Present:
Scientific Orthopaedic Community   Government   Industry
AAOS, ASTM, ORS   FDA, CMS, NIAMS   OSMA


Members reviewed and approved the summation report from the February 2003 meeting of the Orthopaedic Device Forum. New members and guests were introduced to the Forum. All participants disclosed conflicts of interests.

Discussion with Mark Kramer, Director of FDA’s Office of Combination Products

The Office of Combination Products was established on December 24, 2002 as part of the Medical Device User Fee Modernization Act (MDUFMA) of 2002.

Definition of Combination Products- (21 CFR 3.2 (e)):

- A product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed as a single entity, or
- Two or more separate products packaged together (ex. drug and device products), or
- A product packaged separately but intended for use only with an approved, individually specified product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product, the labeling of the approved product would need to be changed e.g. to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.
- Similar to 3rd bullet description but both products are investigational.

Products are assigned to a lead center based on the “primary mode of action” which has never been statutorily defined. However, FDA will open a docket for
public comment to collect and assess proposed definitions on primary mode of action for combination products.

The Office of Combination Products must ensure a timely and effective premarket review by overseeing the coordination of reviews of more than one agency Center currently averaging a 36-day cycle rather than the maximum period of 60 days. Additionally, they must provide consistent and appropriate post-market regulation, resolve disputes, review and update guidance agreements and practices, and report to Congress annually.

The Office of Combination Products is currently revising the 1991 Intercenter agreements. While the basic tenets of the agreements are still appropriate, the examples need updating. Generally, the FDA encourages early meetings with industry. Key early meetings help the FDA determine the mode of action and provide a regulatory framework and direction for industry.

Office of Combination Products website: http://www.fda.gov/oc/combination/

Discussion:
Members conferred about the recent transfer of bone morphogenetic proteins (BMP) to the Center for Drugs, Evaluation and Research. The FDA believes that the new regulatory oversight is appropriate due to the commonalities that BMP has to pharmaceuticals. To date, BMP is usually incorporated with other components such as a spinal cage and a sponge, and therefore is reviewed as a combination product. The CDER consistently meets their review time frames.

Government officials stated that combination products are assessed by their primary mode of action. A manufacturer must provide their rationale for the primary mode of action in the drug, device, biologic, or combination product application. Generally, the FDA agrees with the company’s mode of action assessment. While the Office of Combination Products does not review products, they are mandated to provide timely assignment of all combination products.

Centers for Devices and Radiological Health (CDRH) Fellows Program
The CDRH Medical Device Fellowship Program was established to increase collaborations between the CDRH and the scientific community. The CDRH is seeking a senior level scientist who can address the adequacy or appropriateness of animal testing, mechanical testing, and materials characterization in assessing issues related to spinal devices for novel products. Projects may include the assessment of the potential of the generation of particles due to wear or breakdown; the impact of generated particles on neural structures, blood vessels, bone
and surrounding tissues; the impact of viscoelastic materials used in spinal stabilization; and the impact of motion on metallic or non-metallic implants. In addition, the scientist may assess the minimum loading and performance levels for various spinal levels.

This senior expert would provide support to FDA in its public health mission by reviewing test protocols and test results provided to FDA. The scientist would be able to make a unique contribution by assisting in the development of review policy and guidance in this area of developing new technology. [http://www.fda.gov/cdrh/mdfp/](http://www.fda.gov/cdrh/mdfp/)

**Standards**

The American Society of Testing and Materials (ASTM) recently held a workshop on the cleanliness of implants. A formal proposal for the development of a publication on the findings of the workshop is under development.

Future ASTM symposia include biocompatibility and cell signaling. While the ASTM has ventured into the international arena during the last year, the tissue engineering division, Tissue Engineered Medical Products (TEMPS) appears to be leading the international efforts in this class of products.

Many members of the national standards community contend that the International Standards Organization (ISO) is not as rigorous a process as the ASTM process. Moreover, since majority voting rules in the ISO organization, ISO standards are not as stringent and universally esteemed as in the ASTM process, where all negative votes must be resolved. Forum members suggested utilizing the American Academy of Orthopaedic Surgeons (AAOS) International President’s breakfast as a venue to target members of the international community. Currently, several European countries vote as a block and consistently thwart U.S. efforts to ensure the most rigorous medical/surgical standards.

**Hip Guidance**

Members of the Forum hip guidance subcommittee will continue to develop the clinical trial design for hip replacement systems. A conference call is scheduled for early September 2003 and a final draft is expected prior to the November Forum meeting. OSMA representatives are compiling statistical analyses from published data on products previously cleared for marketing. Benchmarks will be determined for device related complications, pre- vs. post-operative Harris Hip Score ≥15 points and ≥80 points at endpoint, revision rate of device, and radiographic failure rate.
Biological Issues
The Forum has initiated a subcommittee to address emerging biological issues. Surgeons anticipate that a significant percentage of the future orthopaedic treatments will have a biological component.

Osteoinductivity standard
A subcommittee of the TEMPS of the ASTM is currently drafting a standard to test for the osteoinductivity of demineralized bone substitutes. Definitions must be developed and are not universally accepted currently. Scientists and industry are typically involved in the standard writing process. Surgeon input in the development of this standard is imperative to ensure an acceptable endpoint.

Some members contend that the mouse works as a model for ensuring osteoinductivity when tested intra-muscularly. Additionally, the rat model when applied to the leg is appropriate inter-muscularly. Ideally, researchers are attempting to identify multiple animal models. Researchers noted that human models produce bone more slowly than animal models. In 1991, Drs. Boyan and Heckman identified the mid-part of the radial diaphysis of dogs as a non-union model (JBJS 1991 June, 73(5): 750-64).

Proposed Definitions:

Osteoinductivity: The ability to induce bone in a site that would otherwise not grow bone.

Osteogenic: Development and formation of bone.

Members of the TEMPS subcommittees are coordinating a meeting in San Francisco during AAOS Annual Meeting in March 2004. ASTM conducts virtual meetings online with document sharing capabilities.

BMPs
Two bone morphogenic protein (BMP) products have been approved by the FDA for orthopaedic use. AAOS members of the Forum noted that off-label use of BMP products is increasing. However, the cost of the products is still quite prohibitive. Industry estimates that BMPs require an investment of nearly 500 million dollars to market a product in the U.S.

Manufacturers stated that the Center for Medicare & Medicaid Services (CMS) pays for devices in investigational device exemption (IDE) clinical trials through a payment that only allows reimbursement for the cost for conducting research.
Forum members discussed a possible downclassification for BMPs; however, the FDA recently changed the regulatory oversight of BMPs to the Center for Drugs, Evaluation and Research (CDER). Members stated that demineralized bone matrix has been marketed without specificity on the indication for use. Participants inquired if there were lessons in that type of pathway for BMP products. Industry noted that case series are valid scientific evidence. Nonetheless, the product sponsor must provide the evidence of safety and effectiveness to the FDA. Physicians responded that gathering data from charts requires an independent review board (IRB) approval. Researchers suggested that they encourage a physician or researcher to devise a concept and provide information to enable a company to proceed with a clinical trial. Industry noted that they are aware that BMPs are being used in other parts of the anatomy than the spine. The AAOS Committee on Biological Implants will address educational efforts for AAOS Fellows on the off-label use of BMPs.

http://www.fda.gov/cber/transfer/transfer.htm

_Demineralized Bone Products_

In March 2002, known manufacturers of products containing demineralized bone (DMB) plus additives that were not storage, preservation or sterilization agents were sent letters by the Centers for Devices and Radiological Health (CDRH) informing them that this class of products would need to file premarket notification.

Apparently, some DMB manufacturers are finding the requests for additional information related to disease transmission and sterilization (viral load before and after processing and/or inactivation) challenging. Some members inquired if there was any documentation of viral transmission problems. Since standards for tissue banks are currently voluntary, there is wide variability in the processing methods, which may impact viral load levels.

Nonetheless, researchers contend that too much processing of DMB products will render them ineffective and not biologically active. Since most of these products are using the Calcium Salt Bone Void Fillers as predicate devices and following FDA’s Class II Special Controls Guidance Document: Resorbable Calcium Salt Bone Void Filler Device as a special control to claim equivalence, researchers noted that calcium salts are not biologically active materials and therefore viral inactivation would not affect the inert substance. Researchers suggested that a human DNA test might be a better frame of reference for companies to use. FDA noted that for issues related to disease transmission and sterilization of products containing human or animal components that manufacturers have been referred to the Guidance for the Preparation of a
Premarket Notification Application for a Surgical Mesh and the Class II Special Controls Guidance Document: Human Dura Mater; Draft Guidance for Industry and FDA.

FDA Update

A pilot program for global harmonization exists however, the Orthopaedic Surgical Manufacturers Association (OSMA) has not shown much interest in it. The Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED) document is being proposed to adopt global harmonization principles. Nonetheless, industry finds the 510(k) approval process to be predictable and efficient in this country and objects to increased regulatory hurdles.

Top 9 PMA Submission Problems

The Division of General Restorative and Neurological Devices (DGRND) of the Center for Devices and Radiological Health (CDRH)/FDA identified the following common submission problems in clinical trial reporting.

1. Inadequate information about patient accountability
   100 patients may have been enrolled in the trial originally but only 75 were seen in follow-up at later time points. What is known about the missing patients? At each time point where data are reported, which patients are included and which are excluded? What impact does the missing data have on the trial results?

2. Reporting percentages
   If 25% of the patients are noted to have a complication in the trial, is that 25% of the original 100, or 25% of the 75 patients who were seen for longer-term follow-up? Include an explanation of how percentages are determined or provide them with numerators and denominators.

3. Safety information
   A. Sometimes the way in which events are defined does not allow for making a useful comparison to the control group. For example, if 3 patients had each of the following events in the treatment group: abscess, sepsis, wound dehiscence, purulent drainage, and no patient had such an event in the control group, comparing the events in the two groups separately for each event may not illuminate a potential important safety issue.
B. Specific information on safety event, especially serious safety events, such as duration, method of treatment, and extent of resolution or sequelae, may be very important.

4. Clinical trial protocol
A copy of the clinical trial protocol according to which the study was conducted should be included. If the protocol was modified after the outset of the study, the “change history” of the protocol is something often requested by the FDA. If protocols are modified, addressing what (if any) is the impact on the analysis of the data and/or clinical interpretation is helpful.

5. An analysis of the trial according to the protocol should be included, even for those cases in which sponsors wish to present alternative or additional analyses.

6. The impact of baseline values and/or demographic differences of the study results are not always discussed in the submission, and may lead to questions in the review process.

7. Sometimes data are submitted without a summary and interpretation of the results. It is important to include a discussion of why the information submitted supports safety and effectiveness of the device for the indication or intended use.

8. If the methods used to compile a table are not clear, the submission may be confusing. For example, the definitions of terms used in a table may be ambiguous and on occasion the same terms are used elsewhere in the submission with a different meaning.

9. A poorly organized submission, with inaccurate table of contents, without proper pagination (e.g.- repeat page numbers, sections without page numbers) and with tables inaccurately identified, can prolong the review. Although this issue would not lead to a major deficiency, it can make the submission review unnecessarily challenging.

**FDA Educational Program**
The FDA is sponsoring an educational forum on joint arthroplasty for FDA employees in September 2003 (Delayed possibly January 2004). The half-day session will feature sessions from prominent orthopaedic surgeons on: assessing joint arthroplasty outcome, the impact of evolving technologies and techniques on device regulation, alternative bearing surfaces, biological concerns and a clinical practicum.
NIAMS Update
The NIH Consensus Conference on Primary Total Knee Replacement will be held in December 8-10, 2003. E. Anthony Rankin, MD, will chair the non-Federal panel. They will address the following questions:

1. What are the current indications and outcomes for primary total knee replacement?
2. How do specific characteristics of the patient, material, design of the prosthesis, and surgical factors affect the short-term and long-term outcomes of primary total knee replacement?
3. Are there important perioperative interventions that influence outcomes?
4. What are the indications, approaches, and outcomes for revision total knee replacement and salvage procedures?
5. What factors explain disparities in the utilization of total knee replacement in different populations?
6. What are the directions for future research?

http://totalknee.iqsolutions.com/

NIAMS has accomplished the doubling of budgets over the last five years, but is anticipating smaller increases in future years. In conjunction with annual Capitol Hill visits, AAOS is seeking to interact with orthopaedic patient advocacy groups. The AAOS Research committee anticipates that the 2004 Capitol Hill visits will be attended by physicians and their patients to better interact with Congressional leaders. The goal of physician/patient Capitol Hill visits is to provide a more cogent message and to ultimately increase dollars for research.

OSMA Update
- OSMA submitted a reclassification petition for mobile bearing knees to the CDRH.
- OSMA prepared a letter to the CDRH regarding the historical interpretation of the term “pathological fracture” in the pre-market approval of bone cement. Members of the scientific community contend that an osteoporotic fracture of the spine should be considered a pathological fracture.
- Currently, there is a movement in the European Union to increase the classification of hip and knee implants. The classification would be changed from IIB to III. Reportedly, this is in response to the Sulzer Inter-Op recall in 2001. Forum members noted that the company
changed the manufacturing process after their FDA submission; therefore an increase in product classification would not have caught the manufacturing deviations. Manufacturers would experience a restraint of trade if devices were up-classified. If the movement is successful, some companies may have products taken off of the market.

- OSMA will discuss the cleanliness of implants at their fall 2003 meeting.
- OSMA is drafting a demineralized bone guidance document.

**FDA Guidance Documents**
The Forum has convened a subcommittee to review the following CDRH guidance documents:

- Guidance Document for Industry and CDRH staff for the Preparation of Investigational Device Exemptions and Premarket Approval Applications for Bone Growth Stimulator Devices; Draft  

- Reviewers Guidance Checklist for Intramedullary Rods  

- Reviewers Guidance Checklist for Orthopedic External Fixation Devices  

- Guidance Document for Testing Non-Articulating, 'Mechanically Locked', Modular Implant Components  

- Guidance Document For The Preparation of Premarket Notification For Ceramic Ball Hip Systems  

- Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone Or Bone Cement  

- Guidance Document for the Preparation of IDE and PMA Applications for Intra-Articular Prosthetic Knee Ligament Devices  

Members of the Forum reviewed the FDA’s guidance document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone Or Bone
Cement [http://www.fda.gov/cdrh/ode/827.pdf](http://www.fda.gov/cdrh/ode/827.pdf). After a discussion referencing the evolution of porous coated technologies, the subcommittee recommended no changes to the guidance. The subcommittee will assess the remaining six guidances over the next year.

**CMS Update**
The Centers for Medicare & Medicaid Services issued a national coverage analysis (NCA) decision on arthroscopy for the osteoarthritic knee (#CAG-00167N) [http://cms.hhs.gov/ncdr/memo.asp?id=7](http://cms.hhs.gov/ncdr/memo.asp?id=7)

**CMS Decision Summary:**
CMS has determined that the evidence is adequate to conclude that arthroscopic lavage alone is not reasonable and necessary for patients with osteoarthritis of the knee; therefore, CMS intends to issue a national non-coverage determination.

CMS has also determined that the evidence is adequate to conclude that arthroscopic debridement is not reasonable and necessary for patients presenting with knee pain only or with severe osteoarthritis (Outerbridge classification III or IV); therefore, CMS intends to issue a national non-coverage determination. All other indications of debridement for patients with osteoarthritis of the knee will remain at contractor discretion.

Forum members discussed the recent CMS national non-coverage decision and are concerned about future local coverage decisions on lavage and debridement for osteoarthritis of the knee.

**Registry**
The AAOS Joint Registry Oversight Panel initiated a contract with a company to proceed with the development of pilot project for a national joint registry. Additionally, members of the oversight panel are meeting with representatives from OSMA to coordinate information contained in bar codes for orthopaedic devices. Companies generally provide information incorporating the company name, catalog number, and lot number.
**AAOS Committee Update**

**Biological Implants**

Three members of the AAOS Biological Implant committee are moderating symposia at the 2004 AAOS Annual Meeting. Symposia include: Commonly used Enhancers of Bone Healing, The Role of Pharmacological Agents in Fracture Healing and Implant Fixation, and Cell Based Therapies in Bone and Cartilage Repair. The committee also plans two scientific exhibits: one on xenotransplantation and a followup to last year’s allograft safety exhibit. The Biological Implants committee will host a retrospective exhibit of Dr. Marshall Urist’s contributions to medicine at the 2004 AAOS meeting in San Francisco, CA.

**Biomedical Engineering**

The Biomedical Engineering committee is working on a survey to assess the recommended time periods for follow-up care on total joint replacement patients. Staff will conduct a literature search and an advisory statement will be drafted for the AAOS Fellowship.

**Council on Research**

The AAOS Council on Research task force is investigating the feasibility of providing rating information on new technologies. Kyphoplasty and vertebroplasty are nominated topics for assessment.

**Next Agenda Items**

2 possible class action suits for polyethylene failure