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To: 'FDADockets@oc.fda.gov'
Subject: Docket No. 02N-0445

Thanks!

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January 24, 2003

Mark B. McClellan, M.D., Ph.D.
Commissioner
Food and Drug Administration
5630 Fishers Lane
Rockville, Maryland 20852

Dear Dr. McClellan:

The American Academy of Orthopaedic Surgeons (AAOS/Academy), representing over 19,000 Board certified orthopaedic surgeons, welcomes the opportunity to comment on the Food and Drug Administration's (FDA) Regulation of Combination Products: Notice of Public Hearing; Request for Comments (Published in the Federal Register on October 28, 2002 [Docket No. 02N-0445]). Dr. Barbara D. Boyan, Professor and Deputy Director for Research for the Georgia Tech/Emory Center for the Engineering of Living Tissues, presented for the AAOS during the November 25, 2002 meeting.

As technology progresses, the proliferation of combination products will increase significantly. Therefore, it is appropriate that the FDA established an Office of Combination Products as mandated in the Medical Device User Fee and Modernization Act of 2002 (MDUFA) to oversee the coordination of regulatory efforts on such products. The Academy appreciates this opportunity to reiterate our perspectives on the regulation of combination products. The AAOS will limit its comments to the following concerns:

- Combination products will provide unique regulatory challenges for the FDA;
- The FDA should develop a team approach for the review of combination products;
- The FDA should place greater emphasis on safety rather than effectiveness for orthopaedic products;
- Global harmonization efforts should be considered during the regulatory framework development of combination products;
- The FDA should consider creating an Advisory Panel for combination products;
- The definitions of adverse events are too broad and inclusive;

- The FDA must present a consistent and predictable regulatory approach.

Combination products will provide unique regulatory challenges for the FDA

Combination products, particularly device-biologic combinations, provide unique challenges for the FDA in assessing an appropriate regulatory approach. The Academy urges a comprehensive review of combination products that will assess the safety and effectiveness of the product in a reasonable amount of time. Additionally, the AAOS requests that the FDA coordinate their reviews with the Centers for Medicare and Medicaid Services (CMS) to ensure that new therapies will be available to patients in an expedited time frame.

The FDA should develop a team approach for the review of combination products

The Academy suggests that the FDA adopt multidisciplinary coordination in the review of combination products for orthopaedics, regardless of whether the review teams reside within the FDA or are facilitated by a third party review. The teams should be odd in number and at a minimum be comprised of a material scientist, a biologist, a clinician, and an engineer. Additionally, the product sponsor should be provided an opportunity to share supplemental information with the review team.

The FDA should place greater emphasis on safety rather than effectiveness for orthopaedic products

The Academy insists that patient safety initiatives are of paramount importance and that safety measures should not be compromised. Moreover, the effectiveness of orthopaedic products may not be readily apparent for ten to twenty years. While the FDA is mandated to ensure the safety and effectiveness of drugs, biologics, devices, and combinations thereof, the Academy believes that a greater emphasis should be placed on the safety potential of the product rather than the effectiveness of such a product.

In accordance with the Federal Food, Drug, and Cosmetic Act, the FDA assigns premarket review to a Center depending on the interpretation of mode of action of the product. Clearly, each product must be assessed on a case-by-case basis. However, there is a legal precedent for FDA to treat like products accordingly. The Academy suggests the following definitions to define mode of action for orthopaedic products:

Osteogenesis: The cellular elements, either from the host or from the tissue-engineered product, which survive transplantation and synthesize new bone at the recipient site.

Osteoinduction: New bone is realized through the active recruitment of host mesenchymal stem cells from the surrounding tissue, which differentiate into bone-forming osteoblasts or form bone by endochondral ossification. This is facilitated by the presence of growth factors, principally bone morphogenetic proteins.

Osteoconduction: The facilitation of blood vessel incursion and new bone formation into a defined trellis structure.

Global harmonization efforts should be considered during the regulatory framework development of combination products

In 1997, the Food and Drug Administration Modernization Act (FDAMA) mandated that the Secretary of Health and Human Services (HHS) should investigate efforts, participate in meetings, and develop a plan to reduce the burden of regulation and harmonize regulatory requirements. Additionally, the Global Harmonization Task Force (GHTF) formed in 1992, attempts to reduce regulatory differences between countries and encourages performance measures.

Therefore, it is imperative for the FDA to be deliberate in developing a broader scheme of global harmonization efforts. The Academy suggests that the Center for Biologics, Evaluation, and Research (CBER) should actively participate in the standards development process with the American Society for Testing and Materials International (ASTM). Several standards for tissue-engineering products have been finalized through the Tissue Engineered Medical Products (TEMPS) division.

Domestic and international consensus standards address aspects of safety and/or effectiveness relevant to medical devices. As many tissue-engineered medical products will have components of both devices and biologics, it is appropriate to develop and utilize standards for the biological, as well as the device components.

The FDA should consider creating an Advisory Panel for combination products

Tissue engineered medical products will require a unique regulatory assessment unlike drug or biological product reviews. The FDA should consider the establishment of a FDA Advisory Panel with expertise in biologics and devices. Biologists must work cooperatively with engineers during product reviews to ensure a comprehensive and expeditious review.

The AAOS suggests that the method of use of the product should be given sufficient consideration when assigning the primary jurisdiction to a review center. The primary mode of action of the product is an equally important consideration.

The definitions of adverse events are too broad and inclusive

Historically, the FDA's definitions of the term "adverse event" have been too broad and all encompassing. Some patients have co-morbid conditions that contribute to post-operative complications. These events should be assessed on case-by-case basis. The FDA should consider consulting with experienced clinicians when defining the term "adverse event" for combination products.

The AAOS encourages the finalization of the Good Tissue Practice and the Donor Suitability proposed rules. Adverse event reporting will be mandated for biological products with the finalization of those regulations. Additionally, the Academy recommends that the FDA centralize reporting requirements for drugs, devices, biologics, and combination products. Users will not be able to readily ascertain what the regulatory class of the product is, particularly with combination products. Moreover, the FDA should redesign their adverse event data collection system to be interactive and provide the public with usable patient safety information.

Finally, the AAOS is supportive of patient safety efforts and has a long history of producing and implementing programs to prevent medical errors in orthopaedics, such as wrong site surgery. The Academy supported legislation introduced into the 106th and 107th Congress that encouraged a non-punitive approach for reporting that ensures appropriate confidentiality and peer review protections. The AAOS will continue to support similar legislative efforts in the 108th Congress.

The FDA must present a consistent and predictable regulatory approach

The FDA must develop a credible, predictable, and transparent regulatory framework for combination products. The Academy encourages the FDA to work with sponsors and maintain a consistent regulatory approach. During the past year, two tissue-engineering companies have ceased operations, one of which cited regulatory issues as a mitigating factor. Therefore, the FDA must provide a consistent regulatory approach for combination products that will give assurances to companies with products in development.

Conclusion

In summary, we urge the FDA to develop a regulatory approach for combination products in an accountable and consistent manner. The Academy shares the intent of the FDA to ensure safe, reliable combination products for patients. Again, we were pleased to present our perspectives at the open public meeting and welcome this opportunity to comment also. The AAOS appreciates the FDA's attempt to seek views on regulatory measures for combination products in an open and cooperative fashion and to seek the input of professional medical associations.

Sincerely,

William W. Tipton, Jr., MD
Executive Vice President