



AMERICAN ACADEMY OF  
ORTHOPAEDIC SURGEONS

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ORTHOPAEDIC SURGEONS

317 Massachusetts Avenue NE  
Suite 100  
Washington, D.C. 20002-5701

P. 202.546.4430  
F. 202.546.5051

[www.aaos.org/dc](http://www.aaos.org/dc)

October 9, 2007

Andrew C. von Eschenbach, M.D.  
FDA Commissioner  
Division of Dockets Management (HFA-305)  
Food and Drug Administration (FDA)  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Dear Dr. von Eschenbach:

The American Academy of Orthopaedic Surgeons (AAOS/Academy), representing over 17,000 Board certified orthopaedic surgeons, welcome the opportunity to comment on the Food and Drug Administration's Draft Guidance on the Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage [Docket 2007D-0249]. We will provide both general and specific comments on this knee cartilage guidance document.

#### **Guidance Document Development**

The Academy thanks the FDA for the development and dissemination of this cartilage guidance document. The AAOS has commented repeatedly over the last few years on the lack of published guidance documents following the creation of the Medical Device User Fee Act (MDUFMA) of 2002 performance goals. The MDUFMA demanded progressively challenging performance goals for the review of pre-market approval applications, biological license applications, and 510(k) submissions. Prior to the passage of MDUFMA in 2002, the timelines for meeting performance criteria were more discretionary. In order to meet the performance goal timelines, priorities were shifted with fewer resources devoted to guidance document development. Thus, the diminished production of the Center for Devices and Radiological Health (CDRH) guidance documents was an unintended consequence of the MDUFMA of 2002.

The AAOS is encouraged that the structure of the 2007 device user fees and review goals in the Food and Drug Administration Amendments Act of 2007 (FDAAA) provide for more stable operating procedures. The new fee structure and performance goals should provide additional FDA resources for guidance document development.

The Academy acknowledges the success of the utilization and development of FDA guidance documents. These documents assist in predictability and transparency for manufacturers in the development of pre-market device and notification submissions, as well as expediting the review process. Manufacturers often cite receiving different interpretations of product reviews. Guidance documents assist in the standardization of FDA policy and interpretation. Additionally, guidance documents are often used as special control documents to support a downclassification. The AAOS stands ready to assist the FDA in revising and creating guidance documents to address critically important, clinical information.

Therefore, the Academy is pleased that the knee cartilage guidance document was published for review and comment. The document has been developed with thoughtful consideration, and the AAOS finds much of it to be reasonable and clinically relevant. We thank you for your efforts toward transparency and collaboration with interested stakeholders.

### **Consensus Standards Development**

While not statutorily mandated to do so, AAOS acknowledges that the Center for Biologics, Evaluation and Research's (CBER) involvement in tissue standards development is commendable and beneficial for both the national and international biological industry. We thank the FDA for its leadership on global harmonization task forces and the advances in standardization accomplished over the past few years.

In the 2005 AAOS position statement on *Consensus Standards for Medical Devices*,<sup>1</sup> the AAOS states that its fellows must provide assistance in the development of appropriate standards for emerging orthopaedic biological products. Members of the AAOS Biological Implants Committee participate in the development of the American Society for Testing and Materials International (ASTMi) biological consensus standards. It is the belief of the AAOS that standardization of test methods, characterization, terminology, specifications, practices, guides, and classifications of biological products will benefit the national and international practice of medicine.

### **Sham-controlled Studies and Second-look Histology**

Of particular concern is the inclusion of sham-controlled surgical studies in this guidance document. Most Institutional Review Boards (IRBs) or ethics committees will not allow a study to be conducted with this protocol. Furthermore, even if an IRB permitted a sham-controlled surgical study, patient enrollment in the study would not occur in numbers to provide any statistical significance. With the use of the Internet, patients seek information on the availability of clinical trials and opt out of trials in which the cohort to which they are assigned does not provide them with their choice of treatment.

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<sup>1</sup> American Academy of Orthopaedic Surgeons, Consensus Standards for Medical Devices, Sept. 2005, <http://www.aaos.org/about/papers/position/1169.asp>.

In the U.S., sham surgical trials are not feasible or ethical, except in very rare circumstances. If this provision is incorporated into final version of the cartilage guidance, knee cartilage clinical studies will largely be conducted in the European Union.

Likewise, second-look arthroscopies are of the utmost concern to the AAOS. IRBs and ethics committees will not allow the conduct of this protocol. Furthermore, few patients would consent for such a procedure, making patient enrollment problematic. If a surgeon provided a second arthroscopy, the patient would generally only consent to the procedure if that patient were experiencing some adverse effects. Therefore, the cohort of patients experiencing two arthroscopies would have a statistical bias towards a problematic outcome. The Academy strongly encourages the FDA to revise these sections to reflect generally accepted practices of the conduct of clinical trials within the U.S.

### **Device Component**

The fourth reference cited as the “Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA” does not address aseptic processing of human tissue-based or cellular products. Since most tissue manufacturers use aseptic processing, a reference to a guidance document that addresses this issue will assist manufacturers in determining the appropriate specifications.

### **Control Group**

The AAOS notes that comparing treatment effects across a range of investigational product dosages is not an appropriate study design. Similarly, comparing treatment effects among a group of alternative products and procedures is not feasible. We recommend that one comparator arm of a study be used in almost all instances and that the FDA remain flexible in its assessment of a reasonable control group.

### **Study Endpoints**

The Academy recommends that the histological evaluation at both short and long term follow-up should assess matrix zonal organization, cell density, cell morphology, type I or type II collagen concentration, and inflammatory response. We recommend that the FDA delete Aggrecan concentration, size, composition, Dermatan sulfate proteoglycan concentration, and noncollagenous protein concentrations (fibronectin, tenascin) in the histological evaluation section.

Furthermore, it will not be feasible to require two MRI studies. In keeping with the FDA’s least burdensome principles, if investigators chose to include a MRI study, one such study should be sufficient.

### **Investigational Product Administration**

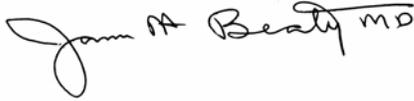
The AAOS agrees that documentation of both surgical technique and plans for post-operative management of care is of paramount importance during the course of a clinical trial. However, surgeons may use different anesthesia, require different rehabilitation methods, and use different pain medications depending on patient allergies, tolerability, and other characteristics. Physical therapy may not be readily available to some patients or access may be delayed. While investigators will attempt to standardize protocols,

inevitably some differences in treatment will occur. The differences in administration should be documented and some flexibility in the protocol should be built into the study.

**Conclusion**

The AAOS appreciates the opportunity to comment on this critically important guidance. We look forward to working with the FDA on efforts to ensure that safe and effective medical products reach patients more quickly.

Sincerely,

A handwritten signature in black ink that reads "James H. Beaty MD". The signature is written in a cursive style with a large initial "J" and "B".

James H. Beaty, MD  
AAOS President

cc: Richard McFarland, MD, PhD  
Aric Kaiser