



AMERICAN ACADEMY OF
ORTHOPAEDIC SURGEONS

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July 14, 2008

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Eunice Kennedy Shriver
National Institute of Child Health and Human Development
(NICHD)
31 Center Drive, Room 2A03, MSC 2425
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Dear Dr. Hirschfeld:

The American Academy of Orthopaedic Surgeons (AAOS), representing over 17,000 Board-certified orthopaedic surgeons, the Pediatric Orthopaedic Surgeons of North America (POSNA), and the Scoliosis Research Society (SRS), welcome the opportunity to comment on your request for information (RFI) regarding possible barriers to the availability of medical devices intended to treat or diagnose diseases and conditions that affect children. While the AAOS/POSNA/SRS appreciate the efforts of federal government 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 AAOS/POSNA/SRS have concerns about the lack of innovative pediatric orthopaedic medical products introduced into the United States marketplace and the deleterious effects it is having on pediatric orthopaedic patient care.

The RFI requests input on identifying unmet medical needs; identifying obstacles and providing recommendations for overcoming them; identifying ethical issues; identifying essential criteria to assess the overall public health need while prioritizing and commenting on the commercial potential of pediatric medical

devices; and providing input on current pediatric device regulatory requirements. The AAOS/POSNA/SRS offer the following comments and we hope that our perspectives are useful to the NICHD and interested stakeholders.

Unmet Needs of the Pediatric Orthopaedic 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.

When an implant is not available for a child, surgeons typically treat the child in one of several ways: by using an adult device, by modifying an adult device, or using an implant designed for other purposes such as using an arm plate in the lower extremity of children, or by using an existing suboptimal implant designed decades ago. Custom devices implants for children tend to be impractical because they are very expensive and manufacturing periods can be lengthy.

In late 2004, the AAOS distributed a survey to members to assess pediatric device needs of the AAOS, POSNA, and the SRS members. To our knowledge, this was the first US survey of medical practitioners to gain meaningful data on this subject. Respondents were asked to provide a list of needed orthopaedic devices. According to the survey results, specific unmet needs of pediatric orthopaedic devices include implantable self-expanding devices for longitudinal limb lengthening, non-reactive bioabsorbable screws and plates, self-expanding spinal deformity control devices for the growing child, minimally invasive growth modulation instrumentation for spinal deformity, intramedullary (IM) rod fixation for trauma, implantable devices for self-expansion angular deformity correction, implantable, long-term mechanical physis, novel drug delivery systems and total joint replacements for children. Additional suggestions were provided as write-in suggestions.¹ The results of this survey were provided to pediatric medical device stakeholders in 2005. Survey data confirmed the need for orthopaedic pediatric device innovation. We have recommended that our survey questions could be used as a template for other pediatric subspecialties' surveys.

Based on our survey results, the pediatric subpopulations in greatest need of innovative medical devices are neonates and infants due to the size limitations of larger orthopaedic 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 have caused them to utilize devices that have been virtually unchanged for the past forty years. Potential liability concerns may limit the off-label use of devices in the future.

Obstacles to Pediatric Device Development

The AAOS/ POSNA/SRS believe that the obstacles to pediatric device development include regulatory hurdles, clinical hindrances, and economic issues.

Regulatory Hurdles

The AAOS/POSNA/SRS have concerns that 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 Food and Drug Administration (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. 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, having a small market impact are extremely disadvantaged when they are denied established and innovative technologies due to complex regulatory burdens on device product development.

The design of clinical trials should optimize available resources. The FDA and clinical trial sponsors should agree on reasonable controls, assessment approaches, and endpoints. Although the FDA may have subspecialty physician expertise on advisory panels, utilizing qualified sub-specialty experts, such as pediatric orthopaedists, to review potential studies before they are initiated would assist in identifying problems and present early solutions. These assessments would serve several important purposes including helping to define details for an IDE study pathway early so economic feasibility can be determined early, determining whether a humanitarian device exemption or premarket approval approach is the most feasible, and in general making development of pediatric devices more economically predictable. 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, and specific populations such as pediatrics. The AAOS has a long history of providing expertise to FDA advisory panels and the AAOS/ POSNA/SRS look forward to assisting in the review of new pediatric product approvals at advisory panel meetings.

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/POSNA/SRS encourage a practical, reasonable endpoint for assessment.

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. When the necessary expertise is lacking within the standard IRB panel, IRBs should be encouraged to seek qualified ad hoc pediatric sub-specialty consultants for individual pediatric protocols to ensure expert, timely reviews. Reasonable guidance on conflict-of-interest issues should be drafted for IRBs to standardize procedures across the nation. 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 AAOS/POSNA/SRS suggest 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/ POSNA/SRS agree that the gold standard of scientific studies is the double-blinded, randomized study with controls, this design is impossible in pediatric surgical trials. Scientifically acceptable controls are possible by comparing outcomes to standard of care controls. Even historical controls are appropriate in some circumstances. Expert subspecialty input into study design can assist the FDA in making these decisions. The AAOS/POSNA/SRS urge that FDA make every effort to adhere to an agreed study design throughout the study, since the 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. Although the Food and Drug Administration Amendments Act of 2007, (FDAAA) granted authority for manufacturers to realize a profit on humanitarian use devices, the cap on the device limit was unchanged from 4,000 units. Therefore, the AAOS/POSNA/SRS are uncertain if the allowance of a profit is enough incentive to generate pediatric device development.

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.

Consortium

Although included in the authorization of the FDAAA, the consortium was intended to provide a venue for limited pediatric device development. Unfortunately, Congress has not allocated the necessary appropriations to date. The AAOS /POSNA/SRS encourage members of Congress to provide appropriations for the pediatric device consortium.

Solutions to Generate Pediatric Device Development

The AAOS /POSNA/SRS strongly support a predictable, transparent regulatory process. Clinical trial protocols should be reasonable and agreed to in early investigational device meetings with the sponsor.

The AAOS/POSNA/SRS support 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, the Medical Device User Fee Modernization Act (MDUFMA) instituted reduced user fees for small device companies. Tax credits for manufacturers should also be explored to provide incentive for device development.

Ethical Issues

A number of ethical issues persist with the conduct of clinical research - especially in the pediatric population. Well-controlled clinical trials are difficult to design and execute; informed consent issues are significant as children are not of the age of majority and they and their guardians may not be fully informed of every possible adverse reaction or outcome; surgical sham arms for children are seldom considered for many reasons and would have difficulty obtaining an IRB approval, and off-label use of many devices is standard of care therefore enrollment of patients in a clinical trial of the same device is usually not a successful venture.

Additionally, while physicians may use devices off-label in cases where they believe the patient will benefit, teaching and conducting research pose significant challenges for clinicians. The physicians may be perceived as promoting off-label use for a company, particularly if the clinician holds any type of consulting arrangement with the manufacturer of that product. Manufacturers and their representatives are careful to avoid violations of the False Claims Act, especially due to the excessive fines imposed on potential violations and the cost of legal expenses needed to challenge the government's allegations.

Essential Criteria to Assess Overall Public Health Needs

Prioritizing the development of pediatric devices is a daunting task that must include the emergent needs of critical patients as well as the needs of stable patients with chronic health issues. While new device development is an expensive and time-consuming venture, many devices could be adapted with relatively minor modifications of adult 510 (k) cleared devices. Acuity of disease and availability of other treatments must be assessed, as should the potential patient population.

We recommend that medical specialty societies provide input on a specialty specific list of devices that could be produced on at least a bi-annual basis. The AAOS/POSNA/SRS stand ready to work with the NICHD and other interested stakeholders to prioritize needed pediatric orthopaedic devices.

Input on Pediatric Device Regulatory Requirements

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, remains a concern to the AAOS/POSNA/SRS. As one of the most recent guidance documents to aid in bringing innovative devices to the marketplace, the AAOS/POSNA/SRS believe there are considerable problems with this guidance; we are not aware of an update to the 2004 draft document.

In the "Premarket Assessment of Pediatric Medical Devices," the FDA proposed 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 AAOS/POSNA/SRS are concerned about defining strict limitations on subpopulations of pediatric patients, when human growth is at times unpredictable. The guidance further asks sponsors to define the pediatric subgroups within the clinical study.

The AAOS/POSNA/SRS are 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.

Defining appropriate and acceptable multiple control groups for each subpopulation will be inordinately challenging for sponsors, and might make many studies impractical. The AAOS/POSNA/SRS recommend 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 a least burdensome approach.

As the guidance is intended for use by industry and the FDA staff, the AAOS/POSNA/SRS are 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.

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/POSNA/SRS contend 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 AAOS/POSNA/SRS encourage 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 AAOS/POSNA/SRS note 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/POSNA/SRS are 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 AAOS/POSNA/SRS contend 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), humanitarian device exemption (HDE), and premarket approvals (PMA), 510 (k) premarket notification 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/POSNA/SRS strongly encourage the use of all least burdensome pathways and resources to bring innovative products to market in a timely manner.

Conclusion

The AAOS/POSNA/SRS share the concerns of the federal government in bringing safe and effective pediatric medical therapies into the U.S. marketplace. We look forward to working with the NICHD and interested stakeholders in any manner possible to ensure that innovative products reach pediatric patients as expeditiously as possible.

Sincerely,



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AAOS President



B. Stephens Richards III, MD
POSNA President



George H. Thompson, MD
SRS President

¹ American Academy of Orthopaedic Surgeons, Survey on Pediatric Device Development Final Report, March 21, 2005, page 10.