

August 20, 2004

Division of Dockets Management
Food and Drug Administration
5630 Fisher's Lane, Room 1061
Rockville, Maryland 50852

RE: Docket Number: 2004N-0254

To Whom It May Concern:

On behalf of the 60,000 pediatrician members of the American Academy of Pediatrics (AAP), I am pleased to respond to the Food and Drug Administration's request for comments on a therapeutic issue of importance to neonates, infants, children and adolescents – the availability of appropriately designed and adequately studied medical devices. These comments are also endorsed by the pediatric academic research community that includes the Ambulatory Pediatric Association, American Pediatric Society, Association of Medical School Pediatric Department Chairs and the Society for Pediatric Research.

AAP and the pediatric societies are grateful for the FDA's inquiry into this issue. For the last 40 years the AAP has been sounding the alarm that children have been left behind on the therapeutic advances that are available to the adult population. Great strides have been made to improve the availability of drugs and biologics for the pediatric population; however, devices remain a therapeutic frontier yet to be adequately opened for children.

The FDA must be commended for its efforts to explore the issues surrounding pediatric medical devices. At the behest of Congress, the agency has recently undertaken a two-prong approach to understanding the pediatric needs and possible solutions to improving the availability of medical devices for children. First, in response to provisions within the Medical Device User Fee and Modernization Act of 2002 (MDUFMA - Pub. Law 107-250) the FDA requested that the Institute of Medicine (IOM) prepare a report to Congress on postmarket surveillance of pediatric medical devices, due in October 2006. The AAP has been actively participating in IOM meetings on this topic and will be providing testimony at an upcoming meeting on August 31. This report will have an important but limited focus on postmarketing issues related to pediatric medical devices.

The second prong is focused on pre-market issues related to pediatric medical devices. The questions posed in this federal docket (2004N-0254) will help illuminate the need for and the challenges to improving the availability of pediatric medical devices.

Another component of the pre-market assessment of medical devices is the FDA's *Guidance for Industry and FDA Staff: Premarket Assessment of Pediatric Medical Devices*, on May 14, 2004. It is notable that the only guidance issued by the FDA focusing specifically on pediatric devices was issued just one year ago. This document is an important step toward assisting device manufacturers in identifying the types of information needed to provide reasonable assurance of safety and effectiveness of medical devices intended for use in the pediatric population.

We are hopeful but not confident that this guidance will serve as a catalyst to encourage development of more pediatric devices. More must be done to ensure that pediatric populations benefit from existing therapies or are the recipients of newly developed ones.

Neonates, infants, children, and adolescents suffer from many of the same conditions as adults (e.g., bone fractures, hearing loss/deafness, ventricular anomalies), yet optimal care of these populations often require that adult devices to address those conditions be modified for their use in children. In addition, some conditions occur only in pediatric populations and require devices specifically designed for children's needs (e.g., many forms of congenital heart disease.) In all cases, pediatric populations deserve devices that are safe and effective with respect to their age, size, developmental status and other physiological characteristics. In our view, it is not a question of whether pediatric populations require devices appropriate to their needs, but rather, how those needs can best be addressed.

Children's medical device needs differ considerably from adults across a broad range of illnesses, conditions, and subspecialties. To ensure the optimal safety and efficacy of devices used by children, it is critical that medical devices address the particular needs of children, including:

- ?? Baseline respiratory and heart rates (e.g., affects appropriate design of heart valves and device durability given rapid pediatric heart beat [140/per minute for infants v. 70/per minute for adults])
- ?? Differences in organ and vessel sizes (e.g., affects sizing of needles and catheters, rigidity of materials)
- ?? High infection rates of central lines in children compared to adults.
- ?? Calcification of heart valves in children.
- ?? Rates of growth (e.g., affects design of prosthetic equipment and implantable devices)
- ?? General activity levels and types of activities (e.g., using plastic playground slides can deprogram cochlear implants)
- ?? Critical development periods
- ?? Biochemistry

In responding to the FDA's request, our comments draw from both the experiences of the pediatricians and researchers and from the discussion and outcomes of a stakeholders' meeting on pediatric device development co-hosted by the American Academy of Pediatrics, the

Elizabeth Glaser Pediatric AIDS Foundation, the National Organization for Rare Disorders, and the National Association of Children's Hospitals on June 28, 2004. In this meeting, participants including pediatricians, children's advocates, biomedical engineers, medical device companies, the FDA, the National Institutes of Health, and the Institute of Medicine identified a range of unmet pediatric device needs, the barriers to addressing those needs, and possible mechanisms for increasing the availability of pediatric appropriate products.

The following is the AAP and pediatric academic societies response to the three questions posed in the Federal Register Notice. For the sake of clarity, we have combined our comments on the second and third questions, to more clearly link the barriers we have identified with proposed solutions.

We begin our comments with a general recommendation: The recent establishment of both an Office of Pediatric Therapeutics (OPT) within the Office of the Commissioner of the Food and Drug Administration and a Pediatric Advisory Committee (PAC) are extraordinarily positive actions that will serve to advance therapeutics for infants, children, and adolescents. The AAP and pediatric academic societies strongly urge the FDA to integrate pediatric devices in the agenda of both the OPT and the PAC.

What are the unmet medical device needs in the pediatric population (neonates, infants, children and adolescents)? Are they focused in certain medical specialties and/or pediatric subpopulations?

There is clearly an unmet need for appropriate therapeutic devices for pediatric populations. Examples are numerous and varied, including the need to improve existing devices or the creation of pediatric-specific devices. The following examples illustrate needs:

- ?? Lack of appropriate sizing of adult devices for children (e.g., the Left ventricular assist devices (LVAD) for support of failing left or right ventricles is not available for children less than 6 years old);
- ?? Lack of efficacy of devices used by pediatric populations (eg., pre-adolescent/adolescent studies of a series of lasers and light sources approved for treatment of acne vulgaris);
- ?? Lack of availability of pediatric-specific devices (e.g., dry powder inhalers designed for low inspiratory flow rates; devices for inhaled and intranasal medications for infants and young children (ages 6 months-6 years), to include better nebulizers, with shorter dosing times, unit dose modules for a variety of medications, etc.)
- ?? Better devices and standards to measure pulmonary function in infants and young children, including more affordable devices to use at home to monitor asthma management.
- ?? Auto-injector for epinephrine with more appropriate dosage for infants and young children.
- ?? New pediatric meter dose inhaler (pMDI) spacers and holding chambers that have been tested with specific medications, and shown to not have an adverse effect on the respirable fraction of medication from the pMDI.

The vast majority of pediatricians and pediatric subspecialists we surveyed reported that many of the devices they needed for their pediatric patients simply were not designed and labeled for pediatric use. The lack of pediatric labeling meant that they were not always confident of the optimal way to use a device nor did they feel like they had sufficient knowledge of risk or potential adverse events. Also, they reported extensive off-label use of adult devices in children that in some cases included the need to fashion make-shift device solutions for pediatric use. In other instances, available adult devices were entirely inappropriate for use in children, often because of sizing. In those situations, the providers were forced to use older or less optimal interventions that they viewed as less effective and/or higher risk.

It is important to note that "off-label" use of a device does not imply an improper or illegal use. Indeed, this off-label use may represent the only, or best, treatment available for a specific illness in a child at the time the device is needed. However, off-label use of a product should not be viewed as the standard of care.

In addition, the lack of pediatric testing and labeling means that the long-term impact of many devices now used by children is unknown. For example, we do not have a full understanding of the impact of long-term device implantation in children (e.g., absorption rate of polymer plating for cranio/facial devices; gastrostomy tubes) or the impact of devices on organ growth for infants and children (e.g., titanium devices used in oral/maxillofacial surgery, "undersized" heart valves used in infants and children). Also, calcification on heart valves is an adverse event in children that cannot be predicted from the adult experience.

Another important consideration is that the deficiency of pediatric devices may translate to an issue of reduction of access to appropriate care for infants, children and adolescents. If proper therapeutic technology is not available for children, then they may be denied appropriate care or the care they receive may be sub-optimal compared to adults. Two examples help illustrate this point:

- ?? A pediatric cardiologist reported that many patients were denied treatments which were effective because the devices were not medically approved for use in children, and hence not covered by insurance or by state-sponsored programs.
- ?? Currently, out of necessity, physicians are forced to improvise a number of devices for pediatric use. In light of the rising cost of health care and the emphasis being placed on institutions to reduce their liability risk, improvising devices for pediatric use may be viewed as a liability risk that will be called under greater institutional scrutiny.

According to our pediatricians, having to use either inappropriately designed devices or less advanced interventions may lead to a range of problems with implications for children's health, including:

- ?? More tissue damage and/or more pain (e.g., when over-sized, more rigid adult scopes are used for endoscopic surgery on children)
- ?? Greater need for sedation (e.g., when more invasive procedures have to be used because the less invasive version of the intervention requires a device not sized for children)

?? Greater inconvenience for child and family (e.g., more advanced chemotherapy catheters that go under the skin are not sized small enough for children under one year of age, so providers have to use a catheter that lies outside the skin, resulting in an increased risk of infections in catheters, lines, etc.)

What are the possible barriers to the development of new pediatric devices? Are there regulatory hurdles? Clinical hindrances? Economic issues? Legal issues? What could FDA do to facilitate the development of devices intended for the pediatric population? Are there changes to the law, regulation, or premarket process that would encourage clinical investigators, sponsors, and manufacturers to pursue clinical trials and/or marketing of pediatric devices?

1) Barrier: Lack of Market Awareness of Pediatric Need

It is important to state that the lack of availability of appropriately designed and studied pediatric devices appears to be based in part on a lack of understanding of need and importance of devices for children; not an intentional effort to bypass the therapeutic needs of infants, children and adolescents. There are important lessons learned from regulatory and legislative efforts to advance the availability of drugs and biologic products for pediatric populations that may be applicable to devices. Part of the solution to this barrier may be to actively encourage device manufacturers to consider the pediatric population as they proceed through the design and application process for new devices or indications.

Recommendations: Congress should consider establishing the presumption that devices manufactured for adults should also be required to be designed for and tested for pediatric populations if the indication occurs in those populations. Similar to the Pediatric Research Equity Act, the parameters of this requirement could be drawn to take into account feasibility, medical and ethical concerns, and the public health interest in not delaying the development of devices for adults.

2) Barrier: Lack of Market Stimulus

Analogous to the situation with pharmaceutical products prior to the passage of the Food and Drug Administration Modernization Act of 1997 and the Pediatric Research Equity Act of 2002, the most significant barrier to the development of devices designed to meet children's needs appears to be the small share of the market represented by pediatric populations. Without either a requirement to design and test products for pediatric use or sufficient incentives to do so, manufacturer interest in producing pediatric devices is limited, particularly for conditions that occur in only small numbers of children.

Another barrier that has been raised is that device manufacturers have expressed ethical concerns related to conducting pediatric trials. Over the last number of years, there have been tremendous advances to ensure that pediatric patients in clinical trials are appropriately protected. Ethical concerns can and have been addressed in clinical trials related to

pharmaceuticals. There is no reason to expect that the device industry need be any less successful in developing well-designed ethical pediatric studies.

Recommendations: Congress should also consider the creation of financial incentives, including grants or guaranteed loans for R&D to small companies, modifying the existing Humanitarian Device Exemption provision to allow for profit, and financial support for prototype development and the conduct of clinical trials, possibly through a network structure.

In considering the creation of these incentives, Congress should weigh carefully the magnitude of the benefit to manufacturers in relation to the likelihood of the incentive to stimulate the development of safe and effective products appropriate for pediatric needs and important to children's health. In addition, thorough consideration should be given to minimizing the potential for misuse of any incentives and to ensuring that federal support supplements, rather than supplants existing manufacturer capacity.

In addition, funding for the expansion of existing grant or loan guarantee programs or the creation of new ones, should not be limited to only federal contributions. Congress should think creatively in identifying means to partner with private entities to develop funding streams for these programs that will be sustainable through tight federal budgets.

3) Barrier: Lack of Mechanisms for Systematically Identifying Pediatric Device Needs

While individual pediatricians and pediatric subspecialists are well aware of the needs faced by their individual patients, no mechanism exists for systematically collecting this information or for conveying it to device manufacturers or regulators. Also, no process exists for prioritizing device needs once identified, e.g., existing devices not sufficiently studied, new devices, "low-hanging fruit". In addition, FDA does not currently have a system for identifying from device applications or approval which devices have pediatric indications or have applicability to pediatric populations

Recommendations: It appears unlikely that simply facilitating the communication of needs by pediatricians to medical device manufacturers will result in any significant increase in general interest by device manufacturers in producing pediatric products, for the reasons stated in the first barrier identified above. However, the development of a mechanism for sharing that information may be useful in select circumstances in helping a manufacturer identify a potential market for a new or modified product. In addition, such a mechanism could be useful for identifying opportunities for collaboration between manufacturers with pediatricians or institutions, (e.g., a manufacturer agrees to try to modify a product for pediatric use with assistance from a pediatric research specialist or children's hospital in conducting a clinical trial.)

We would also recommend that FDA use the recent statutory requirement to exempt pediatric devices from user fees as an opportunity to create a system to identify and track pediatric devices, both those specifically intended for use in children and those devices labeled for adult or general use that are intended for conditions that occur in pediatric populations. Such a system could be used, for example, for FDA to identify devices that require only slight modifications or

minimal additional testing to obtain a pediatric indication and to communicate the necessary data requirement to the manufacturer. This system could also be used to identify devices eligible for incentives or should be subject to a requirement to test in children.

4) Barrier: Lack of clarity about what types of data are acceptable to FDA as valid scientific evidence to demonstrate safety and effectiveness.

Recommendations: FDA should clarify for manufacturers acceptable data for determining safety and efficacy of pediatric devices. Specific issues that need clarification include the acceptability of data gathered in the course of clinical care without informed consent. For example, it would be important for FDA to consider allowing flexibility in developing standards for parameters of efficacy in children that do not depend on measures of pulmonary function, and accept those parameters as proof of efficacy.

5) Barrier: Study Designs

Recommendation: FDA should design studies of new medications that utilize devices so that the drugs and devices will be studied in ways that they will be used clinically. For example, insist that all new hydro-fluoroalkane (HFA) devices that will have pediatric labeling be studied with spacers/holding chambers (e.g., devices that help the drug get delivered to the lungs because the aerosol particles get held in the spacer/holding chamber rather than requiring that small children inhale exactly when the meter dose inhaler is actuated.) In addition, in specific circumstances FDA should consider allowing that certain studies be designed without placebo arms for infants and young children, to improve the ability to recruit patients into such studies.

Thank you for the opportunity to comment on such an important pediatric issue. The American Academy of Pediatrics and the pediatric academic societies stand ready to work with the Food and Drug Administration and Congress to discuss ways to improve the availability of pediatric devices and to implement the proposed recommendations.

Sincerely,

Carden Johnston, MD, FAAP
President

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Endorsed by:

Ambulatory Pediatric Association
American Pediatric Society
Association of Medical School Pediatric Department Chairs
Society for Pediatric Research.