DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

OCT 14 1999

Mr. Lonnie Witham
President
Orthopedic Surgical Manufacturers Association
1962 Deep Valley Cove
Germantown, Tennessee 38138

Re: Reclassification Order:
Docket No. 98P-0035
Polymethylmethacrylate (PMMA) Bone Cement

Dear Mr. Witham:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your petition for reclassification of the polymethylmethacrylate (PMMA) bone cement that 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. FDA concludes that this device and substantially equivalent devices of this generic type, should be reclassified from class III into class II. This order, therefore, reclassifies the PMMA bone cement, and substantially equivalent devices of this generic type into class II, under the generic name bone cement, effective immediately. This order also identifies the special controls applicable to the device as consensus standards, FDA guidance documents, and labeling restrictions.

FDA identifies this generic type of device, the subject of this reclassification, as follows:

> 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 (21 CFR 888.3027).

The Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 *et. seq.*), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), the Safe Medical Devices Act of 1990 (the SMDA) (Pub. L. 101-629), and the Food and Drug Administration Modernization Act of 1997 (the FDAMA) (Pub. L. 105-115), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

The 1976 amendments broadened the definition of "device" in 201(h) of the act (21 U.S.C. 321(h)) to include certain articles that were once regulated as drugs. Under the 1976 amendments, Congress classified all transitional devices, i.e., those devices previously regulated as new drugs, including the PMMA bone cement, into class III. The legislative history of the SMDA reflects congressional concern that many transitional devices were being overregulated in class III (H. Rept. 808, 101st Cong., 2d sess. 26-27 (1990); S. Rept. 513, 101st Cong., 2d sess. 27 (1990)). Congress amended section 520(l) of the act (21 U.S.C. 360j(l)) to direct FDA to collect certain safety and effectiveness information from the manufacturers of transitional devices still remaining in class III to determine whether the devices should be reclassified into class II (special controls) or class I (general controls). Accordingly, in the Federal Register of November 14, 1991 (56 FR 57960), FDA issued an order under section 520(l)(5)(A) of the act, requiring manufacturers of transitional devices, including PMMA bone cement (21 CFR 888.3027), to submit to FDA a summary of, and a citation to, any information known or otherwise available to them respecting the devices, including adverse safety or effectiveness information which had not been submitted under section 519 of the act (21 U.S.C. 360i). Manufacturers were to submit the summaries and citations to FDA by January 13, 1992. However, because of misunderstandings and uncertainties regarding the information required by the order, and whether the order applied to certain manufacturers' devices, many transitional class III device manufacturers failed to comply with the reporting requirement by January 13, 1992. Consequently, in the Federal Register of March 10, 1992 (57 FR 8462), FDA extended the reporting period to March 31, 1992.

Section 520(l)(5)(B) of the act provides that, after the issuance of an order requiring manufacturers to submit a summary of, and citation to, any information known or otherwise available respecting the devices, but before December 1, 1992, FDA was to publish regulations either leaving transitional class III devices in class III or reclassifying them into class I or II. Subsequently, as permitted by section 520(l)(5)(C) of the act, in the Federal Register of November 30, 1992 (57 FR 56586), the agency published a notice extending the period for issuing such regulations until December 1, 1993. Due to limited resources, FDA was unable to publish the regulations before the December 1, 1993 deadline.

As you know, on January 21, 1998, FDA filed your petition requesting reclassification of the PMMA bone cement from class III into class II. The petition was submitted under section 520(l)(2) of the act (21 U.S.C. 360j(l)(2)), and 21 CFR 860.136 of the agency's regulations. In accordance with section 520(l)(1) of the act, the PMMA bone cement was automatically classified into class III because the device was a transitional device, i.e., a device previously regulated as a new drug. In order to reclassify the PMMA bone cement 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 into class II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of safety and effectiveness of the device for its intended use.

Pursuant to 21 CFR 860.125 and 860.136(b)(5), FDA consulted with the Orthopedic and Rehabilitation Devices Panel (the Panel) regarding the reclassification of the PMMA bone cement. The Panel unanimously recommended that the PMMA bone cement 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 be reclassified from class III into class II because the Panel believes that special controls in addition to general controls will provide reasonable assurance of the safety and effectiveness of the device. This recommendation was based on the information and data in the reclassification petition, the summary and analysis of the data in the petition, the information presented during the open public hearing and open committee discussions of the meeting held on April 28,1998, and the Panel members' own personal knowledge of, and clinical experience with, the device.

FDA agrees with the Panel's recommendation to reclassify the PMMA bone cement from class III into class II. The agency has identified the following special controls listed below to reasonably assure the safety and effectiveness of the device:

A. FDA Recognized Consensus Standards

1. American Society for Testing and Material (ASTM) F 451 – 95 "Standard Specifications for Acrylic Bone Cement,"

2. ASTM D 638 - 91 "Standard Test Method for Tensile Properties of Plastics,"

3. ASTM D 732 - 93 "Standard Test Method for Shear Strength of Plastics by Punch Tool,"

4. ASTM D 790 - 98 "Standard Test Method for Flexural Properties of Unreinforced and Reinforced Plastics and Electrical Insulating Materials,"

5. ASTM D 2990 - 95 "Standard Tensile, Compressive, and Flexural Creep and Creep Rupture of Plastics,"

6. ASTM E 399 - 90 "Standard Test Method for Plane-Strain Fracture Toughness of Metallic Materials,"

7. ASTM E 647 - 95a "Standard Test Method for Measurement of Fatigue Crack Growth Rates," and

8. International Organization for Standardization (ISO) 5833:1992 "Implants for surgery - Acrylic resin cements."

B. FDA Guidance Documents

1. "Use of International Organization for Standardization (ISO) 10993, 'Biological Evaluation of Medical Devices Part I: Evaluation and Testing,' "

2. "510(k) Sterility Review Guidance and Revision of 11/18/94 K90-1,"

3. "Guidance Document for Testing Orthopedic Bone Cement," and

4. "Guidance Document for the Preparation of Premarket Notification (510(k)) Applications for Orthopedic Devices."

C. Labeling

The labeling must contain the following statements in the contraindication, warnings, precautions, and adverse events sections:

1. Contraindication

Do not use PMMA bone cement in the presence of active or incompletely treated infection that could involve the site where the device will be implanted.

2. Warnings

a. Adverse cardiovascular reactions, including hypotension, hypoxaemia, cardiac arrhythmia, bronchspasm, cardiac arrest, myocardical infarction, pulmonary embolism, cerebrovascular accident, and possible death: Hypotensive reactions can occur between 10 and 165 seconds after application of the PMMA bone cement and can last for 30 seconds to 5 or more minutes. Some hypotensive reactions have progressed to cardiac arrest. The blood pressure of patients should be monitored carefully during and immediately following the application of the PMMA bone cement. In addition, overpressurization of the PMMA bone cement should be avoided during the insertion of the PMMA bone cement and implant in order to minimize the occurrence of pulmonary embolism.

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

c. Device volatility and flammability and electrocautery devices: The operating room should be adequately ventilated to eliminate monomer vapors. Ignition of monomer vapors caused by the use of electrocautery devices in surgical sites near freshly implanted bone cement has been reported.

d. Irritation of the respiratory tract, eyes, and the liver: Caution should be exercised during the mixing of the liquid and powder components of the PMMA bone cement to prevent excessive exposure to the concentrated vapors of liquid monomer, which may produce irritation of the respiratory tract, eyes, and possibly the liver. Personnel wearing contact lenses should not mix PMMA bone cement or be near the mixing of the PMMA bone cement.

3. Precautions

a. Contact dermatitis: The liquid monomer has caused contact dermatitis in those handling and mixing PMMA bone cement. Strict adherence to the instructions for mixing the powder and liquid components may reduce the incidence of contact dermatitis.

b. Hypersensitivity reactions: The liquid component of PMMA bone cement is a powerful lipid solvent. It should not contact rubber or latex gloves. Double gloving and strict adherence to the mixing instructions may diminish the possibility of hypersensitivity reactions. The mixed PMMA bone cement should not contact the gloved hand until the cement has acquired the consistency of dough, about one to two minutes after mixing.

c. Inadequate post-operative fixation: Inadequate fixation or unanticipated post-operative events may affect the PMMA bone cement-bone interface and lead to micro-motion of cement against the bone surface. A fibrous tissue layer may develop between the PMMA bone cement and the bone that may cause loosening of the prosthesis. Thus, continued, periodic follow-up is advised for all patients.

d. Exothermic reaction: Polymerization of the PMMA bone cement is an exothermic reaction that occurs while the PMMA bone cement is hardening *in situ*. The released heat may damage bone or other tissue adjacent to the implant.

e. Extrusion: Extrusion of the PMMA bone cement beyond the region of its intended application may occur resulting in the following complications: hematuria; dysuria; bladder fistula; delayed sciatic nerve entrapment from extrusion of the bone cement beyond the region of its intended application; local neuropathy; local vascular erosion and occlusion; and intestinal obstruction because of adhesions and stricture of the ileum from the heat released during the exothermic polymerization.

f. Use in pregnant women and children: The safety and effectiveness of the PMMA bone cement in pregnant women and in children is not established.

g. Expiration dating: PMMA bone cement should not be used after the expiration date because the effectiveness of the device may be compromised.

h. Disposal: Because of the volatility and flammability of the liquid monomer of the PMMA bone cement, the liquid monomer should be evaporated in a well-ventilated hood or absorbed by an inert material and transferred into a suitable container (one that does not react with the PMMA bone cement) for disposal.

4. Adverse Events

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

b. The most frequent adverse reactions associated with the use of PMMA bone cement are transitory decreased blood pressure; elevated serum gamma-glutamyl-transpeptidase (GGTP) up to 10 days postoperation; thrombophlebitis; hemorrhage and hematoma; pain and/or loss of function; loosening or displacement of the prosthesis; superficial or deep wound infection; trochanteric bursitis; short-term cardiac conduction irregularities; heterotopic new bone formation; and trochanteric separation.

c. Other potential adverse events associated with the use of PMMA bone cement include allergic pyrexia; hematuria; dysuria; bladder fistula; and delayed sciatic nerve entrapment from extrusion of the bone cement beyond the region of its intended application; local neuropathy; local vascular erosion and occlusion; intestinal obstruction because of adhesions and stricture of the ileum from the heat released during the exothermic polymerization.

FDA's decision to reclassify PMMA bone cement is based on the administrative record which consists of the reclassification petition, the transcript and minutes of the April 28, 1998 Panel meeting, the Panel member's individual data sheets, and all other information identified in this letter. FDA notes that the clinical studies and safety information contained in the petition and identified by FDA constitute valid scientific evidence (21 CFR 860.7 (c )(2)). FDA has determined that the PMMA bone cement 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 as described and identified herein can be reclassified from class III into class II with the establishment of special controls. FDA believes that class II, with the implementation of the special controls identified above, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the PMMA bone cement.

Based on the available information, FDA has identified the following risks to health associated with the PMMA bone cement: hypotension; hypoxaemia; cardiac arrhythmia; myocardial infarctions; cardiac arrest; pulmonary embolism; bronchspasm; cerebrovascular accident; infection; adverse tissue reaction; pain and/or loss of function; loosening or displacement of the

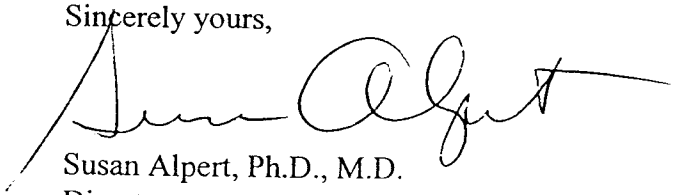
prosthesis; ignition of monomer vapor with electrocautery near non-cured cement; thrombophlebitis; hemorrhage and hematoma; elevated serum(GGTP) up to 10 days post-operation; allergic pyrexia; trochanteric bursitis; trochanteric separation; heterotopic new bone formation; and bone cement extrusion complications due to extrusion beyond the implant site, including hematuria, dysuria, and bladder fistula; local neuropathy; local vascular erosion and occlusion; and intestinal obstruction. In addition, FDA has identified the following user risks to health associated with handling of PMMA bone cement: hypersensitivity; contact dermatitis; and irritation of the respiratory tract, eyes, and possibly the liver. FDA notes that the incidences of the above risks to health were reduced when the implantation procedure was performed by adequately trained surgeons on properly selected patients.

Therefore, FDA is reclassifying the PMMA bone cement 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, and substantially equivalent devices of this generic type of device into class II. The device is subject to all the general control sections of the act, in addition to the special controls FDA identified under section 513(a)(1)(B) of the act (21 U.S.C. 360c(a)(1)(B)) promulgated under section 514 of the act (21 U.S.C. 360d); namely, FDA recognized consensus standards, FDA guidance documents, and labeling restrictions. Thus, pursuant to section 510(k) of the act, persons who intend to market this device must submit to FDA a premarket notification submission containing information on PMMA bone cement they intend to market prior to marketing the device.

A notice announcing this reclassification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

If you have any questions concerning this reclassification order, please contact Mr. Hany W. Demian at (301) 594-2036 extension 184. Please convey this information to your membership. Thank you for your cooperation throughout the reclassification process.

Sincerely yours,



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