



American Academy of
Orthopaedic Surgeons®

AAOS

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August 20, 2004

Lester Crawford, D.V.M., Ph.D.
Acting FDA Commissioner
Food and Drug Administration (FDA)
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Dear Dr. Crawford:

The American Academy of Orthopaedic Surgeons (AAOS/Academy), representing over 19,000 Board certified orthopaedic surgeons, welcomes the opportunity to comment on possible barriers to the availability of medical devices intended to treat or diagnose diseases and conditions that affect children [Docket No. 2004-N-0254]. While the Academy appreciates the efforts of FDA personnel in ensuring that medical devices are safe and effective, pediatric orthopaedic patients are adversely affected when new technologies are unavailable as a result of excessive regulatory burdens. The Academy has grave concerns about the lack of innovative pediatric orthopaedic medical products introduced into the United States marketplace and the deleterious effects it is having on orthopaedic pediatric patient care.

Unmet Needs of the Pediatric Population

As surgeons, it is our duty to advocate for our patients who are unable to advocate for themselves. Children, by their nature, are the most vulnerable patient population. The pediatric population is woefully underserved in the availability of orthopaedic devices to treat cases of injury, deformity, or delayed limb development. Specific unmet needs of pediatric orthopaedic devices include bioabsorbable fracture fixation devices, mechanical growth plates, truly innovative spinal deformity devices that are significant improvements on the Harrington rods of the 1960's, and others. These devices are currently unavailable due to regulatory impediments. Regulatory reform is urgently needed, especially to serve this patient population.

Of the pediatric subpopulations, neonates and infants are in greatest need of innovative medical devices due to the size limitations of larger orthopaedic

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devices. Because of regulatory delays, pediatric surgeons report rampant use of off-label indications for proven orthopaedic technologies. Although these devices should be available to orthopaedic surgeons, most pediatric devices fall into small volume product categories. Principal investigators report that it is difficult to assemble a large enough pediatric patient population to satisfy FDA criteria to proceed with a clinical trial. Pediatric orthopaedic surgeons report that the lack of available innovative products has caused them to utilize devices that have been virtually unchanged for the past forty years.

Pediatric Medical Device Guidance Document

Inasmuch as guidance documents shorten the timeline for premarket assessment and improve the probability of achieving approval for marketing applications, the FDA's "Premarket Assessment of Pediatric Medical Devices" issued on May 14, 2004, is of significant concern to the Academy. As the most recent guidance to aid in bringing innovative devices to the marketplace, the AAOS believes there are considerable problems with this guidance document. The Academy will provide specific written comments to the FDA on the guidance document in a separate letter of comment.

In the "Premarket Assessment of Pediatric Medical Devices," the FDA proposes ranges for pediatric subpopulations as such: neonate: from birth to one month of age; infant: greater than one month to 2 years of age; child: greater than 2 years of age to 12 years of age; and adolescent: greater than 12 years of age to 21 years of age. Furthermore, the FDA notes additional pediatric subpopulations to include: low birth weight: newborns less than 2.5 Kg; very low birth weight: newborns less than 1.5 Kg; and preadolescent: from 11 to 13 years of age.

The FDA recommends that manufacturers specify relevant subsets of the pediatric population rather than using a single pediatric population. While it is appropriate to consider the height and weight of the patient, the Academy is concerned about defining strict limitations on subpopulations of pediatric patients when human growth is at times unpredictable. The guidance asks sponsors to define the pediatric subgroups within the clinical study.

The AAOS is especially concerned about defining all patients greater than 12 years of age to 21 years of age as adolescents. The transition to adulthood with regard to orthopaedic devices is defined as skeletal maturity, which is attained at approximately age 14 for females and age 16 for males. Importantly, the FDA classification ignores this distinction. Many orthopaedic trials, especially those concerning young adults with scoliosis, would require split populations of

pediatric and adult patients to satisfy this definition. This requirement would also be a hindrance to the execution of pediatric device trials, in that the study population would need to comprise a representative sampling within most pediatric subpopulations, thereby fragmenting primary study groups into subgroups too small for statistical analysis. More children will be needed for enrollment in clinical trials and relevant costs associated with device trials will substantially increase. Also, defining appropriate and acceptable multiple control groups for each subpopulation will be inordinately challenging for sponsors, and might make many studies impractical. The AAOS recommends that subsets of the pediatric population be used for clinical trials when outcome variables are critically affected by age or weight. However, when weight and height are not issues of concern, manufacturers should be encouraged to pool subjects into a single pediatric population when practical to provide the least burdensome approach.

As the guidance is intended for use by industry and the FDA staff, the AAOS is unsure of how either could make a reasonable determination about behavioral factors, activity, or maturity levels of an intended patient population during the device development process. The Academy asserts that most device manufacturers will not engage in the development of pediatric devices under the current regulatory scheme.

Barriers to Device Development

The AAOS believes that the barriers to pediatric device development include regulatory hurdles, clinical hindrances, and economic and legal issues.

Regulatory Hurdles

The AAOS has significant concerns that proven orthopaedic products are excessively delayed in development in the U.S. Medical device companies routinely conduct clinical research in foreign countries due to excessive regulatory burdens within the United States. Device companies consider the impact of FDA regulation on all phases of the product development cycle, including the post-approval process. Costs of doing research within the U.S. continue to increase each year and are further exacerbated by user fees. Many orthopaedic device manufacturers report the hardship of complying with FDA regulations as the most important consideration supporting their decisions to conduct clinical trials in foreign countries. American pediatric orthopaedic patients are disadvantaged when they are denied established and innovative technologies due to complex regulatory burdens on device and product development.

The design of clinical trials should optimize available resources. FDA and trial sponsors should agree on reasonable controls, assessment approaches, and endpoints. Although the FDA may have subspecialty physician expertise on advisory panels at the conclusion of studies, utilizing qualified sub-specialty experts to review potential studies before they are initiated would assist in identifying problems and presenting early solutions. Pediatric orthopaedists should review pediatric orthopaedic device applications, not adult orthopaedists. Trial design, length, patient compliance, surgeon investigator compliance, and duration of the government evaluation should be assessed on a continual basis by the FDA for a least burdensome approach and reasonable assurance of safety and effectiveness, or probable benefit for humanitarian use devices. As effectiveness is often difficult to determine, the AAOS encourages a practical, reasonable endpoint for assessment.

For example, the AAOS has become aware of considerable regulatory difficulties with bringing the vertical expandable prosthetic titanium rib device (VEPTR) to the U.S. marketplace. It is our understanding that after 13 years in clinical trials, and one year after a premarket approval application was submitted, FDA staff then decided controls were required, necessitating additional delay in order to resubmit the application as a Humanitarian Device Exemption (HDE) because of the absence of controls. Devices such as the VEPTR, which treat children with congenital thoracic scoliosis, are urgently needed in the American pediatric population.

The Academy supports the recent creation of a Pediatric Advisory Committee within the Office of the Commissioner. When reviewing orthopaedic devices, it is imperative to have experienced and knowledgeable FDA advisory panel members who are familiar with the clinical issues relevant to the device under review. The AAOS has a long history of providing expertise to FDA advisory panels and looks forward to assisting in the review of new pediatric product approvals.

Clinical Hindrances

Principal investigators report that the review of clinical studies by institutional review boards (IRBs) is excessively stringent. Finding appropriate multi-specialty expertise for the composition of the IRB is often challenging for hospitals. Principal investigators acknowledge that a patient death, whether caused by the drug, device, biologic, or combination product, or attributed to another cause of death, is just cause for federal authorities to end a clinical trial.

The Academy suggests a pragmatic approach to the design of pediatric orthopaedic trials. Controls should be reasonable and agreed upon early in pre-investigational device meetings with the sponsor. While the AAOS agrees the gold standard of scientific studies is the double-blinded, randomized study with controls, this design is frequently impossible in pediatric surgical trials. Scientifically acceptable controls are possible by comparing outcome to standard of care controls, and even historical controls are appropriate in some circumstances. Expert subspecialty input into study design can assist FDA in making these decisions. The AAOS urges that FDA make every effort to adhere to an agreed study design throughout the study, since unpredictability of regulatory requirements is a major obstacle to pediatric device development.

In pediatric orthopaedic practice, data is difficult to obtain due to pervasive off-label use. Under the current professional liability crisis, information on the safety and effectiveness of devices used in the pediatric population is generated primarily by peer discussion among surgeons. Regulatory hurdles have profoundly affected pediatric orthopaedic practice in that little data or peer-reviewed literature is available on device use. Without wide spread dissemination of such information, progress in the pediatric population has been significantly delayed when compared with the adult population.

Economic Issues

Many pediatric devices are small volume products and as such generally fall into the humanitarian use classification. However, there is little incentive for manufacturers to develop humanitarian use devices absent a corporate display of altruism.

Large manufacturers have resources to risk on the development of pediatric devices; however, their manufacturing facilities are designed to produce large quantities of devices. It is therefore impractical for these manufacturers to produce a small run of a certain device. Most device manufacturers are relatively small companies and do not possess the capital to design and develop new pediatric devices. Manufacturers report an unpredictable regulatory process and review, which has increased the cost of development significantly and has aided in the financial demise of some manufacturers.

Legal Issues

The Humanitarian Device Exemption provisions must be amended in the Federal Food, Drug, and Cosmetic Act. Manufacturers should be allowed to collect a profit on devices exceeding 250 dollars, thereby providing an incentive to develop medical devices for a small patient population. Manufacturers must currently be audited by an independent certified public accountant if the device cost exceeds 250 dollars, which provides another disincentive for industry to manufacture small volume products. All medical device manufacturers, especially pediatric device manufacturers, granted a HDE should be allowed to recoup investment funds beyond costs for research, development, fabrication, and distribution for their devices.

International Harmonization/Standards

Adherence to consensus standards assists in decreasing the amount of time during a premarket review. The Food and Drug Administration Modernization Act of 1997 (FDAMA) directed FDA officials to meet with representatives of foreign countries in order to reduce the burdens of global regulation and harmonize regulatory requirements. Additionally, officials were directed to engage in efforts to accept mutual recognition agreements relevant to the regulation of devices and good manufacturing practices between the European Union and the United States. Also, FDAMA recognized national and international standards in the review of medical devices.

The AAOS contends that American Society for Testing and Materials International (ASTM) standards are more robust than International Standards Organization (ISO) medical device standards. For example, the voting domination of European countries contributed to the adoption of an ISO hip wear-testing standard that has proven to be inferior when compared to existing scientific literature and that is incompatible with most U.S. hip simulator machinery. The Academy encourages the use of ASTM standards rather than ISO standards due to the sound policy that all negative votes must be resolved prior to the acceptance of ASTM standards rather than following the ISO practices of majority rule voting.

According to the FDA guidance, "Acceptance of Foreign Clinical Studies," issued in March 2001, the FDA asserts that they will accept a foreign clinical study involving a medical device if the study conforms to the ethical principles of the 1983 version of the Declaration of Helsinki or with the laws and regulations of

the country where the research was conducted, whichever provides for greater human subject protection.

The Academy notes the proposed rule [Docket No: 2004N-0018] "Human Subject Protection; Foreign Clinical Studies not Conducted Under an Investigational New Drug Application" published June 10, 2004 in the *Federal Register*. In the rule, the FDA proposes to replace the requirement that studies be conducted in accordance with the Declaration of Helsinki with a requirement that studies be conducted in accordance with good clinical practice, including review and approval by an independent ethics committee. The rule updates standards for a non-investigational drug application trial in foreign countries. The AAOS is aware that a similar rule is being developed by the Center for Devices and Radiological Health (CDRH) and encourages this effort. Data generated from ethically conducted foreign clinical trials must become admissible data in the pursuit of product approvals at the FDA. The Academy contends that the framework for the global harmonization of medical devices does exist, yet the interpretation and implementation of FDAMA does not seem to be progressing at a rapid pace.

Least Burdensome Provisions

The FDAMA added the following provision to the Federal Food, Drug, and Cosmetic Act in section 513(a)(3)(D)(ii): "Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."

All regulatory pathways associated with product approval including the investigational device exemption (IDE), product development protocol (PDP), HDE, and premarket approvals (PMA), should be continually evaluated to ensure a least burdensome investment of time, effort, and resources on the part of the FDA and industry.

Least burdensome provisions include early collaboration meetings with the FDA, special control documents to reduce regulatory burden, evidence models for the least burdensome means to market, and least burdensome training for CDRH

staff and advisory panel members. The AAOS strongly encourages the use of all least burdensome pathways and resources to bring innovative products to market in a timely manner.

MDUFMA

The Medical Device User Fee Modernization Act (MDUFMA) of 2002 instituted user fees for premarket device submissions. Fees for premarket market approval applications for fiscal year 2005 are \$239,327 and provide the FDA with funds to increase the number of device reviewers. The AAOS is pleased that more timely reviews are occurring at the CDRH with the increase in resources, and encourages the FDA to acquire additional expertise in pediatrics. Educational opportunities for FDA staff, needed on an ongoing basis due to staff turnover and retirement of key personnel, are also increasing. The Orthopaedic Device Forum has been instrumental in organizing educational seminars on topics of interest to the FDA review staff. The Academy strongly encourages its Fellows' participation in educational opportunities for FDA staff.

Solutions to Generate Pediatric Device Development

The Academy recommends that Congress pass legislation to amend the humanitarian use device provisions in the Federal Food, Drug, and Cosmetic Act. Manufacturers must be allowed to generate profits from lengthy development costs regardless if the cost of the device exceeds 250 dollars.

The AAOS strongly encourages a predictable, transparent regulatory process. Clinical trial protocols should be reasonable and decided upon in early investigational device meetings with the sponsor.

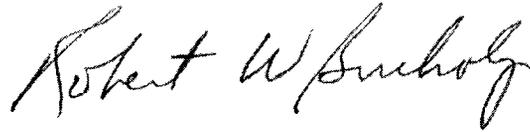
The Academy supports granting mechanisms, research incentives, and aid for small pediatric device companies to proceed with clinical trials. The FDA has precedent for making provisions to small companies. In 2002, MDUFMA granted reduced user fees for small device companies. Tax credits for manufacturers should also be explored to provide incentive for research development.

Conclusion

The Academy shares the concerns of the FDA in bringing safe and effective medical therapies into the U.S. marketplace. We look forward to working with

the FDA in any manner possible to ensure that innovative products reach pediatric patients as expeditiously as possible.

Sincerely,

Handwritten signature of Robert W. Bucholz in cursive script.

Robert W. Bucholz, MD
AAOS President

Handwritten signature of Scott J. Mubarak in cursive script.

Scott J. Mubarak, MD
POSNA President