support the reclassification of PMMA bone cement into class II. The device, as classified, is intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone. This guidance will be issued in conjunction with a Federal Register notice announcing reclassification of this device type.

As stated on the coversheet, this guidance supersedes "Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement 510(k)s; Final Guidance for Industry," dated August 2, 2001. This August 2001 document served to update the information presented in "Guidance Document for Testing Orthopedic Bone Cement" dated November 1, 1993. We have since updated the August 2001 guidance to more clearly reflect that a person may submit an abbreviated 510(k) when relying on a Class II Special Control Guidance Document. While we have reformatted some of the sections, we have not substantially changed any of the recommendations about the performance characteristics or labeling for the device.

Following the effective date of the final rule classifying the device, any firm submitting a 510(k) premarket notification for a PMMA bone cement will need to address the issues covered in the special control guidance. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of PMMA bone cement. Thus, a manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug & Cosmetic Act (the Act), including the 510(k) requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with PMMA bone cement identified in this

guidance and, (3) obtain a substantial equivalence determination from FDA prior to marketing the device, unless exempt from the premarket notification requirements of the Act (refer to 21 CFR 807.85).

This special control guidance document identifies the classification regulations and product codes for the PMMA bone cement to which it applies (refer to Section 4 – **Scope**). In addition, other sections of this special control guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these PMMA bone cement and lead to a timely 510(k) review and clearance. This document supplements other agency documents regarding the specific content requirements of a 510(k) submission. You should also refer to 21 CFR 807.87 and other agency documents on this topic, such as the **510(k) Manual - Premarket Notification: 510(k) - Regulatory Requirements for Medical Devices**, <http://www.fda.gov/cdrh/manual/510kprt1.html>.

Under “**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**¹,” a manufacturer may submit a traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once a Class II Special Controls Guidance Document has been issued. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the statutory and regulatory criteria in the manner suggested by the guidance and in your attempt to address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the “**A Suggested Approach to Resolving Least Burdensome Issues**” document. It is available on our Center web page at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>.

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this special control guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied

¹ <http://www.fda.gov/cdrh/ode/parad510.html>

to address the risks identified in this guidance document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this Class II Special Controls Guidance Document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 9 for specific information that should be included in the labeling for devices of the types covered by this guidance document.)

Summary report

The summary report should contain:

- Description of the device and its intended use. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. You should also submit an "indications for use" enclosure.²
- Description of device design requirements.
- Identification of the Risk Analysis method(s) used to assess the risk profile in general as well as the specific device's design and the results of this analysis. (Refer to Section 5 for the risks to health generally associated with the use of this device that FDA has identified.)
- Discussion of the device characteristics that address the risks identified in this Class II Special Controls Guidance Document, as well as any additional risks identified in your risk analysis.
- A brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Sections 6-8 of this Class II Special Controls Guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to

² Refer to <http://www.fda.gov/cdrh/ode/indicate.html> for the recommended format.

your test results.³ (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

- If any part of the device design or testing relies on a recognized standard, (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a declaration of conformity to the standard.⁴ Please note that testing must be completed before submitting a declaration of conformity to a recognized standard. (21 USC 514(c)(2)(B)). For more information, see FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, <http://www.fda.gov/cdrh/ode/guidance/1131.html>.

If it is not clear how you have addressed the risks identified by FDA or through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a premarket notification for a PMMA bone cement.

4. Scope

The scope of this document is currently limited to bone cement as described in 21 CFR 888.3027 (product code: LOD).

§ 888.3027 Polymethylmethacrylate (PMMA) Bone Cement.

³ If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria, and thus differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

⁴ See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist For All Premarket Notification [510(K)] Submissions), <http://www.fda.gov/cdrh/ode/reqrecstand.html>.

- (a) *Identification.* Polymethylmethacrylate (PMMA) bone cement is a device, intended to be implanted that is made from methylmethacrylate, polymethylmethacrylate, esters of methacrylic acid, or copolymers containing polymethylmethacrylate and polystyrene. The device is intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone.
- (b) *Classification.* Class II (special controls). The special control for this device is the FDA document "Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement; Guidance for Industry and FDA."

Alternate materials may be demonstrated to be substantially equivalent to PMMA used in bone cement. FDA will assign new product codes for bone cements formulated from alternate materials that are determined to be substantially equivalent under section 510(k) of the Act.

5. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the PMMA bone cement addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. You should also conduct a risk analysis, prior to submitting your 510(k), to identify any other risks specific to your device. The premarket notification should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this guidance document, or have identified risks additional to those in the guidance, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
Bone cement implantation syndrome	Sections 7, 9
Polymerization setting problems	Section 7
Loosening or migration of the device	Sections 7, 9
Infection and fever	Section 8
Adverse tissue reaction	Section 6, 9
Pain and/or loss of function	Sections 7, 9
Revision	Sections 7, 8, 9

6. Biocompatibility

The biocompatibility of your device should be evaluated. We recommend conducting an evaluation as described in the FDA-modified **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing**, <http://www.fda.gov/cdrh/g951.html> for blood-contacting, long-term implanted devices. Your summary report should contain either a statement that testing will be conducted as described in the standard (the statement should also include the acceptance criteria to be applied) or declaration of conformity to Parts 5 and 10 of ISO-10993.

7. Material and Performance Characterization

PMMA bone cement is a self-curing, two component system consisting of liquid and powder components. Typically, the liquid component contains the monomer, accelerator, and the inhibitor. The powder contains the polymer, radio-opacifier, and initiator.

We recommend that you provide the following to evaluate the material and performance characteristics of your final sterilized PMMA bone cement.

A. Physical and Chemical Characterization

Physical and chemical analyses are used to characterize the liquid, powder, and cured bone cement. Appendix 1 lists important information, including mixing and application of the cement in which the dough, working, and set times are characterized (ASTM 451 and ISO 5833). You should identify the main ingredients, additives, and trace elements found in a bone cement composition, along with their respective amounts. You should evaluate the residual monomer levels and elution of monomer during initial mixing and after polymerization by gas chromatography or another applicable method (testing performed at 1 hour, 24 hours, and 72 hours after polymerization). You should establish the molecular weight of the powder and cured cement by gel permeation chromatography or solution viscosity measurements. If the polymerization process is other than the free radical polymerization, then you should evaluate the degree of polymerization.

You should provide the final product release specifications for each chemical, along with other specifications for the dough, working, set time, and residual monomer limit and elution of monomer limits for cured bone cement.

You should characterize other physical properties, such as the powder's morphology, size distribution, and dispersion of the polymer and additives. This is typically achieved by light microscopy or scanning electron microscopy (SEM).

You should present a table comparing the similarities and differences in these parameters, including component ratios, between the proposed product and a predicate bone cement.

B. Mechanical Testing

You should evaluate the material's integrity with several *in vitro* mechanical test methods. Appendix 2 includes mechanical characterization testing (i.e., modulus, fatigue, fracture toughness, fatigue crack propagation (optional), flexural strength, compressive strength, shear strength, tensile strength, and creep). FDA recommends using a predicate bone cement as a control when performing these tests. See below for what should be provided as part of a complete test report.

You should consider the morphology of the fracture surface after mechanical testing. Analyses of the fracture surface include:

- porosity measurements of the fracture surface and the bulk material

- additive dispersion measurements on the fractured surface
- failure analysis of the fracture surface

You should use the applicable American Society for Testing and Materials (ASTM) and International Organization for Standardization (ISO) consensus standards listed below to establish the material and performance characterization of your device:

- ASTM F 451-99, “Standard Specifications for Acrylic Bone Cement”
- ASTM D 638-00, “Standard Test Method for Tensile Properties of Plastics”
- ASTM D 732-99, “Standard Test Method for Shear Strength of Plastics by Punch Tool”
- ASTM D 790-00, “Standard Test Method for Flexural Properties of Unreinforced and Reinforced Plastics and Electrical Insulating Materials”
- ASTM D 2990-95, “Standard Tensile, Compressive, and Flexural Creep and Creep Rupture of Plastics”
- ASTM E 399-97, “Standard Test Method for Plane-Strain Fracture Toughness of Metallic Materials”
- ASTM E 647-00, “Standard Test Method for Measurement of Fatigue Crack Growth Rates”
- ISO 5833:1992, “Implants for surgery - Acrylic resin cements”

You should include the following PMMA cement-specific information as part of your test report:

- Description of the following preparation variables that may affect the reported *in vitro* mechanical properties:
 - ➔ mixing – temperature of the environment and mixing surfaces throughout the procedure
 - ➔ centrifugation - amounts of ingredients, monomer temperature, rate (revolutions per minute), and time
 - ➔ method of mixing, i.e., hand mixing, mechanical (machine) mixing, or vacuum mixing - amounts of ingredients, order of mixing, pressure, rate (beats per minute), duration, and geometry of mixer (rotor, container)
 - ➔ molding – design, material, and temperature
 - ➔ machining- number of specimens broken during machining
 - ➔ finishing effects - number of specimens rejected due to surface defects
 - ➔ aging (curing) - sequence stages chronology of events, duration, environment, and temperature

- Summary of results
- Discussion of all specimens prepared but not tested, including the number of rejected specimens, the reasons for rejection, the evaluation methods, and the rejection pass/fail criteria

C. Shelf-life, Product Expiration Dating, and Storage Conditions

You should establish the shelf-life by either real time storage or by using a validated accelerated stability testing protocol (Appendix 2). The appropriateness of conducting accelerated stability studies is related to device composition and the relationship between accelerated study conditions and real-time aging. The value of accelerated stability is dependent on identical decomposition mechanisms at both standard and elevated temperatures. Regardless of the type of study conducted, you should collect data from at least three production lots. Stability studies should monitor the critical physical and mechanical properties of a device that are required to ensure it will perform consistently during its entire shelf-life. Your summary report should disclose the device shelf-life and recommend storage conditions and identify the method used to support the values. Detailed study protocol and underlying data should be maintained at the manufacturing facility in accordance with the Quality System Regulation.

8. Sterility

You should evaluate the sterility of your device. We recommend providing information according to the **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**, <http://www.fda.gov/cdrh/ode/guidance/361.html>.

We recommend your summary report contain the following information for devices sold as sterile:

- the sterilization method that will be used in the sterilization cycle (e.g., dry heat, ethylene oxide (EtO), steam, radiation)
- the maximum levels of EtO and ethylene chlorhydrin residues, if sterilized by EtO
- the radiation dose, if sterilized by radiation
- a description of the method that will be used to validate the sterilization cycle
- a description of the packaging to maintain the device's sterility
- the sterility assurance level specification (SAL)⁵
- a description of the method used to determine non-pyrogenicity (e.g., the limulus amebocyte lysate (LAL) method), if the device is labeled pyrogen free.

⁵ FDA recommends a SAL of 10^{-6} for PMMA bone cement.

9. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR 807.87(e).⁶

Outer Box Label

The outside box label should clearly identify the storage conditions for the bone cement and, if necessary, the equilibration time (i.e., the time to reach optimal temperature) of the bone cement.

Package Insert and Surgical Technique

The package insert and surgical technique should include the following:

Intended Use

PMMA bone cement is intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone.

Contraindications

PMMA bone cement is contraindicated in the presence of active or incompletely treated infection, at the site where the bone cement is to be applied.

Warnings

Monitor patients carefully for any change in blood pressure during and immediately following the application of bone cement. Adverse patient reactions affecting the cardiovascular system have been associated with the use of bone cements. Hypotensive reactions have occurred between 10 and 165 seconds following application of bone cement; they have lasted from 30 seconds to 5 or more minutes. Some have progressed to cardiac arrest. Patients should be monitored carefully for any change in blood pressure during and immediately following the application of bone cement.

Follow the handling, mixing and canal preparation instructions carefully.

- Caution should be exercised during the mixing of the two components to prevent excessive exposure to the concentrated monomer vapors, which may produce irritation of the respiratory tract, eyes, and possibly the liver. Personnel wearing contact lenses should not be near or involved in mixing this bone cement.
- Polymerization of the bone cement is an exothermic reaction, which occurs while the cement is hardening *in situ*. The released heat may damage bone or other tissues surrounding the implant.

⁶ Although final labeling is not required for 510(k) clearance, final labeling must also comply with the requirements of 21 CFR 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of part 801.

- Inadequate fixation or unanticipated postoperative events may affect the cement-bone interface and lead to micromotion of cement against bone surface. A fibrous tissue layer may develop between the cement and the bone, and loosening of the prosthesis may occur leading to implant failure. Long-term follow-up is advised for all patients on a regularly scheduled basis.
- Do not allow the liquid component to contact rubber or latex gloves. The liquid component is a powerful lipid solvent. Should contact occur, the gloves may dissolve and tissue damage may occur. Wearing a second pair of gloves and strict adherence to the mixing instructions may diminish the possibility of hypersensitivity reactions. The mixed bone cement should not make contact with the gloved hand until the cement has acquired the consistency of dough. This usually occurs between one and two minutes after the liquid and powder components are mixed.

Avoid over pressurization of the bone cement because this may lead to extrusion of the bone cement beyond the site of its intended application and damage to the surrounding tissues.

The safety of the bone cement in pregnant women or in children has not been established. Bone cement may adversely affect bone growth and fetal health.

Precautions

Do not use this product after the expiration date printed on the package. This device may not be safe or effective beyond its expiration date.

Follow the handling and mixing instructions to avoid contact dermatitis. Strict adherence to the instructions for mixing the powder and liquid components may reduce the incidence of this complication.

Adequately ventilate the operating room to eliminate as much monomer vapor as possible. The liquid monomer is highly volatile and flammable. Ignition of monomer fumes caused by use of electrocautery devices in surgical sites near freshly implanted bone cements has been reported.

Dispose of the polymer component in an authorized waste facility. The liquid component should be evaporated under a well-ventilated hood or absorbed by an inert material and transferred in a suitable container for disposal.

Adverse Events

Serious adverse events, some with fatal outcome, associated with the use of acrylic bone cements include myocardial infarction, cardiac arrest, cerebrovascular accident, and pulmonary embolism.

The most frequent adverse reactions reported with acrylic bone cements are a transitory fall in blood pressure, thrombophlebitis, hemorrhage and hematoma, loosening or displacement of the prosthesis, superficial or deep wound infection, trochanteric bursitis, and short-term cardiac

conduction irregularities. Other reported adverse reactions include heterotopic new bone formation and trochanteric separation.

Other reported adverse events for acrylic bone cements include pyrexia due to an allergy to the bone cement, hematuria, dysuria, bladder fistula, delayed sciatic nerve entrapment due to extrusion of the bone cement beyond the region of its intended application, and adhesions and stricture of the ileum due to the heat released during polymerization.

Instructions and Training

The instructions for use should include a handling time versus temperature chart to give the user information regarding how fast the bone cement will polymerize at a given temperature and humidity.

The surgeon should, by specific training and experience, be thoroughly familiar with the properties, handling characteristics, and application of bone cements. Because the handling and curing characteristics of this bone cement vary with temperature, humidity, and mixing technique, they are best determined by the surgeon's actual experience.

10. Clinical Studies

The agency does not intend to request clinical studies for new devices unless there is a specific reason to require such information to support a substantially equivalent determination. There may be situations in which FDA believes clinical studies are necessary to support submissions for these devices, e.g., a new intended use or certain changes to the bone cement's chemical formulation, including the addition of certain new chemicals.

If a clinical study is needed to demonstrate substantial equivalence, i.e., conducted prior to obtaining 510(k) clearance of the device, the study must be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR 812. FDA has determined that PMMA bone cement addressed by this guidance document is a significant risk device as defined in 21 CFR 812.3(m)(4).⁷ In addition to the requirement of having an FDA-approved IDE, sponsors of such trials must comply with Parts 50 and 56.

After FDA determines that the device is substantially equivalent, clinical studies conducted in accordance with the indications reviewed in the 510(k), including clinical design validation studies conducted in accordance with the quality systems regulation, are exempt from the investigational device exemptions (IDE) requirements. However, such studies must be performed in conformance with the regulations governing institutional review boards (21 CFR 56) and informed consent (21 CFR 50).

⁷ Refer to Blue Book Memorandum entitled "SIGNIFICANT RISK AND NONSIGNIFICANT RISK MEDICAL DEVICE STUDIES" at <http://www.fda.gov/cdrh/d861.html>.

Appendix 1

PHYSICAL AND CHEMICAL METHODS OF ANALYSES		
	Suggested Testing	Examples of Test Methods
Mixing and Application	Mix liquid & powder components	ASTM F451-95, ISO 5833-92
	Dough time	ASTM F451-95, ISO 5833-92
	Setting time	ASTM F451-95, ISO 5833-92
	Viscosity: Pre-dough stage extrusion Dough stage intrusion	ASTM F451-95, ISO 5833-92 ASTM F451-95, ISO 5833-92
Chemical Composition	Ingredients: chemical formula, structure, additives, etc.	Liquid-NMR, FTIR, HPLC/MS
	Type of radio-opacifier	TGA/gross pyrolysis
	Purity or trace elements	ICP/MS, GC/FTIR/MS, titration
	Residual low MW molecules	GC, HPLC/GPC, liquid-NMR
	Leachables (e.g., low MW molecules)	GC, HPLC/GPC
Molecular Weight and Polymer Structure	MW by viscous flow	Viscosity measurements (e.g., solution)
	MW: Polydispersity, M_n , M_w	GPC with refractive index detector using polystyrene as standard material
	Branched, linear, or crosslinked	Solubility, swelling, liquid-NMR
	% Crystallinity, if applicable	X-ray diffraction, DSC
	Crystallization temperature, if applicable	DSC, DMA
	Glass transition temperature (T_g), if applicable	DSC, DMA
Physical Properties	Powder's morphology, size characterization and dispersion of polymer and additives	Light microscopy, SEM of powder and cured cement
	Porosity characterization	Scanning Acoustical Microscopy of bulk cement (e.g., SLAM, C-SAM) and serial sectioning of the cured cement
	Dimensional changes during curing (shrinkage)	Volume measurement
	% Water absorption (swelling)	Saturation testing
	Aging due to fluid absorption and polymerization	Mechanical testing (Appendix 2)
Stability of Components	Change in monomer viscosity due to artificial aging	ASTM 451 - 95
	Change in benzoyl peroxide levels	Titration method, FTIR, GC
Thermal Properties	Maximum polymerization temperature	ASTM F451 - 95, ISO 5833 - 92

C-SAM=C-mode scanning acoustical microscopy
 DMA=Dynamic mechanical analysis
 DSC=Differential scanning calorimetry
 FTIR=Fourier transform infrared
 GC=Gas chromatography
 GPC=Gel permeation chromatography
 HPLC=High-performance liquid chromatography

ICP=Inductively coupled plasma
 MS=Mass spectroscopy
 MW=Molecular weight
 NMR=Nuclear magnetic resonance
 SEM=Scanning electron microscopy
 SLAM=Scanning laser acoustical microscopy
 TGA=Thermogravimetric analysis

Appendix 2

MECHANICAL PROPERTIES AND SHELF-LIFE			
Mechanical Properties		Suggested Testing	Examples of Test Methods
Modulus	Flexural	4-Point bending	ISO 5833-92
	Compressive	Uniaxial compression	ISO 5833-92 , ASTM F451-95
	Tension	Uniaxial tension	ASTM D638-91 - rectangular or cylindrical specimen
Cyclic Fatigue Properties		Uniaxial tension/compression or tension/tension	ASTM D638-91 <ul style="list-style-type: none"> - rectangular or cylindrical specimen - frequency – physiologically relevant or justified level - sinusoidal wave form - load control - stress levels which are similar to expected in vivo stresses
		3 or 4-Point bending	Use rectangular specimens
Fracture Toughness, K_{IC}		Compact tension	ASTM E399-90
		Notched bending	Compact tension or single-edge notched
Fatigue Crack Propagation (optional)		Compact tension	ASTM E647- 95
Static Strength	Flexural	4-Point bending	ISO 5833-92
	Compressive	Uniaxial compression	ISO 5833-92, ASTM F451-95
	Tensile	Uniaxial tension	ASTM D638-91 – rectangular/cylindrical specimens
	Shear	Single shear (cement-cement)	ASTM D732-93
Viscoelasticity		Uniaxial compressive creep	ASTM D2990-95 or compressive creep of cylindrical specimens
		Dynamic mechanical analysis (optional mechanical testing should be considered if further evaluation is needed)	DMA
Shelf-Life		Measurement of mechanical properties of hardened cement after components have been aged over time.	Real-time storage or a validated accelerated aging condition of sterilized liquid and powder components. Perform testing on cured bone cement.