American Academy of Orthopaedic Surgeons®

AAOS American Association of Orthopaedic Surgeons®

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May 7, 2001

Bernard A. Schwetz, D.V.M., Ph.D.
Acting Principal Deputy Commissioner
Food and Drug Administration (FDA)
5630 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Schwetz:

The American Academy of Orthopaedic Surgeons (AAOS), representing over 16,000 Board certified orthopaedic surgeons, welcomes this opportunity to comment on the FDA's proposed rule: Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; (Published in the Federal Register on Monday, January 8, 2001. [Docket No. 97N-484P]).

The availability of safe allograft tissue is of paramount importance to AAOS members. Orthopaedic surgeons are advocates for their patients, as recipients of tissue, and demand that the tissue supply is safe. Academy members constitute the vast majority of users of musculoskeletal tissue. Allograft bone and soft tissue are used in various reconstructive procedures of the limbs and joints. Primarily, allograft bone is utilized in fracture healing, spine fusions and limb reconstructive procedures. Soft tissues including fascia lata, allograft tendons, menisci, fresh cartilage segments and cryopreserved osteochondral grafts, facilitate joint reconstruction. Certain surgical procedures may only be accomplished with the ready availability of safe human tissue that meet acceptable standards of tissue banking specifically outlined by guidelines of the American Association of Tissue Banks (AATB).

Musculoskeletal allografts have been safely and successfully used to address the reconstructive needs of hundreds of thousands of patients every year. While the incidence of disease transference is very low, we advocate careful donor screening, testing of donor tissue, quarantines for donor tissue, as well as using FDA licensed methods for blood test, PCR tests and RNA tests. The AAOS finds the use of allograft bone safe; no cases of disease transmission have occurred since 1993.

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The Academy greatly appreciates the efforts by the regulatory agency to provide oversight as the guidelines in the proposed rule provide further reassurances for a safe tissue supply. The Good Tissue Practice proposed rule primarily addresses issues relevant to tissue banks and processing and we are generally supportive however, AAOS continues to have some concerns about how these rules may affect the availability of allograft bone and soft tissue. The Academy will limit its comments to the following concerns:

- Tissue bank personnel should be educated on the consequences of not properly performing their duties;
- The interpretation of standard operating procedures is too subjective;
- Parameters are not outlined for good tissue practice violations;
- The definition of an adverse reaction is too broad and all encompassing;
- FDA should question a senior official at the time of inspection;
- Demineralized bone products have significantly different osteoinductive capabilities;
- The credentials of tissue bank directors are quite variable.

Tissue bank personnel should be educated on the consequences of not properly performing their duties

AAOS would like to commend FDA for their proposal to require that tissue bank personnel be educated to possible consequences of improperly performing their duties. Unacceptable tissue practices could have monumental implications in disease transmission. The Academy additionally acknowledges that record keeping on the training of tissue bank personnel is appropriate.

The interpretation of standard operating procedures is too subjective

The Academy does not believe that it is appropriate for the interpretation of standard operating procedures and validation of tissue banks to be subject to the individual regulatory inspector's judgement. The Academy suggests that a more standard approach is needed. Moreover, the variability from one inspector to another concerning the interpretation of the standards of good tissue practice may yield significantly different results. Again, the Academy suggests a more standardized approach.

Parameters are not outlined for good tissue practice violations

AAOS has concerns about how a tissue bank is cited for good tissue practice violations, issues of quarantine, recall and the closure of a tissue bank. Parameters are not outlined adequately in this proposed rule. The Academy suggests that there is ample room for interpretation by different personnel. Of additional concern is a lack of oversight or a venue of arbitration if a tissue bank is cited for alleged violations.

The definition of an adverse reaction is too broad and all encompassing

The GTP proposed rule defines an adverse reaction as "a noxious and unintended response to any human cellular or tissue-based product for which there is a reasonable possibility that the response may have been caused by the product (i.e. the relationship cannot be ruled out)". The rule further explains that this verbiage is consistent with the agency's shift in intention from adverse reaction reporting to adverse experience reporting. FDA states that probable, possible, remote or unlikely relationships would all be considered adverse reactions under the proposed definition. AAOS suggests that the agency is not consistent with their own terminology as to how an adverse event is different from an adverse experience. In any case, AAOS contends that the definition is too broad and all encompassing. A transplant recipient could experience a reaction to a substance in biological tissues even though the manufacturer followed good tissue practices.

FDA should question a senior official at the time of inspection

As currently written in the proposed rule, the FDA would be allowed to question the most responsible person available at the time of the inspection at a tissue bank facility. The rule further states that inspections would be made with or without prior notification and would ordinarily occur during regular business hours. The Academy has concerns that the inspector might question personnel who are not highly knowledgeable about the standard operating procedures of the facility, particularly if the inspector visits unannounced at times beyond the regular business hours of the establishment. The FDA should question a senior official who is well acquainted with the standard operating procedures of the tissue bank facility during regular business hours.

The agency also asserts that the FDA representative can take photographs or make videotapes. AAOS is aware that other professional societies and industry lawyers will be commenting on this particular provision in the rule, therefore we will not make a detailed statement regarding this stipulation. The Academy questions the legal competence and the scope of authority on this provision.

Demineralized bone products have significantly different osteoinductive capabilities

Of great concern to the Academy is the osteoinductive capability of demineralized bone products. Orthopaedic surgeons regularly use demineralized bone products to enhance fracture healing and to effect spine fusion. However, evolving research suggests that not all bone products have the same abilities to induce bone formation. Products may be from different lots in the same company or from different manufacturers and have dramatically different bone induction rates. Approximately 400,000 demineralized bone products are used annually.

The Academy has encouraged the development of a standard to test the osteoinductive capacity of demineralized products. We are aware that efforts continue to evolve in the development of this standard and the AAOS stands ready to work with standards organizations, such as the American Society for Testing and Materials (ASTM) to expeditiously establish this standard.

Moreover, the Academy strongly encourages the FDA to immediately solicit participation from all manufacturers of demineralized bone products to produce a minimum level of osteoinduction and the quantification of such induction. AAOS requests that this information be available on the labeling of the product to enable surgeons to make informed choices for their patients. Orthopaedic surgeons demand the highest quality products available to enable proper healing for patients. The Academy strongly urges that bone inductive capacities must be evident before such products are marketed.

The credentials of tissue bank directors are quite variable

Although not specifically addressed in this proposed rule, AAOS suggests that the parameters for the credentials of tissue bank directors are quite variable. The Academy requests that a more uniform approach may be in order. As advocates for our patients, the Academy wants to make every effort to ensure a safe tissue supply. We believe that training is of the utmost importance and we would encourage the FDA to set guidelines in this area.

Conclusion

In summary, we urge the FDA to further develop good tissue practices regulations in an accountable and understandable manner. The Academy shares the intent of the FDA to ensure a safe, reliable tissue supply for all patients.

Again, we are pleased to have this opportunity to comment on this important proposed rule, and we look forward to continuing to work with the FDA in the future. The AAOS appreciates the FDA's attempt to address good tissue practices in an open and cooperative fashion and to seek the input and guidance of professional organizations.

Sincerely,

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

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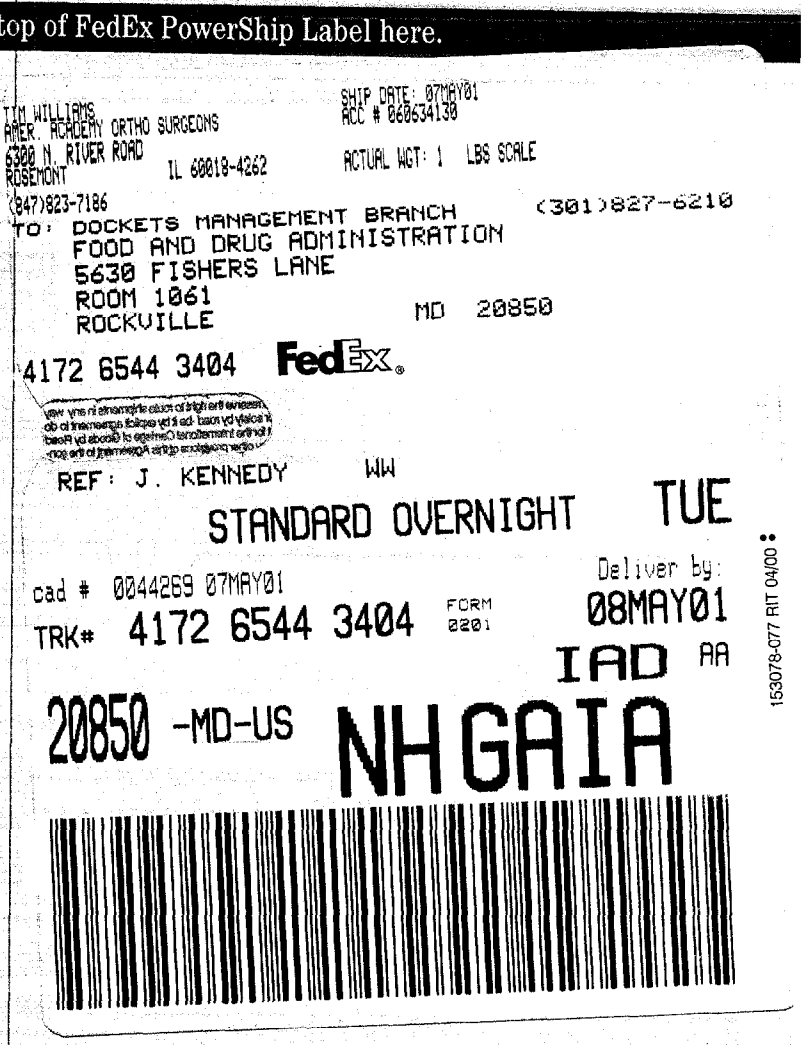

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