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 Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), I am pleased to respond to the Food and Drug Administration's (FDA) request for comments on the barriers to the availability of medical devices intended to treat or diagnose diseases and conditions that affect children. We believe this request for comments, which will assist the FDA in preparing a Congressionally mandated report on pediatric device availability, is an important step in ensuring that children have the same right to safe and effective medical devices that we enjoy as adults.

Neonates, infants, children, and adolescents suffer from many of the same conditions as adults, yet optimal care of these populations may require that adult devices to address those conditions be modified for pediatric use. In addition, some conditions occur only in pediatric populations and require devices specifically designed for children's needs. In all cases, pediatric populations deserve devices that are safe and effective with respect to their age, size, developmental status and other unique 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.

For over 15 years, EGPAF has been a leading advocate for children and families. The Foundation's mission is to create a future of hope for children and families worldwide by eradicating pediatric AIDS, providing care and treatment for people with HIV/AIDS, and accelerating the discovery of new treatments for other serious and life-threatening pediatric illnesses. In 2000, the Glaser Pediatric Research Network was founded as an extension of EGPAF on the premise that collaboration among the nation's leading scientists can advance vital clinical discoveries on behalf of all children. The Network develops and conducts multi-center studies,

allowing research investigators access to larger and more diverse patient populations. This innovative model accelerates scientific discoveries in the laboratory and translates those findings into better treatments for children.

Currently, the Network consists of a partnership among the following five pre-eminent medical centers and children's hospitals: Texas Children's Hospital/Baylor College of Medicine, Children's Hospital-Boston/Harvard Medical School, Lucile Packard Children's Hospital at Stanford University, Mattel Children's Hospital at the University of California Los Angeles and UCSF Children's Hospital at the University of California San Francisco, and is focusing on the study of chronic and life-threatening pediatric conditions such as obesity, cancer, osteoporosis, and rare bleeding disorders. Network institutions encompass a broad range of expertise in pediatric conditions and the medical devices needed to diagnose and treat them.

In responding to FDA's request, our comments draw from both the experiences of the pediatricians and pediatric researchers within the Network and from the discussion and outcomes of a stakeholders' meeting on pediatric device development co-hosted by EGPAF, the American Academy of Pediatrics, the National Organization for Rare Disorders, and the National Association of Children's Hospitals on June 28, 2004. In this meeting, participants including children's advocates, pediatricians, medical device companies, FDA, the National Institutes of Health (NIH), and the Institute of Medicine (IOM) 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 Foundation's 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 in order to more clearly link the barriers we have identified with proposed solutions.

Question 1: 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?

As our long experience advocating for pediatric drug testing has shown us, children are not simply small adults when it comes to their therapeutic needs. Because of differences in metabolism, growth and development, simply "downsizing" dosages based on weight can and has resulted in children being either over-dosed or under-dosed. Drugs may also have different adverse side effects or toxicities in children than in adults. Consequently, extrapolating pediatric safety or effectiveness for medicines found to be safe and effective in adults may not be appropriate. In addition, the lack of age-appropriate formulations (e.g., liquids, chewable tablets) can place some critical products entirely out of reach of the youngest children.

Similarly, pediatric device needs can vary considerably from those of adults across a broad range of illnesses, conditions, and subspecialties. These variations are due to differences in size, rates of growth, critical development periods, anatomical differences (e.g., organ and

vessel sizes), physiological differences (e.g., cardiorespiratory function), and activity levels. Also similar to the situation with pharmaceutical products, meeting pediatric device needs is further complicated by the wide variation within the pediatric population. For example, with regard to size alone, pediatric patients can range from a 500 gm premature neonate to a 200 kg obese adolescent. In addition, there are many pediatric diseases, such as congenital heart disease and neonatal surgical disorders, for which no adult parallel exists and for which devices exclusively designed for children are needed.

Specific pediatric device needs cited by our pediatricians include:

- Central venous catheters for infants and children
- Infant-specific laparoscopy equipment
- Septal closure devices for use in cardiac procedures
- ECMO catheters for infants
- Pulsatile Ventricular Assist Devices for children less than 12-15kg
- Stents designed and approved for children
- Percutaneous PA Bands
- Percutaneous Vessel to Vessel Anastomosis Devices
- Flexible endoscopes and accessories appropriated sized for various pediatric populations

In surveying pediatricians and pediatric subspecialists, the vast majority report that many of the devices they need for their patients simply are not designed and labeled for pediatric use. Consequently, they report extensive off-label use of adult devices in children that, in some cases, includes the need to "jerry-rig" or fashion make-shift device solutions for pediatric use. Such off-label use is neither illegal nor unethical, and may, in fact, be the only therapeutic option available. However, in our view, it is certainly not optimal since it fails to provide children the same reasonable assurance of safety and efficacy that adults enjoy.

One consequence of using an adult device off-label in pediatric patients is that pediatricians may lack sufficient knowledge of risks and potential adverse events. For example, calcification on heart valves is an adverse event in children that cannot be predicted from the adult experience. In addition, without specific testing and labeling for pediatric populations, pediatricians may lack information about the optimal way to use a device. This issue was highlighted recently in a USA Today article, "Doctors Hope Pacemakers Buy Time for Tiny Hearts" (August 10, 2004), which described the use of adult cardiac resynchronizers in children. While the results reported thus far are promising, a physician quoted in the article notes that it is still unclear which children are the best candidates for the procedure and which are more likely to suffer complications that include infection, stroke and death.

The lack of pediatric device testing and labeling also 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).

While some adult devices can be used off-label in children, in other instances, adult devices are inappropriate for pediatric use often because of sizing. In these situations, the providers may be forced to use older or less optimal interventions that are less effective and/or higher risk. Pediatricians cite a range of health implications of having to use less advanced interventions than are available for adults, 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); and greater inconvenience for caregivers (e.g., subcutaneous chemotherapy catheters that allow for easier care management are not sized small enough for children under one year of age).

Question 2: What are the possible barriers to the development of new pediatric devices? Are there regulatory hurdles? Clinical hindrances? Economic issues? Legal issues?
Question 3: 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?

a) Barrier: Insufficient Market
Analogous to the situation with pharmaceutical products prior to 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 market share 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.

Recommendations
Congress should consider establishing the presumption that some devices manufactured for adults also be required to be designed for and tested in 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.

Congress should also consider the creation of financial incentives, including grants or guaranteed loans for research and development to small companies, tax credits, and modifying the existing Humanitarian Device Exemption provision to allow devices that meet significant pediatric needs to be sold at a profit. Consideration should also be given to directly supporting pediatric device research. To be most effective, this support should be flexible enough to target the appropriate phase(s) in the device development continuum, from prototype development through clinical trials. Congress should explore whether a network structure, similar to the Pediatric Pharmacology Research Units, would be the most appropriate mechanism for identifying pressing pediatric device needs and delivering this targeted assistance.

Should Congress choose to pursue any of these incentives, it will be important not to rely solely on federal funding. Congress must think creatively about how to cultivate support from private entities to ensure that these programs will be sustainable through tight federal budgets. In addition, in considering the creation of 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. Thorough consideration should also be given to minimizing the potential for misuse of any incentives and to ensuring that any financial support supplements, rather than supplants, existing manufacturer capacity.

b) 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, or devices that require only minimal design modification. In addition, FDA does not currently have a system for identifying from device applications or approvals which devices have pediatric indications or have applicability to pediatric populations.

Recommendations

For the reasons stated in the first barrier identified above, it appears unlikely that simply facilitating the communication of needs between pediatricians and medical device manufacturers will result in a significant increase in interest by device manufacturers in producing pediatric products. However, the development of a mechanism for sharing such information may be useful in select circumstances in helping a manufacturer identify a potential market for a new or modified pediatric product or in identifying specific mutually beneficial opportunities for collaboration with pediatricians or institutions. For example, this information may help convince a manufacturer to modify a product for pediatric use with assistance from a children's hospital in conducting a clinical trial to support the safety and efficacy of the new device.

We understand that FDA is considering the development of an information system to identify device applications that contain pediatric indications, in order to comply with the requirement in the Medical Device User Fee and Modernization Act of 2002 that pediatric devices be exempt from user fees. We urge FDA to use this system as an opportunity to create a system to also identify and track 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 requirements to the manufacturer. This system could also be used to identify devices that may be eligible for any newly created incentives or devices that should be subject to a requirement to test in children.

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

We believe that the guidance issued by FDA in May 2004, "Guidance for Industry and FDA Staff: Premarket Assessment of Pediatric Medical Devices," is a useful step toward assisting device manufacturers in identifying the types of information needed to provide reasonable assurance of safety and effectiveness of medical devices for use in pediatric populations. However, more must still be done to both clarify data requirements for pediatric indications and to encourage manufacturers to pursue pediatric indications while or soon after the adult device is developed.

Recommendations

After consulting with manufacturers to identify requirements that continue to be perceived as unclear or overly burdensome, FDA should further clarify for manufacturers acceptable data for determining safety and efficacy of pediatric devices. Specific issues that need clarification include the acceptability of the retrospective use of data gathered in the course of clinical care without informed consent.

FDA should also consider taking a more proactive approach toward encouraging manufacturers to pursue pediatric indications of adult product. As device manufacturers meet with FDA during the premarket process to determine the data requirements for adult approval, FDA could identify devices with particular relevance to pediatric populations and clarify for the manufacturer what additional data would be necessary to add a pediatric indication. While it is not feasible to apply such a process to each one of the thousands of devices approved each year, FDA could begin with a more limited category of priority devices, e.g., all premarket approvals (PMAs), and expand the practice if determined to be a useful means of generating pediatric indications.

d) Barrier: Perceived Ethical Concerns with Including Children in Clinical Trials

Device manufacturers have cited perceived ethical concerns about conducting pediatric clinical trials as a disincentive to developing pediatric products. Certainly, all research involves some degree of risk and special care must be given to the protection of children, as a vulnerable population, in clinical studies. However, regulations are in place to help ensure that the particular issues raised by the participation of children in research are appropriately addressed by researchers and institutional review boards (IRBs). A March 2004 congressionally-mandated IOM report on clinical research involving children notes the importance of continuing to strengthen those protections, but also emphasizes that "[w]ell designed and well-executed clinical research involving children is essential to improve the health of future children – and future adults – in the United States and worldwide. Children should not be routinely excluded from clinical studies. No subgroups of children should be either unduly burdened as research participants or unduly excluded from involvement."

As evidenced by the dramatic increase in the number of pediatric studies approved by IRBs and conducted subsequent to the creation of financial incentives for pediatric drug testing in 1997, clinical trials involving pediatric populations can be designed that meet guidelines for the protection of children as human subjects. With concerted attention to children's needs,

there is no reason to expect that the device industry will be any less successful in addressing the special ethical issues raised by pediatric clinical research and in developing well-designed, ethical pediatric studies.

Recommendations:
Medical device manufacturers interested in conducting pediatric clinical trials should consult with experts in pediatric research, including ethicists, to ensure appropriate attention to the special needs of children and compliance with all required human subjects protections.

As recommended in the IOM report, to improve understanding of existing regulations related to research protections for children the Office for Human Research Protections and FDA should cooperate to develop and disseminate guidance and examples for investigators and IRBs to clarify important regulatory concepts and definitions related to assessing research risks and benefits.

In closing, we would also like to note our strong support for the recent establishment of the Office of Pediatric Therapeutics (OPT) within the Office of the Commissioner of the FDA and the Pediatric Advisory Committee (PAC). FDA has always been a leading voice for children on the issue of pediatric drug testing and we have been pleased to work closely with the agency toward a dramatic expansion in pediatric pharmaceutical studies over the past several years. We are very hopeful that the creation of OPT and PAC will also serve to advance pediatric device development and urge that pediatric devices be integrated into the agendas of both entities.

We appreciate the opportunity to comment on this critical issue for children and look forward to continuing to work with FDA to overcome the barriers to the development of pediatric medical devices. If you have any questions or would like any additional information, please contact me or Jeanne Ireland, Director of Public Policy, at 202-296-9165.

Sincerely,

Mark Isaac
Vice President, Governmental and Public Affairs