

August 20, 2004

Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner
Food and Drug Administration (FDA)
5630 Fishers Lane
Rockville, Maryland 20852

Re: **Docket No. 2004N-0194**

Dear Dr. Crawford:

The American Academy of Orthopaedic Surgeons (AAOS/Academy), representing over 19,000 Board certified orthopaedic surgeons, is pleased to express our support for the proposed rule on the Definition of Primary Mode of Action of a Combination Product [Docket No. 2004N-0194 as published in the Federal Register on Friday, May 7, 2004]. This proposed rule aims to furnish manufacturers of combination products with a transparent and predictable process by which combination products are assigned to their proper FDA center for premarket review and subsequent regulation.

The Academy holds patient safety as its highest priority, and supports regulation that protects and improves the public's health. The AAOS shares the concerns of the FDA in ensuring that combination products are assigned to FDA centers in a timely and consistent fashion. We remain committed to protecting consumers and our patients' safety, while at the same time encouraging that advanced medical technologies in orthopaedic device, drug, or biologic product combinations come to the marketplace through a streamlined, timely regulatory review.

We agree with FDA's proposed definition of "primary mode of action" (PMOA) as the "single mode of action that provides the most important therapeutic action of the combination product," and concur that assignment of a combination product to an agency center is most aptly derived from the product's PMOA.

However, in certain combination products, the primary mode of action may be difficult to readily identify. The Academy praises the FDA for the simplicity and consistency of the proposed assignment algorithm. The Academy notes that the FDA's second algorithmic step, assigning combination products to the center that regulates other products with similar questions of safety and effectiveness, requires the Office of Combination Products to take into consideration the manufacturer's statements on the safety and effectiveness features of the combination product. The AAOS calls attention to the value in using a multidisciplinary approach in categorizing such features. We suggest that review procedures draw upon the expertise of staff from the appropriate FDA centers in order to facilitate concurrence between the centers when assigning a combination product that lacks a reasonably apparent PMOA to a lead center. We also support the FDA's consideration of the relative risks of a combination product when neither the PMOA

nor the identification of products with similar safety and effectiveness concerns can be determined.

The Academy commends the FDA for the codification of the proposed rule, as well as for addressing the unique regulatory challenges associated with combination products. In addition, the AAOS encourages future research in developing standards to characterize the biological activity of osteoinductive combination and/or biologic products. The Academy notes that such methodologies will assist clinicians in selecting appropriate products for their patients.

We look forward to collaborating with the FDA in the future to continue to safeguard the public's health through the facilitation of regulatory processes for combination as well as other medical products used in orthopaedic patients and U.S. consumers.

Thank you for your consideration in this matter.

Sincerely,

Robert W. Bucholz, MD
President