

**Possible Barriers to the Availability of Medical Devices
Intended for the Treatment or Diagnosis of Diseases
and Conditions That Affect Children**

Comments to the Docket FR#2004-0254

List of Comments Received

Barriers to the Availability of Medial Devices Intended for the Treatment or Diagnosis of Diseases and Conditions that Affect Children Docket #2004N-0254

Healthcare Professional Organizations

American Academy of Pediatrics – Carden Johnston, MD, FAAP
American Academy of Pediatric Dentistry – Dr. Warren Brill
American Society for Pediatric Nephrology – Sandra Watkins, M.D.
American Thoracic Society – Sharon I.S. Rounds, M.D.
American Association of Orthopedic Surgeons –
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Scott J. Mubarak, M.D.
American Academy of Allergy, Asthma & Immunology –
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Spina Bifida Association of America – Cindy Brownstein

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Gammell Applied Technologies – Dr. Paul M. Gammell
Management Advisory Services – Mr. Richard Podell
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Cook Group Incorporated – Stephen L. Ferguson

Medical Device Trade Associations

Advanced Medical Technology Association (AdvaMed) – Tara Federici

Comments from Healthcare Professional Organizations

August 20, 2004

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Food and Drug Administration
5630 Fisher's Lane, Room 1061
Rockville, Maryland 50852

AUG 24 2004

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

CJ:ehv

Endorsed by:

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

2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments
FDA Comment Number : EC4

Submitter : Dr. Warren Brill

Date & Time: 07/26/2004 04:07:08

Organization : American Academy of Pediatric Dentistry

Health Professional

Category :
Issue Areas/Comments

GENERAL

GENERAL

The American Academy of Pediatric Dentistry is not aware of any barriers to the availability of Medical Devices to treat or diagnose oral diseases and conditions that affect children.

2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments

FDA Comment Number : EC11

Submitter Mrs. Sandra Watkins

Date & Time: 08/25/2004 04:08:47

Organization : American Society for Pediatric Nephrology

Other Organization

Category :

Issue Areas/Comments

GENERAL

GENERAL

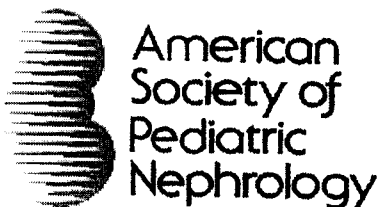
Pediatric nephrologists rely on a number of technologies and devices to provide care for our patients. These include hemodialysis, continuous renal replacement therapy (CRRT), peritoneal dialysis and automated blood pressure measurement. Each of these technologies requires that appropriate medical devices be available that not only fulfill the desired function, but are also appropriately designed for infants and children of various sizes.

For hemodialysis, a specialized central venous dialysis catheter is necessary to deliver adequate blood flow to the dialyzer. Sizes must be available that can be inserted in infants as small as 1.0 kg, up to small adolescents of 50-60 kg. Since the development of the long term indwelling central venous catheter by Robert Hickman and his colleagues, significant strides have been made in the types and sizes of these catheters, but the selection is still limited. Several manufacturers have made commitments to the pediatric nephrology community to develop new catheters and continue to provide them to our patients. However, the number of vendors is quite limited, especially for smaller children and infants. To date the smallest long-term cuffed catheter is 8 Fr, yet this may be too large for some infants with renal failure, in whom long-term hemodialysis is life-sustaining therapy, or for some critically ill newborns with inborn errors of metabolism in whom hemodialysis or CRRT may be life-saving.

Compared to the potential adult market, there is small financial reward for companies to develop such catheters and to continue to provide them. New catheters for children require the same rigorous and expensive testing as for adult catheters; yet only a fraction will be sold compared to new catheters designed for adults. Often most of the technological problems have already been worked out during adult studies. Similar problems exist for choice of the tubing carrying the blood to and from the dialyzer used on dialysis machines. Ideally less than 8-10% of a patient's blood volume should enter the dialysis circuit. For many of the currently available models of dialysis machines, the smallest volume tubing available is 40 ml, which may represent up to 15-20% of the blood volume of the average neonate. Smaller volume tubing is available by one vendor but is incompatible with a number of dialysis machine models. While no hemodialysis machine has been designed specifically for children, many models of machines have been adapted for use in infants and children. However, the lowest blood flow setting on some machines is only 50 ml/min, which is relatively high for use in small infants, making the dialysis procedure technically more difficult, and possibly less safe, than in larger children or adults.

While there have been significant strides over the years in the design and availability of medical devices for pediatric nephrology patients, challenges and barriers remain. The major barrier is the limited profitability of these devices compared to the adult market. Perhaps legislation similar to the Food and Drug Modernization Act of 1997 (FDAMA) mandating the development for and testing in children of new devices designed for use in adults would be helpful. The FDAMA and its successor legislation have been successful in increasing the information available on medication use in children.

PLEASE SEE THE ATTACHED COMPLETE ASPN COMMENT LETTER.



American Society of Pediatric Nephrology

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August 18, 2004

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RE: Docket #2004N-0254

To Whom It May Concern

Pediatric nephrologists rely on a number of technologies and devices to provide care for our patients. These include hemodialysis, continuous renal replacement therapy (CRRT), peritoneal dialysis and automated blood pressure measurement. Each of these technologies requires that appropriate medical devices be available that not only fulfill the desired function, but are also appropriately designed for infants and children of various sizes.

For hemodialysis, a specialized central venous dialysis catheter is necessary to deliver adequate blood flow to the dialyzer. Sizes must be available that can be inserted in infants as small as 1.0 kg, up to small adolescents of 50-60 kg. Since the development of the long term indwelling central venous catheter by Robert Hickman and his colleagues, significant strides have been made in the types and sizes of these catheters, but the selection is still limited. Several manufacturers have made commitments to the pediatric nephrology community to develop new catheters and continue to provide them to our patients. However, the number of vendors is quite limited, especially for smaller children and infants. To date the smallest long-term cuffed catheter is 8 Fr, yet this may be too large for some infants with renal failure, in whom long-term hemodialysis is life-sustaining therapy, or for some critically ill newborns with inborn errors of metabolism in whom hemodialysis or CRRT may be life-saving.

Compared to the potential adult market, there is small financial reward for companies to develop such catheters and to continue to provide them. New catheters for children require the same rigorous and expensive testing as for adult catheters; yet only a fraction will be sold compared to new catheters designed for adults. Often most of the technological problems have already been worked out during adult studies. Similar problems exist for choice of the tubing carrying the blood to and from the dialyzer used on dialysis machines. Ideally less than 8-10% of a patient's blood volume should enter the dialysis circuit. For many of the currently available models of dialysis machines, the smallest volume tubing available is 40 ml, which may represent up to 15-20% of the blood volume of the average neonate. Smaller volume tubing is available by one vendor but is incompatible with a number of dialysis machine models. While no hemodialysis machine has been designed specifically for children, many models of machines have been adapted for use in infants and children. However, the lowest blood flow setting on some machines is only 50 ml/min, which is relatively high for use in small infants, making the dialysis procedure technically more difficult, and possibly less safe, than in larger children or adults. Circuit volume is even more problematic in the newest form of renal replacement therapy, CRRT. In one of the popular machine models, only one circuit is currently available, and it has a blood volume of 90 ml. Because of this relatively large blood volume, the manufacturer does not recommend the use of this device in infants less than 15 kg, but

without other options, pediatric nephrologists have to use this circuit, even in smaller infants. A smaller volume circuit has been available outside the USA for a number of years, but is not yet available in the USA, because it is just now undergoing FDA mandated testing to allow its sale in the USA.

The automated blood pressure machine is another device that pediatric nephrologists use to deliver care to their patients with renal disease and with primary hypertension. These machines are the method of choice for evaluation of small children, because of the ease of measurement compared to manual devices and the need to avoid potentially toxic mercury manometers. There are a number of providers of automated BP machines. However, several studies have demonstrated significant variation in readings for a given measurement between different manufacturer's instruments. The values for systolic and diastolic blood pressure are the result of proprietary algorithms rather than direct measurements. Standardization of automated BP machines would improve the reliability of obtaining BP and facilitate more appropriate management of hypertensive children. Similarly, standardization of cuff dimensions would also be desirable, as cuff size can vary widely from manufacturer to manufacturer. Despite recommendations from consensus organizations such as the American Heart Association and the National High Blood Pressure Education Program, there is no standard size for infant, child, or small adult cuffs among different manufacturers.

While there have been significant strides over the years in the design and availability of medical devices for pediatric nephrology patients, challenges and barriers remain. The major barrier is the limited profitability of these devices compared to the adult market. Perhaps legislation similar to the Food and Drug Modernization Act of 1997 (FDAMA) mandating the development for and testing in children of new devices designed for use in adults would be helpful. The FDAMA and its successor legislation have been successful in increasing the information available on medication use in children.

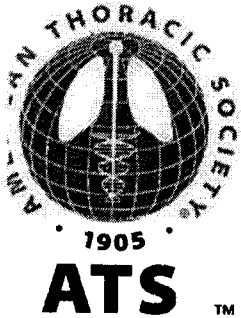
In addition, advocacy by the FDA for NIH or other national support to develop multi-center pediatric renal consortiums designed to provide an infrastructure for investigating devices in more pediatric patients than can be found in a single center would be useful. An example of this is the Prospective Pediatric CRRT Registry, a consortium of centers that is doing the 510K work for the infant M10 CRRT filter. With regard to the automated blood pressure machines, the FDA could develop standards for such machines so that comparable, accurate blood pressures would be obtained with any machine with the same size cuff, and could endorse the recommendation for standardization of blood pressure cuff sizes that was recently issued by the National High Blood Pressure Education Project.

We appreciate the opportunity to comment about the special device needs for children with kidney disease and hypertension. If we can provide you with any more specific information to help in your assessment, please feel free to contact us. The American Society of Pediatric Nephrology is committed to working with the FDA on these issues to develop safer and more effective medical devices for pediatric nephrology patients.

Sincerely yours,



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August 20, 2004

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RE: Docket Number: 2004N-0254

To Whom It May Concern:

On behalf of the 14,000 members of the American Thoracic Society (ATS), I would like to thank the Food and Drug Administration (FDA) for seeking community comment on how to improve the therapeutic medical devices options for pediatric patients. The members of the ATS provide unique expertise and experience in treating children with respiratory disease. We strongly endorse the need for FDA to take steps to increase therapeutic medical device options that are specifically designed, tested and have post-market data collection for children with respiratory diseases.

The ATS appreciates the FDA's interest in this important but long neglected children's health issue. The ATS especially wants to recognize the recent establishment of the Office of Pediatric Therapeutics (OPT) within the Office of the Commissioner of the Food and Drug Administration and the Pediatric Advisory Committee (PAC). These organizations will provide a platform for highlighting the unique medical needs of children. It is our hope and expectation that pediatric medical devices will be an important part of the agenda of both these groups. It is our hope that FDA, by bringing attention to this issue and by taking regulatory action, can improve the availability of medical devices specifically designed, studied and tested for children.

Children are not little adults. While children may suffer from many of the diseases of adults and often benefit from the therapies developed to treat adult diseases, there are fundamental differences in size, growth, chemistry and activity level that create a unique set of factors in dealing with medical devices for children.

Unmet Pediatric Pulmonary Device Needs

There several unmet needs in the pediatric pulmonary community. The ATS offers the following examples:

2004N-0254

C9

Drug Deposition of Aerosolized Drugs

Drug deposition of aerosolized medicine is poorly studied in pediatric populations. While sufficient drug deposition studies exist for the adult population, studies in children under 5 years old and especially under 3 years old are sorely lacking. While the need is most pressing for bronchodilator drugs and steroids used to treat asthma, the recent interest in inhaled antibiotics will also create a need for studies in children. The drug deposition studies should be specific to the administering devices, including metered dose inhalers (MDIs), dry powdered inhalers, nebulizers and transtracheal administration.

Size and Shape of Tracheostomy Tubes

Device manufacturers have provided a wide range of tube sizes for tracheostomy tubes. However, the availability of tube shapes and studies on the optimal shape and size for various age groups is lacking. Studies need to be conducted to provide guidance to clinicians on the optimal size and shape of tracheostomy tubes in children. .

Care of Tracheostomies

As noted in the 1999 ATS statement Care of the Child with a Chronic Tracheostomy, there has been little research done on proper care of tracheostomies in children. The authors of the document state, "Many of the recommendations are by consensus in the absence of scientific data, and suggestions are made for areas of research." Considering the size of the pediatric patient population that has tracheostomies, it is imperative that evidence supported recommendations for the care and prevention of infection of tracheostomies be developed.

Non-Invasive Positive Pressure Ventilation – Mask Interface

Non-invasive ventilators are a significant therapeutic advancement in the treatment of sleep-disordered breathing and respiratory failure. However, children have not enjoyed the full benefit of this therapeutic advancement due to mask interface issues. To ensure proper use of non-invasive ventilators, the mask must fit the patient. . This requires both proper mask size and proper headgear fit. Unlike an adult, the tissues of the face of a young child are highly plastic and are susceptible to remodeling from external pressure. Often the pressure required to keep non-invasive ventilator masks in place with proper fit can cause remodeling of the child's face. Such remodeling can lead to cosmetic and functional abnormalities of the nose, jaw and midface.

Currently, there is a dearth of FDA approved pediatric sized ventilator masks. The ATS notes that pediatric sized masks are available outside the United States.

The alternative to non-invasive ventilation is invasive ventilation through tracheostomies or intubation. Both of these more invasive options have higher

costs, greater length of stays, higher risks of infection, and long-term morbidity such as speech impairment and scarring of the airway.

More research is needed to create pediatric masks and headgear that assure proper fit without leading to face remodeling.

Non-Invasive Positive Pressure Ventilation – Triggering/cycling mechanisms

A related issue concerns the breathing cycle algorithms used in non-invasive positive pressure ventilators. The machines used in adult populations generally try to accommodate the breathing cycle of a 150-pound adult. Using non-invasive ventilators for children, especially neonates, requires significantly different timing and airflow rates to trigger the inhalation/exhalation breathing cycle.

Again, little research has been done by manufacturers or by clinicians to best adapt the breathing algorithms of these machines for pediatric applications. Research is needed to provide appropriate devices to adequately ventilate young children.

Home Pulse-Oximetry Monitoring for Children

Home pulse oximetry is often used by clinicians to assist adult patients in weaning from ventilator devices. However, pulse oximetry readings are very sensitive to motion, making continuous pulse oximetry readings in a child extremely difficult to obtain. The inability to collect accurate home pulse oximetry readings for children means clinicians often manage ventilator weaning in the absence of clinically important data.

Additional research is needed to develop pulse oximetry devices that can accurately provide home oxygen saturation readings that are not compromised by motion artifact.

The above are just a few of the more pressing examples of medical device challenges in the pediatric pulmonary community. In all these cases, research has been conducted to create evidence-based recommendation for the use of these devices in adults. However, follow up research for pediatric indications remains unaddressed.

Recommendations

The ATS offers the following recommendations to improve availability of medical devices that have been specifically designed and tested for pediatric patients. These recommendations closely follow the recommendations developed by our colleagues at the American Academy of Pediatrics:

- The FDA should establish a 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. Giving the FDA the authority to establish this presumption would likely require an act of Congress.

- 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.
- The FDA should 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.
- FDA should clarify for manufacturers acceptable data for determining safety and efficacy of pediatric devices.
- FDA should design studies of new medications so that the drugs or devices will be studied in ways that they will be used clinically.

On behalf of American Thoracic Society, I want to again thank the FDA for allowing us to comment on issues surrounding pediatric medical devices. We look forward to working with the FDA, our sister medical societies and the device manufacturers to develop new therapeutic medical devices for children.

Sincerely,



Sharon I.S. Rounds MD

American Thoracic Society



American Academy of
Orthopaedic Surgeons®

AAOS American Association of
Orthopaedic Surgeons®

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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



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.

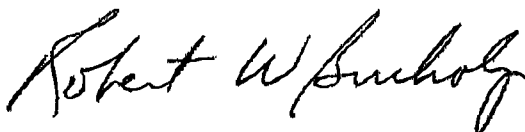
The Academy supports granting mechanisms, research incentives, and aid for small pediatric device companies to proceed with clinical trials. The FDA has precedent for making provisions to small companies. In 2002, MDUFMA granted reduced user fees for small device companies. Tax credits for manufacturers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

Conclusion

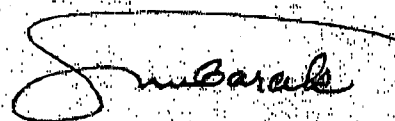
The Academy shares the concerns of the FDA in bringing safe and effective medical therapies into the U.S. marketplace. We look forward to working with

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

Sincerely,



Robert W. Bucholz, MD
AAOS President



Scott J. Mubarak, MD
POSNA President



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August 19, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fisher's Lane, Room 1061
Rockville, Maryland 20852
www.fda.gov/dockets/ecomments

RE: Docket Number: 2004N-0254

To Whom It May Concern:

On behalf of the over 4750 allergist, and specifically the approximately 2600 pediatric allergist members of the American Academy of Asthma, Allergy & Immunology (AAAAI), we are pleased to respond to the Food and Drug Administration's request for comments on the availability of medical devices intended to diagnose or treat diseases or conditions that affect children.

We feel strongly that more must be done to ensure that children benefit from devices designed and tested for use specifically in pediatric populations, rather than continue to use those that have been adopted or modified from adult use. Although many allergic diseases occur in both children and adults, there are definite differences with respect to disease diagnosis, treatment, and progression in children of differing ages, size, and developmental status.

Our comments draw from the experiences of pediatric allergy specialists involved in clinical care, clinical research, and basic science research on asthma and allergic and immunologic diseases of children.

What are the unmet medical device needs in the pediatric population?

- Better devices and standards to measure pulmonary function in infants and young children, including more affordable devices to use at home to monitor asthma.
- Devices for inhaled medications for infants and young children, to include better nebulizers, with shorter dosing times, and unit dose modules for a variety of medications.
- Dry powder inhalers for low inspiratory flow rates for use in younger children.
- Better devices for intranasal delivery of medications for infants and young children
- Auto-injectors for epinephrine with a broader range of doses suitable for infants and children.

In addition, there are some devices that currently exist, but, because of the lack of data, have questionable efficacy when used in infants and young children. For that reason, this suggestion has been made:

- Spacers/holding chambers that are designed and tested with specific medications in children so that pediatricians and specialists alike will be able to recommend combinations with documented efficacy.

Administrative Services, Inc. 10/1/04

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2004N-0254

C 10



AMERICAN ACADEMY OF ALLERGY
ASTHMA & IMMUNOLOGY

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

We believe that there are barriers that involve all of these issues. Specifically we feel that the following barriers are most important in our specialty:

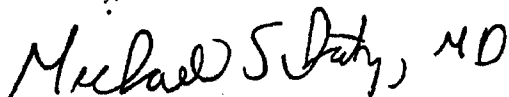
- Lack of accepted parameters of efficacy other than pulmonary function tests when studying asthma in children.
- Reluctance to study specific devices with specific medications, for fear of "marrying" a device to a medication. For example, spacers/holding chambers are used with medications in clinical practice, and are recommended for use by national expert panels. However, we need to be able to make choices based on data generated from studies of individual spacers/holding chambers with medications other than those for which they have been recommended.
- Need for a placebo arm in clinical studies for NDAs often hinders recruitment.
- Funding for novel uses for pediatric devices is often lacking and there are insufficient incentives for manufacturers to sponsor studies in children.
- There is reluctance to accept data from small independent studies.

What could the FDA do to facilitate the development of devices intended for the pediatric market? 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?

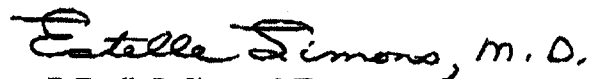
We would like to make the following suggestions:

- Develop standards for parameters of efficacy in children that do not depend on measures of pulmonary function, and accept those parameters as proof of efficacy
- Design studies of new medications so that the drugs or devices will be studied in the ways in which they will be used clinically. For example, insist that all new HFA devices that will have pediatric labeling be studied with spacers/holding chambers.
- Allow studies without placebo arms for infants and young children, to improve the ability to recruit patients.
- Have device manufacturers pay a portion of profits to fund studies on the use of these devices with other medications, or in other age groups.

Sincerely,



Michael Schatz, MD MS
President, AAAAI



F. Estelle R. Simons, MD
President-Elect, AAAAI



Paul V. Williams, MD
Chair, Ad Hoc Pediatric Asthma Task Force

Cc: Elaine Vining, Assistant Director, American Academy of Pediatrics

Comments from Healthcare Practitioners

Ortega, Gloria M

From: Scott-Tibbs, Gloria [GScott-tibbs@optometry.osu.edu]
Sent: Tuesday, August 17, 2004 10:40 AM
To: Less, Joanne
Subject: Response to the MDTCA

AUG 24 2004

Ms. Less,

The letter below is from Joseph T. Barr, OD, MS. He tried to submit this to you via the online link but was not able to do so. He requested that I send this to you so that it arrives by the August 20th deadline. Thank you for your attention to this.

Gloria Scott-Tibbs

August 15, 2004

Joanne Less

Center for Devices and Radiological Health

FDA, 9200 Corporate Blvd

Rockville, MD 20850 301 594 11909

Dear Ms Less

I am responding to the MDTCA of 2004 and request for comments on barriers regarding devices intended for children. The following editorial I wrote in Contact Lens Spectrum and the fact that 1.2 to 6.0/10,000 babies is born with a congenital cataract and will require contact lenses to prevent amblyopia should help understand this need. The attached link should help you understand as well. New high DK/T, DIPOSABLE contact lenses are needed and approval should be facilitated. Babies lose many lenses. If low cost lenses were available instead of paying over \$100 per lens these patient's parents would pay more like \$10 per lens.

Babies Need Contact Lenses, Too

BY JOSEPH T. BARR, OD, MS, FAAO, EDITOR

In the past few months, we've fitted two young aphakic children with high Dk scleral RGP contact lenses. Scleral lenses? I'm sure you're thinking, "You must be kidding." But I am not joking. Once the pediatric ophthalmologists and their staff in our area give up on costly silicone elastomer, soft and RGP lenses due to lens loss or poor fits, scleral lenses may be the only way to save these patients from vision loss. The obvious need here is for a low-cost, well-fitting, disposable silicone hydrogel lens or even a low-cost hydrogel disposable pediatric aphakic lens. Yes, I'm talking to you big manufacturers. You could even charge more for these lenses than the ones you're selling to low myopes and hyperopes. I realize not many babies need these lenses, but they sure need them more than any of your other patients.

In the early to mid-1980s when Dow Corning was planning to get out of the silicone contact lens business, a prominent pediatric ophthalmologist, John W. Simon, threatened Dow Corning with negative media exposure if they exited the pediatric aphakic lens business. A cagey Dow Corning Health Care Business VP offered to sell Dow Corning's unprofitable silicone lens business to Dr. Simon so he could make the lenses and save the babies' vision. Fortunately, Bausch & Lomb bought the silicone elastomer lens from Dow Corning, so these lenses are still available, and Dr. Simon didn't have to invest his life savings in making contact lenses for babies.

But these lenses are expensive and sometimes just don't work. I have discussed this need for pediatric aphakic lenses with the current silicone hydrogel lens manufacturers, and they are responding with some efforts to develop these designs. Let's hope their regulatory, legal and marketing priority challenges don't get in the way of helping the babies. You disposable hydrogel lens manufacturers may want to think about the babies, too. Not only would it be a good PR move, but you might actually save some sight.

2004N-0254
8/24/2004

EMC 2

<http://www.emedicine.com/oph/topic45.htm>

Many thanks for you interest.

Joe Barr, OD, MS, FAAO

Professor of Optometry and Vision Science

The Ohio State University

Gloria Scott-Tibbs

Coordinator

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Author: **C Corina Gerontis, MD**, Attending Staff, Departments of Pediatrics and Ophthalmology, Schneider Children's Hospital/Long Island Jewish Medical Center

C Corina Gerontis, MD, is a member of the following medical societies: [Alpha Omega Alpha](#), [American Academy of Ophthalmology](#), [American Association for Pediatric Ophthalmology and Strabismus](#), and [American Medical Association](#)

Editor(s): **Richard W Allinson, MD**, Associate Professor, Division of Ophthalmology, Texas A&M University Health Science Center, Associate Professor, Department of Surgery, Scott and White Clinic; **Donald S Fong, MD, MPH**, Assistant Clinical Professor of Ophthalmology, UCLA School of Medicine; Consulting Physician, Department of Ophthalmology, Southern California Permanente Medical Group; **J James Rowsey, MD**, Consulting Staff, Department of Corneal and Refractive Surgery, St Luke's Hospital; **Lance L Brown, OD, MD**, Ophthalmologist, Regional Eye Center, Affiliated With Freeman Hospital and St John's Hospital, Joplin, Missouri; and **Hampton Roy, Sr, MD**, Clinical Associate Professor, Department of Ophthalmology, University of Arkansas for Medical Sciences

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Background: A cataract is an opacification of the lens. Congenital cataracts usually are diagnosed at birth. If a cataract goes undetected in an infant, permanent visual loss may ensue. Not all cataracts are

visually significant. If a lenticular opacity is in the visual axis, it is considered visually significant and may lead to blindness. If the cataract is small, in the anterior portion of the lens, or in the periphery, no visual loss may be present.

Unilateral cataracts usually are isolated sporadic incidents. Bilateral cataracts often are inherited and associated with other diseases. They require a full metabolic, infectious, systemic, and genetic workup. The common causes are hypoglycemia, trisomy (Down, Edward, and Patau syndromes), myotonic dystrophy, infectious diseases (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex [TORCH]), posterior lenticonus, persistent hyperplastic primary vitreous, and prematurity.

Pathophysiology: The lens forms during the invagination of surface ectoderm overlying the optic vesicle. The embryonic nucleus develops by the sixth week of gestation. Surrounding the embryonic nucleus is the fetal nucleus. At birth, the embryonic and fetal nuclei make up most of the lens. Postnatally, cortical lens fibers are laid down from the conversion of anterior lens epithelium into cortical lens fibers.

Any insult (eg, infectious, traumatic, metabolic) to the nuclear or lenticular fibers may result in an opacity (cataract) of the clear lenticular media. The location and pattern of this opacification may be used to determine the timing of the insult as well as the etiology.

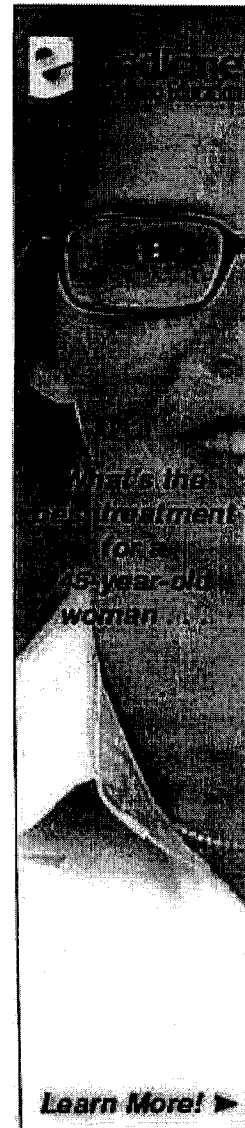
Frequency:

- **In the US:** Incidence is 1.2-6.0 cases per 10,000.
- **Internationally:** Incidence is unknown; although the World Health Organization and other health organizations have made outstanding strides in vaccinations and disease prevention, the rate of congenital cataracts is probably much higher in underdeveloped countries.

Mortality/Morbidity:

- Visual morbidity may result from deprivation amblyopia, refractive amblyopia, glaucoma (as many as 10% post surgical removal), and retinal detachment.
- Metabolic and systemic diseases are found in as many as 60% of bilateral cataracts.
- Mental retardation, deafness, kidney disease, heart disease, and other systemic involvement may be part of the presentation.

Age: Congenital cataracts usually are diagnosed in newborns.



CLINICALSection 3 of 9 [[Back](#) [Top](#) [Next](#)][Author Information](#) [Introduction](#) [Clinical](#) [Differentials](#) [Workup](#) [Treatment](#) [Follow-up](#) [Miscellaneous](#)
[Bibliography](#)**History:**

- Congenital cataracts are present at birth but may not be identified until later in life.

Some cataracts are static, but some are progressive. This explains why not all congenital cataracts are identified at birth.

- Not all cataracts are visually significant. If a lenticular opacity is in the visual axis, it usually is considered visually significant and requires removal.

Physical:

- A lenticular opacity is called a cataract. Not all cataracts are visually significant.
- Description of a congenital cataract must include location, color, density, and shape for purposes of identification.
- An irregular red reflex is the hallmark of visual problems. If an irregular red reflex is detected at the initial screening, this is usually an indication that a congenital cataract is present and an ophthalmology consultation is warranted.
- Slit lamp examination of both eyes confirms not only the presence of a cataract, but it also may identify the time when the insult occurred in utero and if there is other systemic or metabolic involvement.

Causes:

The most common etiology includes intrauterine infections, metabolic disorders, and genetically transmitted syndromes. One third of pediatric cataracts are sporadic; they are not associated with any systemic or ocular diseases. However, they may be spontaneous mutations and may lead to cataract formation in the patient's offspring. As many as 23% of congenital cataracts are familial. The most frequent mode of transmission is autosomal dominant with complete penetrance. This type of cataract may appear as a total cataract, polar cataract, lamellar cataract, or nuclear opacity. All close family members should be examined.

- Infectious causes of cataracts include rubella (the most

common), rubeola, chicken pox, cytomegalovirus, herpes simplex, herpes zoster, poliomyelitis, influenza, Epstein-Barr virus, syphilis, and toxoplasmosis.

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Retinoblastoma

Other Problems to be Considered:

Corneal opacity (ulcer, scar, dermoid)
 Persistent hyperplastic primary vitreous
 Retinal detachment
 Lenticular coloboma

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Lab Studies:

- Unilateral cataracts
 - Prenatal and family history
 - Slit lamp examination in both eyes (dilated pupil)
 - Dilated fundus examination
 - Laboratory studies include TORCH titers and Venereal Disease Research Laboratory (VDRL) test.
- Bilateral cataracts
 - Prenatal and family history
 - Slit lamp examination in both eyes (dilated pupil)
 - Dilated fundus examination
 - Genetics evaluation
 - Laboratory studies include CBC, BUN, TORCH titers, VDRL, urine for reducing substances, red cell galactokinase, urine for amino acids, calcium, and

phosphorus.

Imaging Studies:

- CT scan of brain

Other Tests:

- Hearing test

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Medical Care: Prevention of amblyopia

Surgical Care:

- Cataract surgery is the treatment of choice and should be performed when patients are younger than 17 weeks to ensure no visual deprivation. Most ophthalmologists opt for surgery much earlier, ideally when patients are younger than 2 months. The delay in surgery is because of glaucoma. Since glaucoma occurs in 10% of congenital cataract surgery, many surgeons delay the cataract surgery. Unfortunately, the improved surgical techniques of the 1990s have not lowered the incidence of glaucoma from the series published in the 1980s. The development of glaucoma (which occurs in later years) only occurs in cataract eyes that undergo surgery. This may be in part due to the immaturity of the angle at the time of surgery. A delay of a few weeks allows the angle of the immature eye to develop.
- Extracapsular cataract extraction with primary posterior capsulectomy and anterior vitrectomy is the procedure of choice (via limbal or pars plana approach). Intracapsular cataract extraction in children is contraindicated because of vitreous traction and loss at Wieger capsulohyaloid ligament. Vitrectomy instrumentation is the preferred method since the lens material is very soft. The whole procedure can be performed using one intraocular instrument. Young eyes develop capsular opacification very quickly necessitating primary capsulectomy at the time of cataract extraction.
- A new US study is under way to determine if intraocular lens placement in children younger than 6 months is a viable option (several articles already have been published in the British Journals).

Consultations:

- An ophthalmology consultation is essential to prevent visual loss as well as make the appropriate diagnosis of the type of cataract.
- Genetics evaluation if bilateral or any other anomalies are present

Diet: Restriction of galactose, if galactosemia is present, may reverse the progression of the

classic "oil droplet" cataract.

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Deterrence/Prevention:

- A red reflex is essential not only in the newborn nursery but in all office visits.
- Amblyopia prevention by frequent eye examinations
- Frequent glaucoma screenings throughout life

Complications:

- Loss of vision even with aggressive surgical and optical treatment
- Amblyopia
- Glaucoma
- Strabismus
- Retinal detachment

Prognosis:

- Of persons with unilateral cataracts, 40% develop vision of 20/60 or better.
- Of persons with bilateral congenital cataracts, 70% develop vision of 20/60 or better.
- Prognosis is poorer in persons with other ocular or systemic involvement.

Patient Education:

- Removal of the cataract is only the beginning. Visual rehabilitation requires many years of refractive correction (contact lenses or aphakic glasses), possible patching for amblyopia, possible strabismus surgery, and glaucoma screenings.
- Awareness of the risk of potential visual loss either from amblyopia, retinal detachment, or glaucoma.
- Possible need for repeated surgical procedures, including secondary lens implant if other modalities of refractive correction fail.
- If this is a de novo chromosomal change or a familial abnormality, all siblings and future offspring are at risk.



MISCELLANEOUSSection 8 of 9 [[Back](#) [Top](#) [Next](#)][Author Information](#) [Introduction](#) [Clinical Differentials](#) [Workup](#) [Treatment](#) [Follow-up](#) [Miscellaneous](#) [Bibliography](#)**Medical/Legal Pitfalls:**

- Since there is a high association of systemic and metabolic abnormalities, genetic consultation is essential in bilateral cataracts. Some diseases may be preventable if diagnosis is made early.

BIBLIOGRAPHYSection 9 of 9 [[Back](#) [Top](#)][Author Information](#) [Introduction](#) [Clinical Differentials](#) [Workup](#) [Treatment](#) [Follow-up](#) [Miscellaneous](#) [Bibliography](#)

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NOTE:

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2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments

FDA Comment Number : EC10

Submitter : Dr. Stuart Goldstein

Date & Time: 08/25/2004 04:08:33

Organization : FDA

Federal Government

Category :

Issue Areas/Comments

GENERAL

GENERAL

I am a pediatric nephrologist who serves as a special government employee and member of the CDRH advisory panel. I want to first thank you for your interest in children.

I forwarded the 3 questions posed in your request for comments to the medical and surgical division chiefs at Texas Children's Hospital, which is the largest pediatric hospital in the United States. While the specific device needs were obviously peculiar to each specialty, a number of themes emerged. I have distilled these for each question, and attached a copy of their individual responses for your review.

Sincerely,

Stuart L. Goldstein



Texas Children's Hospital
www.texaschildrenshospital.org



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August 13, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fisher's Lane
Room 1061
Rockville, Maryland 20852

Re: Docket Number 2004N-0254

Dear Center for Medical Devices and Radiological Health Director,

I am responding to your request for comments regarding the possible barriers to the availability of medical devices intended to treat or diagnose diseases and conditions that affect children. I am a pediatric nephrologist who serves as a special government employee and member of the CDRH advisory panel. I want to first thank you for your interest in children.

I forwarded the 3 questions posed in your request for comments to the medical and surgical division chiefs at Texas Children's Hospital, which is the largest pediatric hospital in the United States. While the specific device needs were obviously peculiar to each specialty, a number of themes emerged. I have distilled these for each question, and attached a copy of their individual responses for your review.

2004N-0254

C13

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?

Almost every specialty responded that appropriately sized instruments are not readily available, or certainly no significant choice exists, for the entire range of patient sizes seen in pediatric sub-specialty settings. The major areas of deficits are:

1. Renal – Dialysis catheters, hemodialysis and continuous renal replacement therapy circuit tubing, hemodialyzers, blood pressure cuffs and ambulatory blood pressure monitors
2. Pulmonary – Bronchoscopy equipment, nasal and facial oxygen supplementation equipment, fiberoptic scooping devices
3. Cardiology – Intravascular stents and devices, cardiac assist device technology (artificial hearts, left-ventricular assist devices)

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

The major barrier to development for all pediatric subspecialty equipment is economic. Just as existed with drug development for children, companies are unwilling to develop and formally study devices in children for fear of liability from a bad outcome coupled with lack of significant economic incentives or profit in the relatively small pediatric population. I have personally tried to work with catheter companies to develop smaller catheters for infants with multi-organ system failure who require dialysis and need a small but reliable vascular access. Manufacturers have told me the R&D and FDA regulations make such endeavors cost prohibitive, given the small market. Furthermore, conducting the appropriate studies to attain FDA device approval requires most often a multi-center pediatric effort in order to enroll sufficient patients. I have spearheaded such an effort with respect to pediatric CRRT. The Prospective Pediatric CRRT (ppCRRT) registry group is now conducting a four-center trial of an infant CRRT filter, which is available in Europe, Canada and Mexico, to attain FDA 510K approval. Gambro Renal Products is funding the study, which they could not previously get initiated since no collaborative group existed previously, and the contractual negotiations

between a company and separate institutions creates more burden on the whole development and testing process.


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?

The FDA may have a number of options to facilitate the device development process.

1. As with drugs, the FDA could extend patent exclusivity for certain device types developed for children. While we want to increase the choice when it comes to catheters for instance, other areas where no pediatric device exists may be appropriate for this type of patent protection.
2. Lower the cost of FDA application by identifying pediatric chronic illness populations as orphans, thereby making them subject to the orphan drug act. Many smaller companies have told me that a significant reduction in application costs would lower their threshold to enter into the pediatric market.
3. Encourage the FDA Centers and the NIH to support multi-center collaborative networks to expedite device testing and application in pediatric patients. Out ppCRRT registry is serving as a model to the adult nephrology community in this regard. These networks can decrease and simplify the contractual processes, provide the FDA with a quality control mechanism and foster rigorous scientific evaluation of the devices.

I have attached the specific responses I received at the end of this letter. Once again, thank you for your interest in improving the healthcare of children.

Sincerely,


Stuart L. Goldstein, MD
Associate Professor of Pediatrics
Baylor College of Medicine
Medical Director, Renal Dialysis
Texas Children's Hospital

E-mail comments received

**From George Mallory, MD,
Pediatric Pulmonologist and Director Pediatric Lung Transplant Program at
Texas Children's Hospital**

Let me address medical devices that have to be adapted with growth. This is, I believe, our biggest problem in pediatric pulmonology. With respect to endotracheal and tracheostomy tubes, we have very good choices now a days. With respect to nasal masks for nasal ventilation (BiPAP and CPAP), we often have the cheapest forms only since the more adaptable devices are more expensive and insurers almost always will not pay the hospital for in-patient and home care companies for out-patient uses. Not only that but these devices often need to change with growth so expense is a built-in part of treating growing children. Our current market forces penalize children, providers and manufacturers in this regard.

Bronchoscopes have moved from fiberoptic technology to video-chip devices. Obviously, adult scopes came first but Olympus is moving chip technology into the smaller scopes and all manufacturers need to be encouraged to spend the money on miniaturizing all such equipment, preferably with governmental incentives and not threats. It is more expensive and there will be less profit because the volume for pediatrics will not be so great. The government needs to find incentives along the lines of orphan drugs to encourage these devices.

**From Yadin David, Director of Biomedical Engineering at Texas Children's
Hospital**

Hi Stu:

I'm delighted to see the attention this issue is getting at the FDA level. Over the years several issue regarding medical devices for pediatrics repeated themselves again and again. Here are some quick few comments I would like to share with you:

1. lack of market needs understanding by manufacturers. Pediatric device is not a "smaller" adult device.
2. the pediatric device is a smaller volume market and does not attract industry, perhaps government should exercise incentives to change that.
3. labeling for use and warnings affixed to devices and disposables are not appropriate for parents nor for children who may use them.
4. the environment of use maybe in noisy areas on one hand and in noise-free (like our NICU) on the other, however device features (like alarms) do not accommodate that.
5. sibling protection should be standard feature on devices, and finally,

6 I recommend we apply for a grant to develop resource center to support families who needs to use medical devices out side the hospital and do not have a point of information to go to.

From David Wesson, MD, Chief of Pediatric Surgery at Texas Children's Hospital

Stuart,

We reviewed this at our faculty meeting on Friday but didn't come up with anything apart from the 2 well know issues:

1. Devices for kids may not be profitable
2. It's hard to do research on children

David Wesson

2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments

FDA Comment Number : EC1

Submitter : Mr. Philip Kong

Date & Time: 07/19/2004 05:07:42

Organization : Children's Hospital Boston

Health Professional

Category :

Issue Areas/Comments

GENERAL

GENERAL

I am the Director of the Pediatric Product Development Initiative (the PPDI) at Children's Hospital Boston. Please see: http://www.childrenshospital.org/cfapps/Research_2004/data_admin/mainpageS49P17.html.

The goal of the PPDI is to foster the development and commercialization of pediatric medical devices. Pediatrics is generally an underserved population as the populations in various pediatric indications are not large enough to provide a financial incentive for medical device companies to invest in the infrastructure to produce medical devices for pediatric use. Transferring pediatric medical device technology to companies that will bring them to market required overcoming daunting challenges. The challenges affecting the availability of medical devices intended to treat or diagnose diseases and conditions that affect children include the limited size and fragmented nature of the pediatric market, and the fact that clinical development pathways require specialized expertise in design, development and testing before the medical device industry will evaluate product ideas. In the absence of initial development, the return on the investment required to develop these products usually falls below the target profit goals of most medical device companies. Reimbursement is also a very important issue. The CPT codes, for example, do not exist for many procedures involving children. This makes the billing and reimbursement process more complicated and is a factor taken into consideration when medical device companies contemplate whether to develop a product that treat pediatric conditions. The process of getting these codes in place is time consuming and expensive and without the attendant market size to go after, companies and their shareholders are unwilling. The prospect of profitable economics isn't there. But if we are able to take some of the risk out of the development process, then we help to 'jump start' this process.

As with most technologies, 'gap funding' is an issue. With pediatric medical devices, it is an even more important issue if the economics of the market is not enticing enough to prompt capital investment. There is a gap between the ideas that we have to create needed pediatric medical devices and the ability to make prototypes, put those prototypes through well run clinical trials and get them to the children that need them. It is money that will bridge this gap. For example, if a program such as ours had access to product development funding, then with the organization that we have built, we could engage in the risky early stage development process where a company is unlikely to get involved and then gather the data that would show that a particular device idea has merit. Thereafter, we can engage with medical device companies in order to take the idea further and eventually into the clinic's, hospitals and pediatrician offices where they can positively impact children's health care. We carefully select the device ideas based on a number of criteria here at the PPDI, and have chosen with our very limited resources to begin with the development of a couple devices that have a not-insignificant market size. The hope is that with hoped-for success in commercializing some of those devices, we can turn our attention to developing and commercializing those devices that would not have a chance of being developed at all. Devices that are needed in the area of fetal surgery come to mind. The area of pediatric medical devices generally is an area that desperately needs attention and I hope that we can find a way to do the right thing for the sake of children in America. Thanks for your attention. I am available for follow-up at philip.kong@childrens.harvard.edu or (617) 355-2835.

Sincerely, Philip Kong, JD, MBA, Director Pediatric Product Development Initiative, Children's Hospital Boston

The Pediatric Product Development Initiative

Children's Hospital Boston (CHB) has created the Pediatric Product Development Initiative (PPDI) to translate innovative ideas for improving pediatric care into commercial products. Because of the small market size and challenging product development requirements in pediatric medicine, businesses are usually unwilling to invest in significant and much-needed pediatric innovations at the early stage. To address this situation, PPDI will develop selected ideas into practical products, test them, and license them as reduced risk and value-added opportunities to the medical device industry. The first strategic focus will be on the Neonatal Intensive Care Unit. PPDI has engaged a network of highly qualified engineering, testing, manufacturing, and regulatory experts to work with Children's Hospital clinicians in this endeavor. Three products are currently being developed and the PPDI has already received two NIH SBIR Phase I grants with a third on the way. In addition, an Investors Circle is currently being formed that will provide the capital to finance product development programs. Additional financing will be solicited from not-for-profit sources. PPDI expects to become financially self-sufficient as a result of royalties obtained from developed products or from the sale of equity in companies formed around PPDI-developed technologies. The PPDI is affiliated with the CHB Intellectual Property Office (IPO).

Components of the PPDI include:

The Product Imagination Forum – forming groups to brainstorm new product ideas according to needs in the patient care environment;

Stimulating invention disclosures from faculty and staff

Capabilities for developing new products at pre-clinical and clinical stages; and

Alliances with external resources in the areas of product design, prototype development, testing, and regulatory affairs. These include the following organizations:

AlvaMed, a network of consultants with experience in device design, project management, reimbursement issues and business strategy,

Product Genesis, one of the premier product development houses in the country

Technology Partners, a combination of engineering expertise (*Foster Miller*), product design and development expertise (*Herbst Lazar Bell*) and manufacturing expertise (*Nova Biomedical*)

CIMIT, the Center for Integration of Medicine and Innovative Technologies

Project Selection Criteria

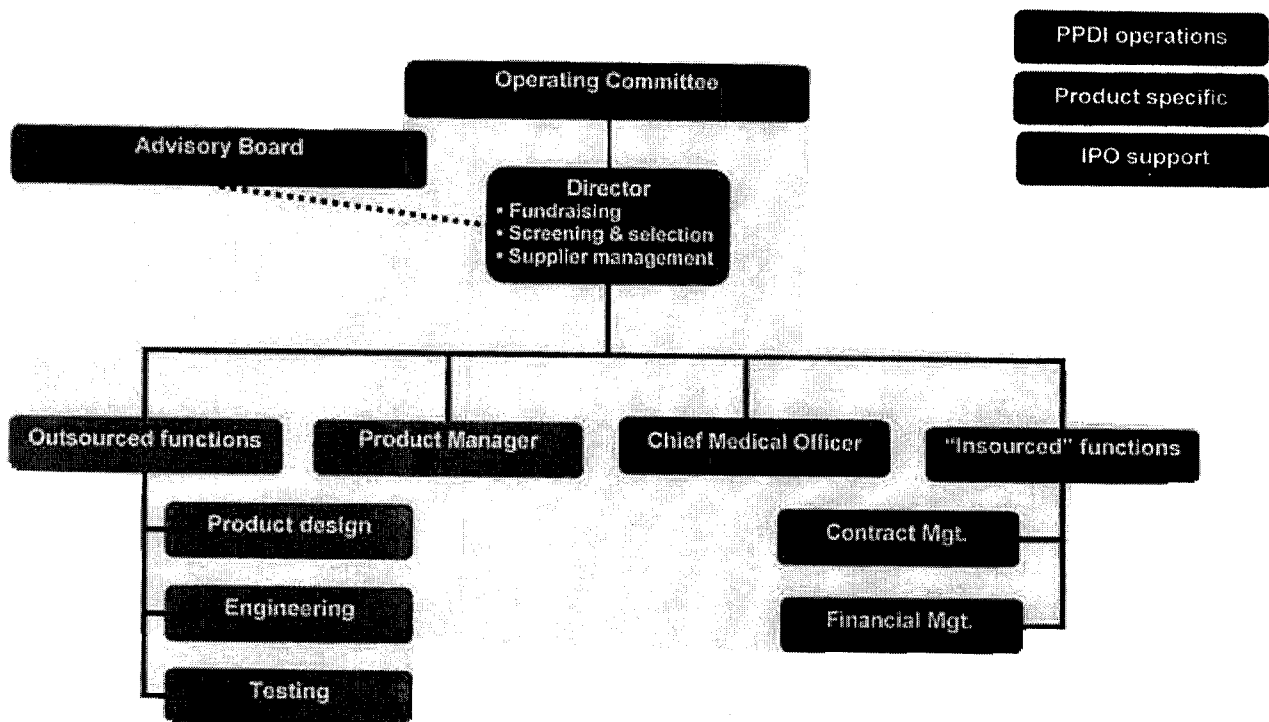
Product ideas and opportunities are evaluated according to the following criteria:

- Patient Benefit – Would the technology reduce mortality and morbidity? What would be the improvement in cost and access in comparison to other technologies?
- Competitive landscape – Does the technology address an unmet need? Does it introduce a new paradigm for treatment?
- Market size – What is the size of the market in dollars?
- Remaining Technical Risk – What technological obstacles need to be overcome in order for the technology to be viable?
- Regulatory Risk – Is the device invasive or does it require special approval?
- Development Stage – Does a prototype exist?
- Intellectual Property Status – Has a patent application been filed?

Because PPDI's mission is to focus on unmet needs in pediatric care, Competitive Landscape and Patient Benefit are weighted most heavily. Market Size, Remaining Technical Risk and Regulatory Risk are significant because the products need to be commercially feasible, but these factors are weighted less heavily than they would be if return on investment were the only goal. Development Stage is weighted least heavily because PPDI will be adding value and developing IP through the product development process. The PPDI is also working with the US Congress to favorably change the regulatory dynamic of the pediatric medical device sector.

The Team

Philip Kong is serving as PPDI Director. He holds a JD from Harvard Law School and an MBA from the MIT Sloan School of Management. His professional experience includes business development, product development and marketing in the semiconductor, wireless and biotech industries, and corporate legal work in securities law and mergers and acquisitions. Mark Cox serves part-time as Engineering Consultant. He holds an MS in Manufacturing Economics from MIT. He has extensive experience in product development, intellectual property management, and technology investment at Arthur D. Little and is currently President of Alvamed, Inc, engineering firm. A Product Manager will be hired upon receipt of product funding.



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http://www.childrenshospital.org/cfapps/Research_2004/data_admin/mainpageS49P17.html

2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments

FDA Comment Number : EC5

Submitter : Mrs. Patricia Tierney

Date & Time: 08/24/2004 05:08:48

Organization : Mrs. Patricia Tierney

Health Professional

Category :
Issue Areas/Comments

GENERAL

GENERAL

As a school nurse in Mesa, AZ, I was amazed to find that insurance will not pay for a wheelchair lift for a child with spinal muscular atrophy (children's form of Lou Gehrig's disease), who weighs 100 lbs and has no use of his legs, and is very weak in the arms. His mom has to unfold a huge metal ramp, attach it to the van, and push the electric wheelchair up the ramp with the child in it. The insurance company does not consider an electric lift a necessity.

2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments

FDA Comment Number : EC9

Submitter : Dr. Arlan Rosenbloom

Date & Time: 08/25/2004 04:08:09

Organization : University of Florida College of Medicine

Academia

Category :

Issue Areas/Comments

GENERAL

GENERAL

The following comments reflect thoughtful input from: Richard Melker MD, Professor of anesthesiology, biomedical engineering, and pediatrics in the Department of Anesthesiology; Max Langham MD, Professor and chief of pediatric surgery; Mike Chen MD, pediatric surgeon; Joseph Paolillo MD, pediatric cardiologist; Arno Zaritsky MD, director of the pediatric ICU; and Janet Silverstein Professor and chief of pediatric endocrinology. This is a broad but not comprehensive representation of the pediatric spectrum, somewhat limiting the response to question number 1, but it is unlikely that responses to questions number 2 and 3 would be different for other specialists.

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?

Pediatric endocrinologists and surgeons are unable to offer massively obese children and adolescents intervention to reverse this life threatening condition, because restrictive banding as is used in adults with some success and particularly gastric pacing which holds promise in this situation, is unavailable to children. Implantable insulin pumps that talk to glucose sensors are being tested in adults, and it is unclear when children and adolescents can benefit from such testing. There has always been a problem getting life support equipment in pediatric sizes.

2. What are the possible barriers to the development of new pediatric devices? Are there regulatory hurdles? Clinical entrances? Economic issues? Legal issues?

The hurdles are all listed in the question. Although sick children are not a great revenue source for institutions, they are capable of using a disproportionate share of the health-care dollar if they are not adequately cared for. Reimbursement for simple devices such as gastrostomy ports is below their cost and physicians are increasingly disinclined to lose income providing such equipment to underfunded patients. The loss to institutions on implantable devices, whether instrumentation for scoliosis, vagal nerve stimulators, or baclofen pumps is much higher on a per unit basis, and many hospitals will no longer provide these services. Medicaid insists on funding the devices as part of their disproportionate share dollars. This mechanism allows hospitals that are not providing expensive medical devices to share in the revenue stream meant to fund the devices, ultimately making the losses for those hospitals providing the service more severe. The poor reimbursement is the basis for the commercial problem of development of new pediatric devices. We are one of the few countries wealthy enough to provide such care to children, and the incidence of disease is low enough that the US market is relatively small...with little or no export potential. This numbers game makes the return on investment small for medical device manufacturers providing pediatric devices, unless they are dual use with adults. This is a major brake on development and manufacture of appropriate devices of all types for our children.

The reality of the free-market system and the small market size of the pediatric population for most devices, together with the inability to charge a premium for these devices or even assure recovery of costs is undeniable.

The current regulatory environment requiring IRB approval at each individual institution is an important barrier. These devices typically represent niche uses for which a large number of institutions must collaborate to answer questions about safety, efficacy, and cost benefit. It is increasingly difficult to do product development at universities to do federal and state

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regulations and the legal issues are staggering. Companies are loath to invest heavily in new technology if reimbursement is not available in research is increasingly difficult to do because of IRB hurdles, intellectual-property hurdles, and conflict of interest hurdles.

Liability insurance can currently account for over 30% of the cost of a medical device. Many companies shy away from new product development for the insurance risk is too great, particularly in the field of pediatrics.

FDA regulations are threatening progress in the field of pediatric cardiac intervention.

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?

Appropriate funding mechanisms are needed to pay for medical devices and industry incentives will need to be provided to stimulate research and development on new devices. Funds to innovative investigators with good ideas who may not have a research track record should be available for breakthrough ideas; the current environment tends to lead to small increments.

It would be extremely helpful for the FDA to fund an independent, centralized IRB review process to assure that the risks are appropriate and the science is appropriate. This would remove the variation in interpretation and local bias as well as needless wordsmithing of consent forms, facilitating studies of new devices and therapeutics. Cost savings might encourage more companies to undertake multicenter trials.

Although research and children must be carefully and forcefully regulated, this should not stifle innovation, but this is what is currently happening, largely because of liability issues. Taking the lawyers out of the equation is likely not feasible, given the trial lawyers' power.

It has been suggested that Dr. Robert Bartlett at the University of Michigan, a father of ECMO, would be a knowledgeable resource on medical devices, with regard to regulatory hurdles and legal issues.

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July 14, 2004

To: Food and Drug Administration
Center for Devices and Radiological Health

From: Mark H. Hoyer, MD
Director, Cardiac Catheterization and Interventional
Cardiology
Riley Hospital for Children
Associate Professor of Clinical Pediatrics
Indiana University School of Medicine

Re: Possible Barriers to the Availability of Medical Devices
Intended to Treat or Diagnose Diseases and Conditions that
Affect Children; Request for Comments [Docket No. 2004N-
0254]

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MEDICAL
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Specialty Care

This letter is a response to the request for feedback concerning possible barriers to medical devices for children. Specific questions posed by the FDA and CDRH include:

- 1 What are the unmet medical device needs in the pediatric population? Are they focused in certain medical specialties and/or pediatric subpopulations?

As a pediatric cardiologist practicing for 15 years, I have been excited to see the recent strides made in studying and approving devices for children with various congenital heart defects. Nowadays, we can treat patent ductus arteriosus (PDA), secundum atrial septal defect, pulmonary and aortic valve stenosis, and occlude various vessels with devices or open them with balloon catheters or stents. Interestingly, however, many of the devices we use for catheter intervention/therapy involve off-label uses to deliver direct benefit for these children. The medical literature is replete with information regarding the use of "biliary" stents in the treatment of pulmonary artery stenosis, coarctation of the aorta, maintenance of ductal patency, and so forth. Likewise, embolization coils, initially released nearly 30 years ago for peripheral vessel occlusion, have been adapted for use in closing patent ductus arteriosus and even unusual abnormalities, such as surgical Fontan baffle leaks or intended fenestrations, as well as paravalvar leaks after prosthetic valve replacements. A device is now available for treatment of PDA for which it was designed and investigated. However, this device, the Amplatzer Duct Occluder, has been used in a variety of other vessel occlusions.

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While we now have a device designed for ASD and one for PDA closure, not all ASD's or PDA's have the same size or morphology. Most congenital heart defects have considerable variability in morphology and location. In other words, it is desirable to ultimately have the right tool for the job, rather than trying to adapt one device for all (i.e. trying to use the Amplatzer device to close every kind of PDA).

Another example of an unmet need is nonsurgical management of the neonatal PDA. In some cases, a large PDA needs to be closed, but currently existing materials and devices are not appropriate. Further, we are embarking on different ways to treat hypoplastic left heart syndrome, which will include implanting a stent to maintain patency of the ductus arteriosus. Some centers are using stents designed for adult problems (self-expanding or balloon expandable stents). The length and diameter of stents for our neonates is critical to achieve a good result. Covered stents hold tremendous interest for the benefit of our patients. Balloon angioplasty or stent implantation to treat coarctation really should involve either the primary use of a covered stent or the availability of a covered stent as a bailout in the event of an unexpected aortic rupture. Materials and stent designs particularly suited to these patients is essential. Drug-eluting stents are now available, but are designed for adults with coronary artery disease. As pediatric interventional cardiologists, we use what is available and adapt it the best we can to treat our patients and offer them the chance to avoid major surgeries. Ventricular septal defect devices are undergoing investigation, but different devices may be needed to treat the various types of VSD.

To summarize our current practice, we are involved in treatment of native defects (unoperated), residual/recurrent defects, palliative procedures that may bridge to further surgery, and are just beginning "hybrid" surgery (the use of endovascular catheter techniques with surgeon-assisted more direct cardiac access in the Operating Room).

2. What are the possible barriers to the development of the new pediatric devices? Regulatory? Clinical? Economic? Legal?

The overall lower volume/numbers in the pediatric population as compared to the adult population results in long time needed to enroll enough patients for any one device. Further, the variability of cardiac congenital defects, such as VSD, results in data that is less uniform. This often results in the need to extend the investigation even longer. Also, congenital heart disease itself entails a broad range of very different anatomic defects with vastly different physiologies.

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Therefore, one specific defect is not seen daily over and over again, as coronary artery disease is seen by adult cardiologists.

As for regulatory considerations, each new design modification has required a complete regulatory process, including a new clinical trial. An example is the Amplatzer Duct Occluder. It was investigated in sizes ranging from 5mm to 16 mm. However, the largest 2 sizes, 14 mm and 16 mm, were utilized in too few patients for them to be marketed after FDA approval of the device. The design is exactly the same, just that the larger two sizes were implanted in enough patients. This resulted in an additional trial sponsored by the manufacturer, but this study was terminated by the manufacturer because enrollment was so slow. Unfortunately, I had a patient who could have benefited from one of these larger devices. I was barely able to get by with the 12 mm device, but the smaller size created some concern about device embolization. A higher level of safety would have been achieved with the larger device.

Because of the low numbers in pediatrics, industry has been reluctant to invest in pediatric devices because of the small market. Some companies have made the effort and investment and hold a significant share of the pediatric market as a result.

3. What could FDA do to facilitate the development of devices intended for the pediatric population?

Any studies need to be done on as large a scale as possible in order to maximize patient enrollment. Larger centers with a track record of successful clinical trials and data submission should be included. The acceptable numbers for patient enrollment nationwide may have to be modified. For instance, if it takes 5-6 years to gather enough data with a device, but during the process, we discover that a modification to the device would improve its design, safety, and efficacy, then it takes another 5-6 years to complete a study of the modified device. So, in 12 years, we can provide the better device to many patients. In our current technology climate, this seems inordinately long to wait. Maybe decreasing the required enrollment number satisfactorily could shorten these studies to 2-3 years, at the longest.

Given the increasing longevity for patients with congenital heart disease, maybe industry can be persuaded to invest in congenital heart disease and tailor devices for the anticipated needs of those patients. Some financial incentive for research and design by these manufacturers might prove to be effective.

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The time period from submission of PMA application to completion of data analysis and FDA market approval needs to be significantly shortened. This process adds another year to the entire process.

Finally, any one center should be allowed to be involved in several ongoing clinical trials for different devices intended for the same clinical situation/diagnosis. This allows the investigators to form their own opinions about different devices for the same job, thereby allowing them to remain unbiased but also streamline the medical understanding of which device works best in which situation. Likewise, the FDA should approve trials for different devices that serve the "same" purpose in order to expedite the understanding and improvement of device designs.

Naturally, this question is the hardest to answer, but hopefully, others in the FDA who know the workings of the government can use these suggestions to brainstorm as well. Thank you very much for the opportunity to provide these comments.

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Docket No. 2004 N-0254

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July 12, 2004

These comments address the needs of children with congenital heart defects. Such children benefit from catheter implanted devices for occlusion of cardiovascular defects and for devices, such as stents to maintain patency of vessels.

I have been a practicing paediatric cardiology during the whole development of catheter interventions for congenital heart disease. The first intervention to be widely employed was balloon atrial septostomy, introduced in 1966. This dramatically improved survival of newborns with transposition. This improvement was evident within a few months of its introduction. As far as I know this procedure and the catheter for performing it were not subject to any regulatory control. This meant that as soon as the catheter became available it was used world wide and, within 3 or four years hundreds of baby's lives were saved¹. Had there been the prolonged FDA regulatory process, as there is now, most of these babies would have died.

Heart disease in children is a particular problem. The patient base is small. It is estimated that in England and Wales approximately 4000 babies are born annually with a congenital heart malformation. Of these half need no treatment. Of the 2000 needing treatment approximately 1000 to 1200 need treatment within the first months of life. Contrast this with the number of patients receiving treatment for coronary artery disease, approximately 35000 in 1994² in England and Wales. Furthermore, those babies and children needing treatment have a wide variety of anatomical anomalies each requiring a different type of treatment, some need surgery, some balloon valvoplasty some a device implantation; and each of these broad treatment categories has many anatomical and physiological variations. In

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addition equipment has to be produced to cater for all sizes of children from 3 or 4 pounds weight up to adult weights. There is no such thing as 'one size fits all' in paediatric cardiology. If we take as examples balloon dilation catheters and defect occlusion devices. The manufacturer of balloon catheters has to produce a wide variety of sizes and make them to pass through very small introducer sheaths, yet, compared to coronary angioplasty balloons, they will sell only small numbers. The occlusion device manufacturer has to design a different device for each of; atrial septal defects, muscular ventricular septal defects, perimembranous ventricular septal defects and patent ductus. And again carry a large inventory. It is also a feature of the speciality that frequently a custom balloon or device is needed, tailored to the needs of a particular patient, the small number of companies catering for the paediatric cardiology community have been most helpful in this regard.

This small market accounts for the lack of interest that major equipment manufacturers show in paediatric patients. Few companies cater for this field and they are small.

The small patient base means that it is well nigh impossible to build up clinical trial numbers to compare to, say, coronary trials. In a multi centre study it took 4 years to amass 829 patients having had surgery for transposition of the great arteries, one of the commonest anomalies presenting in infancy³. It is therefore unreasonable for regulatory bodies to impose the same patient number standards on trials of paediatric devices as they do for devices or drugs used in adult practice. The small market means that, to surmount the regulatory process, a disproportionate amount of company finance and time is used up by manufacturers in the paediatric field.

As a result of all these factors the delays and costs are putting children at a disadvantage and, in addition, tend to stifle innovation. The irony is that although the manufacturers are based in the United States, it is the children of your country who are most disadvantaged, being denied methods of treatment that have often become routine in Europe.

In my opinion, an approach more like that in the European Union would help break down the barriers. Any device should be examined for its structural integrity and biocompatibility. Then the Institutional Review Bodies or Ethics Committees should be relied upon to recommend if the device should be released for general use. Of course the integrity of the investigating or innovating doctors has also to be relied upon. This is not a problem, nobody gets rich in our speciality so there is little incentive to cheat.

I have to declare an interest; I am in receipt of royalties from NuMed Inc.



Michael Tynan, MD, FRCP.

Emeritus Professor of Paediatric Cardiology

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References

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It would help tremendously if devices designed for pediatric cardiac applications were evaluated specifically by pediatric cardiologists familiar with the field. In my experience, the devices are currently often evaluated by people who have so little knowledge about the current state of the field that they are paralyzed from effective action. If experts were utilized, less clear and voluminous data could still be reasonably interpreted. I was involved with a group through the Society for Cardiovascular Angiography and Interventions which tried to use expert consensus to define criteria for approval of new pediatric catheter intervention devices. If companies know explicitly what is expected in terms of safety and efficacy, they would be in a much better position to evaluate the likelihood of approval. Experts in the field may be able to come to a consensus proactively about criteria that should be met for a new type of device to be approved. In the current environment, criteria for eventual approval are very ambiguous, and the uncertainties make companies loath to consider a marginal product (which all products in our field would be).

I believe that the goal of the FDA should be to develop reasonable mechanisms that promote the availability of new technology for children more quickly. This can be done by more active use of experts in the field earlier in the process. Experts who are already familiar with the field can better define for the FDA, and the manufacturer's, criteria for device performance that would at least equal current practice. Devices could be made available with smaller trials if longer term follow up is mandated for all early recipients of a new device approved under this type of streamlined pathway. There may need to be legal considerations given to companies with devices approved along such a streamlined pathway. There may need to be mechanisms developed to insure that mandated long term follow-up is carried out and reported appropriately. Insurance companies may need to be engaged to rapidly approve payments for the use of new technology which may reduce overall long-term health care costs.

I am certainly aware that there are many issues involved with simultaneously safeguarding the public health and making new technology available in a timely manner. I do feel that significant improvements could be made in the speed of the approval process for devices for children with congenital heart defects without compromising overall safety for this population of patients.

I hope my comments may be helpful to the FDA and others reviewing barriers to availability of devices intended for treatment of diseases and conditions that affect children. Many pediatric cardiologists, myself included, would be happy to be involved with developing better approval mechanisms for patients with congenital heart disease.

Sincerely,



Larry A. Latson, M.D.

/tm



July 19, 2004

Linda S. Kahan
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Re: Docket No. 2004N-0254

Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments

Dear Linda:

I would like to thank the FDA for the invitation to comment on barriers to the availability of devices intended for treatment or diagnosis of diseases and conditions that affect children. I am the Chairman of Pediatric Cardiology at the Cleveland Clinic Foundation and Professor of Pediatrics at the Case Western Reserve Medical School in Cleveland, Ohio. I have been a practicing pediatric cardiologist for 23 years. During that time, there have been dramatic advances in the knowledgebase about congenital heart defects and heart diseases that affect children. I have had the opportunity to work with numerous companies trying to develop drugs and devices applicable to this special population of patients. As an advocate for these children, I have been continually frustrated by the difficulties in obtaining potentially lifesaving technology designed specifically for pediatric patients.

Significant congenital heart disease requiring treatment occurs in only about two of every thousand children. However, congenital heart disease is the leading cause of death in young infants. Another six of every thousand children born has a heart defect that may not cause significant symptomatology until they are teenagers or adults. Companies that deal with cardiovascular diseases understandably focus their attention on adult cardiovascular diseases which are at least 100 times as common. Repeatedly through the years, I have seen devices developed for adult patients that could be extremely valuable to our patient population with slight or no modifications. The companies making these devices, however, point to the vastly larger adult market, the high cost of trials specifically for pediatric application, the limited market compared to adult applications, and product liability issues for devices that are specifically targeted for children.

Even if a company has an interest in developing a PMA for pediatric application, there is tremendous uncertainty. The size of the affected pediatric patient population makes large scale studies (that have

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become the standard for adult patients) impossible to be completed in a reasonable time frame. The total number of patients affected is relatively small and the tremendous variability in patient characteristics (such as the exact type of defect, coexisting other congenital defects, patients sizes ranging from a few pounds to hundreds of pounds, and the low number of patients seen at any particular pediatric heart center) make achievable sample sizes very small in comparison to potential sample sizes for adult patients. Even companies with the best intentions to make technology available without large profits are stymied by the uncertainty that they can even remotely recoup development costs and costs for prolonged trials at many sites.

These difficulties have definitely resulted in very delayed availability of new devices in the US market. A large number of devices have actually been invented by pediatric cardiologists in the United States and developed through the animal testing stages in the United States. They then are made available in Europe and other countries around the world years before they are available in the United States. The primary reason for the delay is the extremely high costs and long times required to obtain approval in the US under the current system. Even when devices, such as stents, became available in the US they were not approved for pediatric applications. The vast majority of devices used to treat congenital heart defects are actually used "off label" in the current environment. Single modifications to a member of adult approved devices could greatly improve applicability in children. Manufacturers, however, feel there are multiple disincentives to obtain approval for even single modifications.

Over the years, I have had the opportunity to interact with leaders of numerous companies that do, or potentially could, provide devices for pediatric patients. The majority of these individuals seem to be truthfully committed to trying to help the patients and they understand that the profit potential is considerably less than in the adult market. One of these individuals in particular, Mr. Allen Tower, of NuMed, Inc. has been exceptionally helpful to the field. He has repeatedly been willing to make custom devices and modifications for specific patients. His efforts were recognized at the 2003 Pediatric Interventional Catheterization Symposium which, is the largest meeting of pediatric catheter interventionalist in the world. Recent scrutiny, however, has resulted in his having to decline requests for custom devices. This unfortunately has made it nearly impossible to get devices such as covered stents, that could be lifesaving in an emergency situation. We are aware of at least one patient who did not survive because a covered stent, that could have been lifesaving, was not allowed to be available in the catheterization laboratory due to current FDA enforcement regulations.

In my opinion, the FDA could do more to foster the more rapid evaluation and availability of devices for treatment of pediatric and congenital heart diseases. The FDA must implicitly recognize that the patient population is relatively small and must develop reasonable ways to assess safety and efficacy that do not mandate huge prospective, controlled trials. The Humanitarian Device Exemption mechanism for device approval could potentially help in this area. However, the interpretation of regulations appear to be quite vague and confusing. Institutional review boards are unclear about how to handle these approvals. Insurance companies are uncertain whether these devices should be treated as investigational or approved. Physicians and institutional review boards are not certain whether the devices can be used "off label". In our field, it is virtually impossible to stipulate every potential use for a device and it is essential that leeway be given to the use of devices for other than narrowly defined indications.

THE CLEVELAND CLINIC
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July 20, 2004

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Re: Docket No. 2004N-0254 (Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children)

Dear Ms. Kahan,

As an SGE bioethicist and former medical device engineer, I comment on this issue from multiple vantage points. Decisions about pediatric medical device development often focus on several factors, the most ethically significant of which is level of seriousness of the disease (e.g., life-threatening). Other factors include: the prevalence of the condition to be treated in the pediatric population; the population size (n) of the age ranges of the children likely to be treated with the device; and the availability, suitability, efficacy, and adverse event profile of alternative interventions for the condition. Large net profit potential and large market potential are key variables for corporate R&D. If a pediatric population is small, it has the potential to be reduced to smaller subpopulations when one factors in mental/physical/physiological maturity and comorbidities. This shrinks market potential.

In developing devices for children, there are a multitude of factors to reflect upon including, the patient's stage of immunity and neurological/organ system development; small body size (BMI, BSA) and the often technical inability to 'simply' miniaturize an adult device; impact of patient growth (including rapid growth spurts); compliance issues with children (especially when they are in settings of limited psychosocial support); ability of children to operate and maintain their device by themselves versus the need for adult assistance; possible hormonal effects during puberty; and the ability of children to modify/restrict their activity level to foster safe and effective device function.

As an example, in some cases (e.g., pulmonary devices for aerosol delivery), specific pediatric formations and delivery systems are needed due to inherent

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anatomical, physiologic, pathophysiologic, and technical considerations in children versus adult patients (Resp Care 2000;45:646-651).

From a financial perspective, one wonders how many parents could afford medical devices for their children if insurance companies and Medicaid did not cover the costs. In the case of implants, cost estimates must reflect upon the surgery, the implant, and post-surgery care.

From a research ethics/clinical trial perspective, children are a "vulnerable" population and the regulatory requirements for such trials are viewed by many in industry as burdensome. Heightened regulatory and media spotlights often make pediatric clinical trials "too hot to handle" for some manufacturers, so they continue with projects that are adult-focused. Because children give "assent" rather than informed consent, clinical trials in this population involve more parties (the child and his/her parents). These are more people to deal with, more potential risk due to the emotional bond between parent and child (creating increased fear of litigation), and potentially a corporate "*Is it worth it?*" attitude.

If industry does not fund this research, and government research monies continue to shrink, the potential for increased pediatric devices seems remote.

In addressing these multiple matters one must ask, *What is the motive for device development? Corporate profit? Relief of patient suffering? Some of both? Are smaller corporate profits justified when the benefit is improved patient quality of life? What about the value of emotional benefits to families when their children recover or experience reduction in symptoms? Are companies and their shareholders willing to accept smaller profits when they are due to such benefits? When is net profit unacceptably low or high?* These are values-based questions that require the diligent attention of medical industry personnel, preferably with the input of pediatric patients and their parents, as well as bioethicists.

Easing research ethics requirements is likely not the answer, as the protection of human subjects is critical, especially when these subjects cannot make informed choices (then can only assent) and they often have serious or life-threatening conditions with limited medical and surgical options.

Thank you for the opportunity to comment on this important topic.

Sincerely,



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August 18, 2004

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Gentlemen:

This letter is in response to the request for comments regarding the barriers to the availability of medical devices for children. My comments specifically pertain to devices for pediatric and congenital heart patients.

I am a Professor of Pediatrics at Baylor College of Medicine and director emeritus of the cardiac catheterization laboratories at Texas Children's Hospital, Houston, Texas where I have been in practice for 35 years. My comments/suggestions are on the basis of 40+ years of experience in the field of pediatric/congenital heart disease and in particular, in the area of cardiac catheterization and catheter interventions (since its inception). I had the privilege of collaborating in the investigations of all of the early devices used in pediatric/congenital heart patients except the Rashkind balloon and am still active in the use and development of pediatric and congenital heart devices and techniques.

1. The unmet medical device needs specifically in the pediatric and congenital heart patients:

The barriers to obtaining devices for the pediatric and congenital heart patients are ongoing and represent significant delays in obtaining available devices as well as barriers to developing new and/or improving existing devices. My concept of the barriers are listed below with examples under items I - X. There is some redundancy, since the "barriers" often overlap.

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2. Barriers to the development/availability of new devices for pediatric/congenital heart use:

I. Pediatric congenital heart disease is a relatively rare disease with *all patients* accounting for less than 0.5 % of live births and all *lesions*, which might require devices being less than half of those. Of that number there are several hundred *different defects in patients in a huge range of age and size*, each of which requires a different device. As a consequence, there are extremely small numbers of any particular lesion and/or the requirement for any particular intracardiac device. This results in:

- a. Inadequate total numbers of any particular lesion to provide a "control" and/or achieve "statistical significance" in a "study." Unlike adult cardiac disease where thousands of similar lesions can be gathered (from one center!) in a short period of time, "significant numbers" of "identical" congenital patients either are not available at all and/or require collaborative studies of 10 – 20 institutions over several (many) years.
- b. Because of the small numbers, the pediatric patients do not represent a reasonable and/or sensible "commercial investment" for the expensive development of a "small volume" device.
- c. This lack of interest in the pediatric population by industry is aggravated by the threats and real risks of financial penalties from both regulatory and legal sources for perceived deviations and not perfect results.

II. Most devices, which are used in the pediatric/congenital cardiac population are used "off label" as "hand-me-downs" of devices approved for humans, but only for *adult* humans--although many of the devices and/or the procedures are recognized as the "standard of care" by all knowledgeable professionals caring for these patients. Examples:

- a. Coils used for PDA occlusions.
- b. The balloons used for the dilation of stenotic valves and vessels in pediatric/congenital lesions
- c. Intravascular stents in pulmonary arteries, systemic veins, central systemic arteries

III. Most devices in pediatric/congenital cardiac patients are used to avoid the significant physical and mental trauma of "comparable" surgery. When a new device is developed, it usually is suggested (or even required) that the surgical procedure be the "control" in "clinical trials" of new procedures and/or devices. No knowledgeable and/or moral person can require that a child and/or older patient, who happen to be "randomized" to the "short straw," be subjected to the additional trauma and risks of the surgical procedure, which has been established previously and usually over decades with no "controlled trials" of the surgery itself. Examples:

- a. All ASD and PDA occlusion devices.
- b. Balloon valvuloplasties of pulmonary and aortic valve.

IV. Regulatory agencies appear to be afraid to commit to full approvals for "pediatric devices" which results in considerable regulatory foot-dragging to avoid a true commitment:

- a. Rashkind PDA device-never allowed to be commercialized even a year after IDE panel approval.
- b. Muscular VSD occlusion devices-Humanitarian use approval only although several generations of devices have been demonstrated to be equally effective as surgery over almost two decades-total numbers of patients over this time still too few to become statistically significant.
- c. Coils for PDA occlusion have been used successfully "off label" for over a decade in the US and now are considered the standard of care by the medical community, but they officially still "don't exist" for PDA occlusion in the US - "Ostrich technique" at avoiding a decision.
- d. Intravascular stents in branch pulmonary stenosis and systemic veins. Used in these lesions "off label" for over a decade. The results are exceptional, far better than can be achieved by *any* surgery and accepted by the profession as the standard of care, but still not "approved" for this use.

V. Regulatory agencies unwilling to consider and/or accept data from over-seas without the total repetition of studies in the US although, thanks to restrictions in the US, the rest of the world now leads the US in the use of pediatric/congenital (and most other) devices in spite of most of the new devices and procedures being conceived and developed in the US. For example:

- a. ASD occlusion devices
- d. VSD occlusion devices
- e. Detachable/controllable coils for PDA occlusion
- e. New intravascular stents in unique and different sizes and configuration for the unique congenital lesions.
- f. Covered stents in larger sizes for central vessels in congenital lesions.

VI. Rather than a support and advisory role to US medical device industries, there appears to be an adversarial attitude and distrust of US industry by the regulatory agencies with the threats of extreme fines and/or the destruction of a company for perceived "deviations." For example, discussing the use of an "adult device" in a pediatric/congenital patient, much less a modification of such a device with a pediatric cardiologist is construed as illegal "marketing" of a "non-approved" product. This does not produce an atmosphere, which is at all conducive for industry even to talk to the pediatric/congenital physicians much less to provide any support. As a consequence, the large manufacturers of medical devices avoid even talking to pediatric cardiologist, much less supporting educational meetings and/or seriously discussing new products! Examples:

- a. Development of new balloons specifically for pediatrics- Cordis and Boston Scientific in particular.
- b. Pre mounting large stents for specifically intravascular use in congenital lesions

VII. As a consequence of their fear of reprisals from the FDA, industry has become unwilling and/or afraid to produce any changes in existing devices specifically for pediatric/congenital heart patients in the US--even though the changes in the devices have been demonstrated to be safer and more effective in use outside of the US and/or in compassionate use cases. Examples:

- a. Dilation balloons for congenital cardiac defects-Pediatrics have been stuck with hand-me-downs from the "adult" labs for the last two decades with industry still unwilling and/or afraid to make changes specifically for pediatrics.
- b. STARFlex ASD occlusion device, which is a simple centering modification of older CardioSEAL device, which makes device easier to implant and seat better--available in Europe.
- c. A simpler, safer attach/release and delivery system for CardioSEAL/STARFlex devices--in use in Europe.
- d. Larger diameter, stronger (six legged) CardioSEAL/STARFlex device which would be applicable for larger ASDs and VSDs. These devices were tried in Europe and probably are better than any available device for post myocardial infarction VSDs and as such hopefully and eventually will become available as "hand-me-downs".
- e. 6 & 8 mm cutting balloons for use in congenital vascular stenosis--in routine use in Europe.
- f. Covered stents for both emergency bail-out and for rare and imaginative uses in extremely rare congenital lesions--also commonly used in Europe.

VIII. Pediatric/congenital heart disease represents a very small *commercial* market, which, combined with the fear of regulatory reprisals, results in little or no support from the major medical manufacturers for research and/or new product development for *pediatric/congenital* devices per se. The larger medical device manufacturers are far more responsive to their stockholders than to individual patient care. Examples:

- a. J & J and P-308 stents: Data from a 5 year clinical trial of more than 200 patients was not in "commercial goals" of company and PMA was never submitted.
- b. Cordis-J & J: Larger pre mounted stents, which allow a much safer delivery and use in central vessels--have been produced and used in animals, but no need for them in the large "adult market" so not produced for pediatrics.
- c. Boston Scientific: Larger cutting balloons for Pediatric use. These are available and used in pediatric centers outside of the U S and centers in the US are willing and anxious to study but no funding for a study of 2-3 patients per center per year -"only" a market of few hundred children per year!

IX. Many pediatric/congenital heart lesions represent very diverse anatomy in a very small population along with a wide distribution in the size and age of the patients, which, in turn, makes it impossible to achieve "statistical significance" in clinical "trials".

- a. Systemic and pulmonary vascular stenosis in congenital heart disease requiring dilation with stent implants.

- b. Abnormal intravascular communications (systemic to pulmonary fistulae, coronary arteriovenous fistulae, pulmonary arteriovenous fistulae).
- c. Complex "Fontan" or cavopulmonary circuits in single ventricle patients.

X. Achieving adequate numbers in a pediatric cardiac trial, when attempted, takes so long that the devices frequently are improved by the manufacturers during the trial. Even though the improvements make the device/procedure easier and safer, they cannot be incorporated into the "trial" without starting the "trial" all over and/or without incurring severe penalties for the sponsor/manufacturer. Example:

- a. The initial, rather crude "Owens" balloon was approved for "pulmonary valve dilation" on the basis of data from the large VACA registry. By the time it received "approval" that particular balloon was no longer available and had been superseded by balloons, which were much smaller and had better profiles. These and newer balloons still are not "officially approved" for pediatric/congenital use.
- b. Improved delivery system for CardioSEAL/STARFlex Devices, which make delivery safer and more secure are in routine use in Europe.
- c. The use of newer, improved versions of Amplatzer PDA device and/or minor changes to improve the ease of delivery and safety of the existing devices, which are available in Europe are prevented in the US by the requirement of a new trial.
- d. Nit-Occlud PDA occluders from PFM are an improvement over the existing Duct-Occlud, but require an entirely new trial.

3. Suggestion to facilitate availability and approval of devices for pediatric and congenital heart patients:

I. The apparent distrust of the FDA toward physicians as well as industry in the medical field must be overcome in order for these, often life saving techniques/devices to become available for pediatric patient care. Most pediatric/congenital cardiologists who are involved with the development of techniques and/or devices are salaried and in academic institutions. Many of the congenital heart patients are under and/or non-insured, yet all comers are accepted to pediatric hospitals. Many of the long and complex cardiac procedures actually cost the hospital money and utilize the physician's time far beyond any monetary compensation. Without support from both regulatory agencies and industry, the pediatric/congenital patients increasingly will be denied optimal care.

There are several organizations of pediatric cardiologists and more specifically pediatric interventionists who could and would be willing to provide *true expertise* in the field, without commercial or financial bias. These include the Congenital Heart Committee of the Society of Catheterizations and Interventions, The Pediatric Committee of the American College of Cardiology and the Cardiology Section of the American Academy of Pediatrics.

II. There are extremely rare and bizarre lesions in human congenital heart disease. There is no possibility of creating a comparable animal model or a controlled "trial" even if they could be "funded." As a consequence, "trials" of promising new technologies in the rare, more exotic

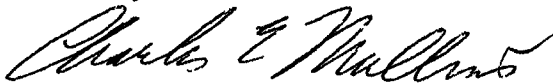
lesions must be performed on human patients during compassionate use. These trials should be very *closely supervised* by a "peer" review group of *knowledgeable physicians* who are *expert in the particular field*. When successful even in a small group of patients, such trials should lead to "official" approval for use by recognized cardiac centers. Examples:

- a. The Rashkind balloon atrial septostomy, which has saved the lives of thousands of infants over its three and one half decades of use, would *never* have received approval--in the *present regulatory environment*, but on the basis of a single center small trial was approved in 1966.
- b. Branch pulmonary artery stenosis of multiple etiologies, each of which is different, cannot be lumped into a single meaningful trial—yet with off label use of stents in this lesion is the current standard of care for these lesions, but is non "officially approved" for this use.
- c. Completion of "Fontan" circuits following "single ventricle" repairs—potentially avoiding two cardiac surgical procedures within the first 2-3 years of the patients life! These are relatively rare patients, each of which is different and, in turn, cannot be prospectively studied any more than the "semi-annual: variations, which are now made in their surgical repairs can be studied by the surgeons.
- d. Percutaneous pulmonary valve replacement for pulmonary valve regurgitation following "total repairs" of tetralogy of Fallot, pulmonary atresia with ventricular septal defect and truncus arteriosus. This procedure/device now is available and fortunately has continued to have improvements in the equipment/technique, which hopefully *never* will be completed but should not require "restarting" trials each time an improvement is introduced.

III. Investigate, through a panel of *knowledgeable practitioners* in the field of pediatric/congenital interventional procedures, changes, which are made in devices/procedures during the course of studies and approve improvements in the devices without restarting study. These investigations and approvals would have to be in a timely manner—weeks to a few months; not years!

IV. Encourage US industries who are interested in the pediatric/congenital field without the threat of reprisals for supporting innovative ideas. Provide guidance for expedited studies/approval.

Sincerely,



Charles E. Mullins, M.D.
Professor of Pediatrics
Baylor College of Medicine
Medical Director Emeritus, Cardiac Catheterization Laboratories
Texas Children's Hospital

CEM:cc

Comments from Special Health Organizations

2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments
FDA Comment Number : EC13

Submitter : Mr. Mark Isaac

Date & Time: 08/25/2004 04:08:11

Organization : Elizabeth Glaser Pediatric AIDS Foundation
International Organization

Category :
Issue Areas/Comments

GENERAL

GENERAL

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. Please see attached document.

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



Spina Bifida Association of America

August 18, 2004

Food and Drug Administration
Division of Dockets (HFA-305)
5630 Fisher's Lane
Rm. 1061
Rockville, MD 20852

Re: Docket 2004N-0254

To Whom It May Concern:

The Spina Bifida Association of America is pleased to submit these comments in response to the Request for Comments on Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children.

The Spina Bifida Association of America is the only voluntary health agency that exclusively serves children and adults with spina bifida and their families. The Spina Bifida Association of America is the national voluntary health agency working on behalf of people with Spina Bifida and their families through education, advocacy, research and service. The Association was founded in 1973 to address the needs of the spina bifida community, and today serves as the representative of 57 chapters in more than 125 communities nationwide. In recent years research has become a priority for the Spina Bifida Association of America. Relatively little funding is dedicated to research about spina bifida, its causes and consequences. Specifically, in 2004 a total of only \$14M has been dedicated to spina bifida medical research by the federal government.

Spina bifida is a neural tube defect affecting 70,000 people in the United States. It is the most common permanently disabling birth defect and affects 3,000 pregnancies each year. The result of this neural tube defect is that most children with spina bifida suffer from a host of physical, psychological, and educational challenges - including paralysis, developmental delay, numerous surgeries, and hydrocephalus. The challenges associated with spina bifida are such that it is not uncommon for children to have had 20 or more surgeries by age 18. It is estimated that over 80% of people with spina bifida have hydrocephalus, living with a shunt in their skulls which seeks to ameliorate their condition by helping to relieve cranial pressure associated with spinal fluid that does not flow properly.

2004N-0254

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The Spina Bifida Association of America is pleased that the Food and Drug Administration (FDA) is seeking to obtain input from all stakeholders pertaining to

- the unmet medical device needs in the pediatric population in the United States;
- ascertaining whether medical device needs are focused in certain medical specialties and/or pediatric subpopulations;
- the possible barriers to the development of new pediatric devices including regulatory hurdles, clinical hindrances, economic issues or legal issues; and
- the steps that the FDA could take to facilitate the development of devices intended for the pediatric population.

Given the needs of people with spina bifida, we will address our comments particularly to devices related to treating hydrocephalus in children and those designed for treatment of children with a neurogenic bladder.

There is no cure for hydrocephalus but in most cases it can be treated effectively with a mechanical implant device to relieve the cerebrospinal fluid. However, according to a 1998 study, fifty percent of shunts will fail in two years. Shunt failure is an all too common problem in children with spina bifida, causing numerous insidious complications, increased hospitalizations and their associated costs, and countless absences from school causing these children, many of whom often live with learning disabilities, to fall further and further behind. While advances in shunt technology have taken place they have represented only small improvements. The problem of minimal improvements in technology is exacerbated by the fact that FDA standards dictate significant requirements involving randomized trials. These stringent requirements are a disincentive to industry to make improvements or to create new products for a relatively small patient population. While this is a concern for the Spina Bifida Association of America and its constituents, the Association is sensitive to and supports maintaining high standards of safety in devices for children with spina bifida.

Similarly, a high priority in urologic treatment and for urologic research is to bring some "normalcy" into the lives of children who live with a common outcome of spina bifida—a neurogenic bladder caused by abnormal innervation. Few satisfactory treatments are available, so a priority in urologic research would focus on abnormal innervation with a treatment that would involve neuromodulation. Unfortunately this type of research is difficult for many reasons, including the high cost and the lack of an animal model to study the effects of such therapy. There are scientists interested in exploring this therapy, but the barriers of little available funding and low motivation on the part of industry to pursue such research for a small population is a frustrating deterrent. Specifically, industry is forced to evaluate future innovations against the costs associated with mounting a major research and development initiative in this area. They must look at the cost of R & D against what payers will support.

Given combined concerns of little research funding, a small population, and stringent standards of the FDA, there has been little innovation and few improvements for the care of children with spina bifida. It is clear that increased research in these areas is critical and from such research, reasonable standards can be developed by the FDA in the

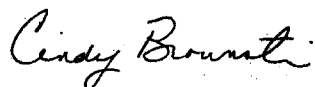
treatment of hydrocephalus and the neurogenic bladder. If adequate research was being funded it would be in the patients' interests to wait for the results in order to create critical safety standards. However since adequate research is not currently underway and not currently planned, how can we as a nation say no to results that look promising from research that is underway? Should children with spina bifida continue to lead lives predicated on inferior quality of life when promising technologies and treatments are on the horizon? While the Spina Bifida Association of America is first and always concerned about the safety of the people we represent, we understand the current reality of cost versus quality and wish the FDA to continue reviewing innovations for spina bifida in a careful and thoughtful manner. We ask the FDA, however, to consider a new paradigm to review innovations for products that would affect smaller patient populations.

We respectfully ask the FDA to consider instituting an innovative program that would review devices developed to answer the needs of people with spina bifida and other orphan diseases. If such a program exists, we request the expansion of the program to further accommodate and recognize current economic realities. For people who suffer from conditions or diseases where there is limited or little adequate research, the balance between patient need and the level of risk may be different than it is for others. For people with spina bifida and other orphan diseases and conditions, there is an immediate need for creating safe standards that at the same time streamline the process for review.

The Spina Bifida Association of America stands ready to join the FDA as it explores the notion of such a demonstration or any other program that will increase the likelihood of improving the quality of life for people with spina bifida.

Thank you for opportunity to comment.

Sincerely,



Cindy Brownstein
Chief Executive Director

Comments from Medical Device Manufacturers



August 20, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

AUG 24 2004

Subject: Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments [Docket No. 2004N-0254]

Ladies and Gentlemen:

The purpose of this letter is to respond to FDA's request for comments concerning the above mentioned subject that was published in the *Federal Register* on June 21, 2004.

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Inamed Corporation (Inamed) is a medical device manufacturer located in Santa Barbara, California, which manufactures (among other products) medical devices for the treatment of obesity, including the LAP-BAND® System. By applying FDA's existing final and draft guidances pertaining to the addition of indications for use of devices that have already been approved through the Premarket Approval (PMA) process for use on adults, Inamed believes that the FDA has an opportunity to expand the availability of medical devices such as the LAP-BAND® System that could offer significant clinical benefits to adolescents.

In response to the three questions posed by FDA below, Inamed offers the following comments that specifically address a serious epidemic in the United States: **severe obesity in children.**

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?

Inamed's Response:

Among the unmet medical device needs in the pediatric population is the need for access to a safe, effective, less invasive, adjustable and reversible treatment for severe obesity. Such a treatment is already available to the adult population: Inamed's LAP-BAND® System, a laparoscopically placed, adjustable gastric band for the treatment of severe obesity.

2004N-0254

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Additional information regarding the extent and consequences of this unmet need and the potential benefits of access to the LAP-BAND[®] System follows:

The problem of obesity has reached epidemic proportions and is very costly.

- The United States and other countries are experiencing an epidemic of obesity affecting all age groups including children and adolescents.¹ Recent estimates suggest that over 15% of children and adolescents are obese (body mass index, BMI of $\geq 95^{\text{th}}$ percentile for age).²
- Obesity is the most frequent nutritional disease of childhood and adolescents.³
- Obesity ranks as a close second to smoking as a preventable cause of death and is well ahead of all other causes.⁴
- It is estimated that overweight and obesity account for 85% of cases of type 2 diabetes, 45% of cases of hypertension and 35% of cases of coronary artery disease.⁵
A recent analysis of the extent of overweight among U.S. children concluded that not only have more children become overweight, the overweight children are becoming heavier.⁶

The societal costs of the obesity epidemic are very significant.

- It is estimated that obesity-related disease accounts for 5-12% of developed countries health costs, with type 2 diabetes alone accounting for 2-7%.^{7,8,9}
- A conservative analysis concludes that annual obesity-related hospital costs for adolescents increased from \$35 million during 1979-1981 to \$127 million during 1977-1999, a three-fold increase.¹⁰
- For adults, the expenditures related to obesity in 2002 were estimated at \$93 billion.¹¹

Obesity has serious negative effects on children and adolescents.

Obesity in adolescents has a significant negative effect on current physical and psychological health and has major implications for future health with increased morbidity and mortality. Features of the metabolic syndrome, hypertension, dyslipidemia, impaired glucose tolerance and type 2 diabetes, are all reported in increased frequency in obese adolescents.^{12,13,14,15}

- It is alarming that approximately 60% of overweight 5-10 year old children already have one biochemical or clinical cardiovascular risk factor, such as hyperlipidemia, elevated blood pressure, or increased insulin levels, and 25% have 2 or more.^{16,17,18}
- The prevalence of the metabolic syndrome in adolescents in the U.S. is 4.2%, but for subjects below the 85th percentile, at the 85th-95th percentile and >95th percentile, the prevalence were 0.1%, 6.8% and 28.7% respectively.¹⁹

Other conditions, including nonalcoholic steatohepatitis,²⁰ obstructive sleep apnea,²¹ and the polycystic ovary syndrome,²² that are associated with the

metabolic syndrome and insulin resistance, are also being reported with increasing frequency in obese adolescents.

- Almost 50% of cases of cholecystitis in children and adolescents are associated with obesity.²³
- Several cross-sectional and longitudinal studies have shown an increased prevalence of asthma in adolescents, especially girls.^{24,25,26}
- Pseudotumor cerebri may be a cause of headaches in severely obese young women²⁷ and a number of orthopedic complications including Blount's disease²⁸ and slipped femoral epiphysis²⁹ typically occur in overweight or obese children.

Obesity is associated with a greater mortality burden in younger people.³⁰ When estimated as years of life lost due to obesity, younger age and a higher body mass index (BMI) combine to reduce life expectancy. A white male in his 20's of BMI 36 is estimated to lose 4-years of life and with a BMI of 45 or greater, 13-years of life. At BMI 46 this represents a 22% reduction in remaining years of life.³¹

Obesity in adolescents is a very strong predictor of obesity as an adult.

- The risk is greatest for extreme overweight and when overweight is carried through late adolescence.^{32,33}
- Once a child or adolescent reaches an overweight or obese percentile, spontaneous improvement is unlikely.³⁴
- There is evidence that overweight and obesity during adolescence increases the risk of poor health in adult life independent of adult body mass index (BMI).^{35,36}
- Among women but not men obese during adolescence, obesity has a variety of adverse psychosocial consequences. These include completion of fewer years of education, higher rates of poverty, and lower rates of marriage and household income.^{37,38}

The psychosocial consequences of severe obesity in adolescents provide serious and pressing short-term comorbidity.

- The social burden of adolescent obesity may have lasting effects on body image, self-esteem and economic mobility especially in young women.³⁹ Obese adolescents suffer social bias, prejudice and discrimination as a result of their appearance.^{40,41} In fact, the targeted discrimination of obese children starts early and is systematic.³
- These factors have been reported as the obese person's heaviest burden⁴² and are experienced overwhelmingly by obese subjects.⁴⁰
- This discrimination and bias has been recognized as coming from all sectors of the community including parents, teachers, medical and nursing professionals, and their fellow peers.^{43,44}

The overall effect of physical and psychological impairment can be estimated, and compared with other conditions using health related quality of life measures.

Schwimmer et al found, using a pediatric Quality of Life (QOL) inventory, that all domain scores were lower in obese children and adolescents when compared with non-obese controls.

Obese children and adolescents were more likely to have impaired health-related QOL than healthy children and adolescents and were similar to children and adolescents diagnosed as having cancer.⁴⁵

Non-surgical treatment has not been effective for severely obese adolescents.

The development of programs to reduce the incidence of pediatric obesity, including severe obesity, is needed and should be supported. However, there is a need to treat those who are already severely obese and are suffering from the consequences.

The conventional treatment of obesity in children and adolescents is the same as those in adults and include:

- a reduction in energy intake by dietary means,
- an increase in energy expenditure through an increase in both planned and lifestyle activity,
- an increase in energy expenditure through reduced sedentary behavior,
- modification of the behavioral habits associated with eating and activity, and
- involvement of the family in the process of change.³⁴

Optimal and continuous application of a combination of dietary and drug therapy in association with increased exercise and behavioral modification can, at best, achieve and maintain a 5-10% loss of body weight in adults.^{46,47,48,49,50} These methods may be adequate in cases of less severe obesity.

Use of these and more intensive therapies such as very low calorie diets⁵¹ and pharmacotherapy^{52,53} in adolescents has been very limited and have not produced significant and sustained weight loss. Of all the intensive therapeutic options for pediatric severe obesity, only bariatric surgery has produced significant sustained weight loss.⁵⁴

Surgical treatment provides sustained and significant weight loss and improves or resolves obesity related conditions.

Remarkable and sustained changes in obesity related comorbidity have been reported following obesity surgery, including the gastric bypass and laparoscopic adjustable gastric banding. Over recent years the effect of significant weight loss following laparoscopic adjustable gastric banding surgery has been measured and documented^{55,56,57,58,59,60,61,62,63,64,65,66,67,68} for a broad range of obesity related conditions including:

- type 2 diabetes,
- insulin resistance,
- dyslipidemia,

- hypertension,
- steatohepatitis,
- polycystic ovary syndrome,
- infertility,
- problems of pregnancy,
- sleep problems including obstructive sleep apnea,
- lung function,
- asthma,
- gastroesophageal reflux,
- health related quality of life,
- depression and
- body image.

Measures of quality of life and depression that are grossly impaired prior to surgery return to normal community values with weight loss.⁶⁹

It is now recognized that type 2 diabetes, a serious condition strongly related to obesity, responds best to weight loss when treated early.

- Severe obesity, insulin resistance, and their metabolic and inflammatory consequences cause irreparable and progressive damage to insulin secreting pancreatic beta cells leading to the development of type 2 diabetes.
- Weight loss reverses this process, improving insulin sensitivity and allowing the reversible component of poor beta-cell function to recover.^{64,65}
- If treated early, significant weight loss allows total remission of type 2 diabetes.^{64,70,71}
- This is also very powerful in preventing the development of type 2 diabetes in those at greatest risk.

Weight loss following obesity surgery has been shown to reduce mortality.

- Benotti et al following 5178 patients after restrictive gastric stapling procedures, found mortality in these patients to be similar to those of non-obese men and women.⁷²
- MacDonald et al found a marked reduction in mortality rates in severely obese type 2 diabetic subjects surgically treated for obesity (1% risk of death/year) when compared with controls (4.5% risk/year).⁷³
- Flum and Dellinger looked retrospectively at the mortality data in Washington State and found that subjects who were surgically treated had a reduced mortality when compared with non-surgically treated severely obese individuals. This benefit was more marked in the younger age group. In those under the age of 40 years the operated group had a mortality of 7.6% during the follow-up period compared to 15.9% in non-operated subjects.⁷⁴
- A recent Canadian study by Christiou et al⁷⁵ reported a major reduction in mortality (89%) and reduced risk of developing obesity related comorbidity when compared with controls.

The gastric bypass procedures which were used in these studies have high peri-operative mortality (0.3-2%) when compared to adjustable gastric banding surgery (0.05%).^{69,76} The benefit to risk ratio is strengthened greatly by the very low mortality associated with laparoscopic adjustable gastric banding surgery.

Weight loss surgery is successful in adolescents as well as adults, and has been recognized with recommendations from professional societies, but only the more invasive options are currently available for adolescents.

While there have been fewer reports published regarding bariatric surgery in an adolescent population, studies have reported positive benefits.

- Reports of both the gastric bypass and the LAP-BAND[®] System, including reports in the United States,^{77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93} have concluded that they are safe and effective in producing sustained and significant weight loss and health improvements in both adolescents and adults.
- Most of the over 500 publications on the use of the LAP-BAND[®] System include patients 18-21 years of age, who are within the FDA's definition of adolescence.

Guidance for the surgical treatment of severe obesity in the pediatric population, including the LAP-BAND[®] System, has been provided:

- Focused primarily on concerns related to the gastric bypass but including laparoscopic adjustable gastric banding, recommendations were published in the July 2004 issue of *Pediatrics*.⁹⁴
- In the same issue of *Pediatrics*, the American Society of Bariatric Surgeons supported and made recommendations in regards to obesity surgery in adolescents.⁹⁵
- In August 2004, the Massachusetts Department of Public Health in collaboration with the Betsy Lehman Center for Patient Safety and Medical Error Reduction issued a report on patient safety issues in relation to obesity surgery in which obesity surgery was recognized as an appropriate treatment for severe obesity.⁹⁶

Severely obese adolescents who are seeking obesity surgery are most frequently offered the gastric *bypass*. The FDA does not control the indications for use of the gastric bypass because it is a surgical procedure and the surgical staplers used in the procedure do not require FDA pre-market approval. On the other hand, use of the less invasive LAP-BAND[®] System on an adolescent is currently considered to be "off-label" use and would cause increased liability concerns. Therefore, the procedure that is commonly available to severely obese adolescents in the United States carries a greater risk of mortality, life-threatening complications and long-term nutritional deficiencies.^{76,97,98}

The LAP-BAND® System offers important advantages for adolescents.

In 1993, Inamed introduced the LAP-BAND® Adjustable Gastric Banding (LAGB®) System, an adjustable gastric band, for the treatment of severe obesity, in Europe. In June 2001, after review of data from a 3-year multi-center clinical study in the United States and longer-term international data, the FDA approved the Premarket Approval Application (PMA) for this device for the treatment of severe obesity in adults.

- The LAP-BAND® System was granted “Expedited Review” by the FDA because it offered significant advantages, including reduced mortality, patient specific adjustment without further surgery, and reversibility. Following premarket approval, the FDA described it as a “significant medical device breakthrough.”
- Globally, nearly 150,000 LAP-BAND® Systems have been used to provide significant and sustained weight loss.
- As noted above, this weight loss has been documented to be accompanied by the resolution or improvement of serious comorbidities of obesity (such as type 2 diabetes, obstructive sleep apnea, hypertension, dyslipidemia, gastroesophageal reflux, depression and others) and significant improvements in quality of life.
- There are no physical or anatomical reasons why the LAP-BAND® System would not function appropriately in adolescents, and patient management concerns can be addressed by labeling that specifies the need for assessment and support by appropriate and trained personnel.
- In its August 2004 Executive Report, The Massachusetts Department of Public Health, in collaboration with the Betsy Lehman Center for Patient Safety and Medical Error Reduction, recognized “[gastric bypass] as the procedure with the best long term data and [laparoscopic adjustable gastric banding] as the procedure with the least apparent risk to adolescent patients.”⁹²

Recently, the American Diabetes Association sent an “E-Mail Alert” to 75,000 health care practitioners, attaching a “Review of obesity and weight loss surgery,” by Thomas L. O’Connell, MD, of Duke University Medical Center, which noted that...

“[Obesity surgery] has proven to be a safe and effective means of losing significant and lasting weight and should be considered in those who are morbidly obese.”

“...The adjustable gastric banding procedure has recently gained recognition as a surgical option and offers some significant advantages. Unlike the vertical banded gastroplasty and RNYGB (Roux-en-y gastric bypass), the adjustable gastric band... involves no stapling of the stomach wall, no cutting or opening of the stomach, and no alteration of the gastrointestinal tract. Should it become medically necessary, the band can be removed and normal stomach

anatomy restored. Also, the degree of restriction created by the band can be adjusted by injecting or withdrawing saline through a port under the skin. This allows the size of the stoma (opening between the upper and lower stomach) to be changed to fit each patient's nutritional and weight loss needs."⁹⁹

Factors of particular importance to adolescents include:

- The procedure has a much lower risk of death or life-threatening complications.
- There is no malabsorption with this procedure and thus there is a low risk of a significant nutritional deficiency that might affect growth or result in birth defects related to inadequate prenatal nutrition.
- The adjustability of the LAP-BAND[®] System offers flexibility in ongoing weight management. The band can be deflated for greater intake, as needed for example, during pregnancy or illness or remote travel.
- Should better therapy for obesity become available at some time in the future, if the patient could not adapt to the band, or for any other reason, the band can be removed laparoscopically with no significant change to the patient's original anatomy.

The availability of a minimally invasive, laparoscopic procedure that is safe, effective, easily adjustable, completely reversible, already available to the adult population and generally recognized as safer and less invasive than other procedures currently being used for adolescents should not be delayed.

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

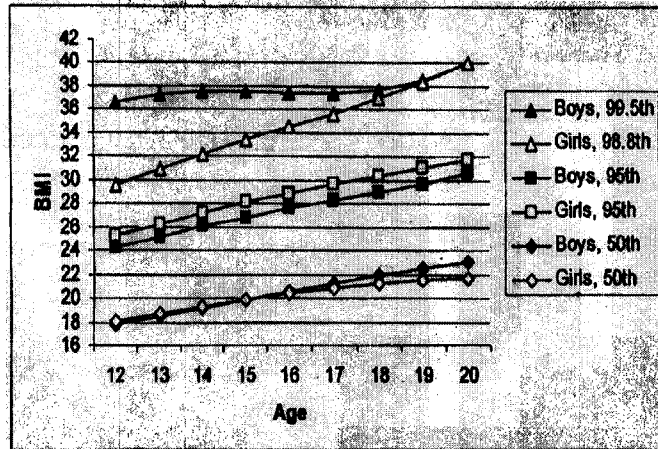
Inamed's Response:

Barriers to the development of new pediatric devices include:

- 1) FDA's requirement for clinical studies in pediatric populations in order to obtain approval for commercial distribution. This includes FDA requests for *randomized controlled trials*, although no such trials may have been required for approval of the indications for adults. Randomized controlled trials with surgical devices are often difficult to design due to ethical and practical concerns. For example, randomizing adolescent patients to gastric bypass or the LAP-BAND[®] System would expose some adolescents to risks that may be considered excessive. Many surgeons believe that subjecting patients (whether young *or* adult) to gastric bypass surgery when the use of the LAP-BAND[®] System is a safer alternative would be unethical in an investigational study. Even non-randomized prospective clinical studies significantly delay access and impose high costs that manufacturers may be unable or unwilling to incur. For example, the manufacturer may be required

to pay all costs, including the surgical procedures, in order to obtain adequate enrollment.

- 2) Potential FDA reluctance to apply existing draft guidance regarding the application of medical devices to pediatric populations (Premarket Assessment of Pediatric Medical Devices: July 24, 2003). This guidance requires an analysis of the various issues of concern in applying a device to a pediatric population but acknowledges that clinical studies *should not be necessary* if there is no substantial change to the device or its application.
- 3) Potential FDA reluctance to accept literature evidence and population analysis in lieu of prospective clinical studies, although an FDA final guidance (Guidance to Industry Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review; Final; May 20, 1998) exists.
- 4) Lack of stratification of pediatric populations in terms of regulatory requirements. For example, the risk of using an adult device in a 16 year-old adolescent is very different from using that same device in a 6 year-old child or a 6 month-old infant.
- 5) Potential FDA emphasis on possible risks, rather than known benefits, of technologies already applied to adults, and on restricting access rather than working with manufacturers to provide safe but earlier access. For the LAP-BAND[®] System, for example, surgeon and site qualifications, training, and the appropriate screening and management of adolescent patients by qualified personnel could be specified in the labeling.
- 6) The small market size (and thus smaller financial opportunity) associated with pediatric indications compared to indications for adults presents an economic challenge. As can be seen in the growth chart below, severely obese adolescents comprise only a small fraction of the pediatric population, and also only a small fraction of the total population of severely obese patients. Investment by a manufacturer in the introduction of products for a small market that also is associated with increased liability concerns and additional marketing, training and sales costs is made more difficult when regulatory barriers are expensive and difficult to overcome.



- 7) The cost associated with manufacturing and stocking additional versions of a product can be significant. Although this is not anticipated with the LAP-BAND® System, it is an issue that increases the costs associated with other types of pediatric devices. The shorter life cycles and lower barriers to entry of medical devices (when compared to pharmaceuticals) result in more frequent changes to products. Multiple sizes of products increase the costs of these changes. In addition, the effects of the change must be assessed for all populations and may require regulatory activity and resources.
- 8) Another barrier is the significant liability risk associated with pediatric use of medical devices for health care practitioners, institutions and industry.
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?

Inamed's Response:

To encourage manufacturers to pursue marketing of devices for the pediatric population, the FDA could:

- 1) Encourage submissions for adolescent indications using PMAs based on data obtained in clinical studies on adult populations plus a rationale using existing pediatric guidance, combined with post-market studies, if appropriate.
- 2) Complete and apply reasonable guidances for pediatric applications of adult medical devices, which would emphasize access under appropriate controls.

- 3) Accept design analysis, literature and non-clinical evidence in lieu of prospective clinical studies for products already approved for use in adults, for example as described in the final FDA guidance on the use of literature, noted above.
- 4) Stratify regulatory requirements for pediatric populations to facilitate expansion of availability of adult devices to older groups who are more similar physiologically to young adults than to young children. Adolescence has been defined as ages 12-21, and this includes patients from 18 to 21 for whom the LAP-BAND® System and other "adult" devices are already commercially available. It appears reasonable that there should be fewer barriers to expanding the use of adult devices to teenagers than to toddlers.
- 5) Require additional clinical studies on devices that have gone through the Premarket Approval process only when significant uncertainties exist and pose serious risks that outweigh the benefits of access to such devices.
- 6) When issues that affect risk can be addressed through labeling modifications (i.e., user qualifications, indications and contraindications, training, warnings), this method should be used. It will facilitate earlier access to important technology.
- 7) Maintain existing policy of no user fees for applications for pediatric indications for adult medical devices.
- 8) Reduce user fees applied to all medical device submissions, which discourage and slow implementation of improvements and which decrease manufacturers' resources for development and introduction of pediatric devices.
- 9) Reduce post-approval clinical risks by working with manufacturers on labeling which restricts use to qualified and trained physicians at centers having appropriate staff, facilities and programs. This has been carried out successfully with the adult indication for the LAP-BAND® System, for example.
- 10) Reduce the liability risk associated with the use of medical devices in the pediatric population through legislation.
- 11) Apply "expedited review" to pediatric regulatory applications or otherwise shorten the review time, particularly for applications aimed at expanding indications for use of devices already approved for use in adults.

These rather detailed comments have been provided to illustrate, by example, an urgent, unmet need in a pediatric population and to suggest ways of satisfying that need. Not all the support and rationale for expanding access of the LAP-BAND® System to adolescents have been presented.

To summarize:

Although obesity has reached epidemic proportions in the pediatric population and has serious and long-lasting negative consequences for health and quality of life, the current non-surgical weight loss treatments, at the very best, achieve a sustained weight loss of 10% of body weight, which is unlikely to substantially influence the medical, physical and psychological problems of severely obese adolescents.

Obesity surgery is the only effective therapy in this population, whether adult or adolescent.

- Because of the recognized advantages of the LAP-BAND® System, including safety, minimally invasive placement, adjustability and reversibility, Inamed believes that this device should be available for use on appropriate severely obese adolescents in qualified centers with minimal delay.

Inamed suggests that stratification of the pediatric populations, recognition of the similarities between adolescent and adults, application of existing FDA guidances, and greater focus on labeling to optimize results during commercial distribution will expedite the availability of beneficial therapies for adolescents.

Respectfully,



Ronald J. Ehmsen, Sc.D.
Senior Vice President,
Clinical and Regulatory Affairs
Inamed Corporation

cc: Dr. Joanne R. Less

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2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments
FDA Comment Number : EC2

Submitter Dr. Paul M. Gammell

Date & Time: 07/21/2004 11:07:30

Organization : Gammell Applied Technologies

Private Industry

Category :
Issue Areas/Comments

GENERAL

GENERAL

I do not have experience that is specialized in pediatric devices, although I have worked in ultrasound and was a reviewer in the Radiological Devices Branch of what was then DRAERD.

I do have a suggestion that may help in the long run. In an earlier job with the Navy I was the Contracting Officer's Technical Representative (COTR) for several Small Business Innovative Research (SBIR) proposals. In possible collaboration with one of the National Institutes of Health (NIH) SBIR funding could be provided in this area. It has been my experience that when the COTR provides useful suggestions and orientation (but not attempting to actually direct the project) the end result is more relevant to society and profitable to the company. I know it is a delicate balance, but a completely "hands off" approach can be a complete waste of money. The COTR must be interested in seeing the project through. In phase 2 of the SBIR the COTR should help the company learn of the regulatory considerations. The company should be encouraged to discuss their regulatory plans with the FDA at an early point in order to conserve valuable resources.

2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments
FDA Comment Number : EC3

Submitter : Mr. Richard Podell

Date & Time: 07/26/2004 04:07:53

Organization : Management Advisory Services

Device Industry

Category :
Issue Areas/Comments

GENERAL

GENERAL

Small size of pediatric device market would require economic incentive to device developers, such as orphan drug incentives.

Reluctance to expose younger patients to clinical trial risks requires even more stringent guidelines for IDE and more comprehensive education for parent/guardian, including issues relating to informed consent.

2004N-0254 - Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments
FDA Comment Number : EC12

Submitter : Ms. Adele Bindon

Date & Time: 08/25/2004 04:08:52

Organization : Fisher

Device Industry

Category :
Issue Areas/Comments

GENERAL

GENERAL

Please find attached Fisher & Paykel's comments regarding the 'Possible Barriers to the Availability of Medical Devices Intended to Treat or Disgnose Diseases and Conditions that Affect Children' [Docket No. 2004N-0254].

Fisher & Paykel

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FDA & MEDICAL DEVICES IN PEDIATRICS

Introduction

Fisher & Paykel Healthcare Limited is a designer and manufacturer of a range of innovative healthcare devices which incorporate unique features to improve patient care.

Our headquarters, research and development and manufacturing facilities are based in New Zealand. Fisher & Paykel Healthcare have sales and marketing operations throughout the world, with North America and the EU being major sales locations.

We operate principally in the growing respiratory; sleep disordered breathing, critical care and operating room markets. Our products currently include respiratory humidifiers, breathing circuits and accessories, CPAP devices for the treatment of obstructive sleep apnea (OSA) and radiant warmers, infant resuscitators and accessories.

Fisher & Paykel Healthcare hold certification to ISO 13485:2003 "Medical devices – Quality Management systems – Requirements for regulatory purposes" issued by TÜV Product Services (an EU Notified Body). Market clearances for our devices in the US are sought primarily via the 510(k) process, which are designed in compliance with the QSR. We CE mark and sell medical devices to EU via Annex II (Declaration of Conformity except EC Design Examination) of MDD 93/42/EEC.

Current Interest & Experience

Fisher & Paykel Healthcare Limited have a current interest in improving access of medical devices to the pediatric population in all three areas of its business. Our experience with the FDA regarding device usage in pediatric populations is varied across the 3 businesses.

In the Respiratory business we design and market globally a range of neonatal breathing circuits. At present we only sell two of these neonatal circuits to the United States market. We are going through the 510(k) process for another two neonatal circuits.

The Neonatal division have designed and developed a CPAP device based upon a therapy that has been used in hospitals in the USA for a very long period of time. The device is specifically for newborns. This device is currently going through the regulatory approval process in the USA. There has been difficulty with this submission due to the fact that the FDA does not regard the current device as a predicate (even though US hospitals regard the therapy as standard of care).

OSA design and develop medical devices for the treatment and prevention of obstructive sleep apnea in adults. Extension of the indication to include use in pediatrics is currently being explored.

Current FDA Status

The FDA has come some way in encouraging the development and regulatory approval of devices for use in pediatrics.

There has been one guidance document put out by the FDA on pediatric devices – “Premarket Assessment of Pediatric Medical Devices” (14 May 2004).

With the onset of MDUFMA, 510(k)'s and PMA's for pediatric devices are at no cost. From our experience, the review times for a pediatric device and for an adult device are of an equivalent length of time.

(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?

We have no comment to make regarding this question.

(2) What are the possible barriers to the development of new pediatric devices? Are there regulatory hurdles? Clinical Hindrances? Economic issues? Legal issues?

We have identified the following possible barriers to the development of new pediatric devices:

Regulatory:

- The review of a pediatric medical device may invoke an emotional response from the FDA reviewers resulting in judgement being clouded
- In the review of a submission of a pediatric medical device, the risk level of the device is considered to be greater and more documentation/evidence is required.
- There does not seem to be consistency in the regulatory requirements applied for an medical device that is to be used in adults and for a medical device that is for pediatrics

Clinical:

- IDE approval by an Institutional Review Board is harder and takes longer for a clinical trial in a pediatric population
- The pediatric population is a smaller group making it harder to get the numbers required in a clinical trial. This increases the length of time before the company is able to gain any return on their investment in product development
- An ill child is an emotional stress for any parent. There may be some reluctance to try a new medical device on your already sick child. This makes parental consent, recruitment and follow-up more difficult

Economic:

- Pediatric trials are more expensive to set up (IDE approval is a longer process); they take longer to run (to get significant numbers the trial must run for longer to recruit sufficient patients from a limited patient population); and therefore limit the return the company can obtain from the device
- For example, newborns with a very low birth weight (between 500 – 1500 g) represent approximately 0.5-1% of all live births in the USA. This is a market with a small commercial return. The costs associated in clearance to market in this population are large. The population available to conduct clinical trials is small so

any trials will last for an extended period of time. Additionally, there is no sale premium associated with pediatric devices

- This leads to companies questioning the financial viability of running trials to gain a pediatric indication. In turn, this leads to the use of the product by doctors and consumers in an off-label manner

(3) What could the 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?

We have identified the following areas that may encourage the pediatric approval of medical devices:

Regulatory:

- Expand the definition of predicate device – Are the FDA prepared to accept a therapy or a custom-made device (not distributed commercially) as a predicate device when that device (and the therapy it employs) is considered by medical professionals to be "standard-of-care"? For example, what about devices that deliver therapy that are considered best practice?
- Streamline the *de novo* 510(k) application.
Currently a 510(k) must be submitted, evaluated, and determined to be "Not substantially equivalent" (NSE), Class III, before a *de novo* 510(k) request can be made.
This process is too long for manufacturers. Why can't manufacturers have the option of submitting a *de novo* 510(k) right from the start?
- Publicise the *de novo* 510(k) option to manufacturers
- Allow on-line applications for pediatric submissions
- More guidance from the FDA on specific pediatric submissions and the options available to industry in gaining approval
- Develop an additional 510(k) process for a pediatric device or a paediatric extension (traditional; special; abbreviated; pediatric, etc)
- Apply consistency of the level of evidence required for an pediatric device compared to an adult device
- Reduce review time for new pediatric devices / pediatric extension of existing devices

Clinical:

- Define further the level of consent required. Perhaps the level of parental consent required correlates with the type of new device i.e., a new type of breathing circuit from a company with a confirmed history of selling breathing circuits in the USA may need a different level of parental consent than a company with no history.
- The FDA need to more readily accept pediatric trials from the EU and other developed countries. The FDA should work with industry to explain the ways in that the EU clinical trials need to be run to satisfy the FDA requirements.
- Acceptance/acknowledgement of experience/approval of the device from other developed countries with recognised device regulation and design controls i.e., EU, Canada, Japan, Australia

Economic:

- Currently a 510(k) for a pediatric device is free. What about giving the option to companies of having an expedited 510(k) review if they pay a fee?

Other:

- Education and guidance from the FDA to doctors, health professionals, consumers and manufacturers on the possible consequences of the use of a device off-label and advertising an off-label use (on websites, etc).

If you have any questions regarding any of our comments please contact via the following details:

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Yours sincerely



Adele Bindon
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August 13, 2004

Ms. Joanne Less
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 13852

Re: Docket No. 2004-N-0254

Dear Ms. Less:

This comment is filed on behalf of the Cook Group, Inc. ("Cook"), a holding company of international corporations engaged in the manufacture of diagnostic and interventional products for radiology, cardiology, urology, gynecology, gastroenterology, wound care, emergency medicine, and surgery. Cook pioneered the development of products used in the Seldinger technique of angiography, and in techniques for interventional radiology and cardiology. Cook products benefit patients by providing doctors with a means of diagnosis and intervention using minimally invasive techniques, as well as by providing innovative products for surgical applications. Cook sells over 15,000 different products which can be purchased in over 60,000 combinations. Many of these devices are used by physicians in the care and treatment of children.

We are writing in response to the request from the Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH), for comments concerning possible barriers to the availability of medical devices intended to treat children. As mentioned above, Cook manufactures and markets many products for children, and we believe our nation should be firmly committed to providing children with the highest quality and most current medical technology. There are barriers to fully serving pediatric markets, however, and we are gratified to have the opportunity to share our views of those barriers with FDA and to make suggestions for overcoming them.

At the outset, we should not be confused about the types of devices we need to address in these comments. The safety and effectiveness of most devices is immediately known for children as well as adults. There is a smaller group of devices, however, that may have long term effects upon pediatric populations. With respect to these types of devices, we make the following observations:

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- The principal difficulty in serving pediatric markets arises from the small number of children that are affected by most conditions. It certainly is a good thing that relatively few children face serious medical problems. However, it is difficult, if not impossible, to enlist a significant number of pediatric patients in a clinical trial with a novel product, because so few patients are available, and those that are available are scattered across the country.
- Because the demand for pediatric devices is so small, and the cost of developing pediatric devices is so large, manufacturers are reluctant to develop them or to label medical devices for pediatric indications.
- The pediatric population is constantly changing. Today's pediatric patient is tomorrow's adult. Artificial limbs, for example, which may be appropriate at one stage of pediatric development, may be wholly inappropriate at a later stage.
- Materials which are biocompatible with adults are generally biocompatible with children, but, in a few instances, are not.
- Growth factors, extent of psychosocial development, and the difficulty in obtaining informed consent from the patient are just several of the additional factors which compound the difficulty of conducting clinical trials in pediatric populations.

Due to the unique characteristics of the pediatric population, we believe that it is important that the government take steps to improve access to pediatric products, and we offer the following suggestions for your consideration.

1. Humanitarian Device Exemption (HDE)

The humanitarian device exemption was enacted by Congress to encourage the development of products to treat or diagnose conditions which affect small patient populations of less than 4,000 patients per year. The concept of the HDE is to reduce the regulatory burdens and costs for sponsors of orphan products in recognition of the fact that such products will not generate significant revenues. It should be emphasized that the provision **reduces** regulatory barriers. It does not eliminate them. There are a number of requirements which must be met by sponsors before a product is approved to assure protection of the public health. Unfortunately, in addition to these requirements, sponsors are prohibited from making profits on products which have been awarded an HDE.

Since enactment of the HDE provision in 1990, there have been only thirty-four HDE's approved by FDA. The fetal bladder stent manufactured by Cook was the first HDE granted by FDA. Some of these products, like the fetal bladder stent, have been life saving. None of these products would have come to market without the

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HDE because of the difficulties associated with populating clinical trials or the heavy financial burdens of such trials.

We believe that many more products would have reached patients through the humanitarian device exemption, had not the prohibition on profits been included in the law. We have consistently advocated that this prohibition be eliminated. As it focuses on the needs of children, we urge FDA to recommend to Congress that the prohibition be removed, at least for the pediatric population. The key in these small marketplaces is to reduce costs and increase incentives for manufacturers wherever possible. The humanitarian device exemption has provided a way to reduce costs. Economic incentives provided by the opportunity for profit should be allowed to work freely. In our opinion, this will encourage manufacturers to address pediatric needs. Many manufacturers will readily enter markets of only a few thousand per year if there is a streamlined regulatory process and the ability of the marketplace to generate a profit, present everywhere else in our healthcare system, is unfettered.

We also recommend that the requirement for IRB approval for each individual use of a device approved under the HDE should be significantly modified or excluded. This requirement has created confusion among institutions and added to the burdens of those trying to provide these products through the exemption.

Finally, we suggest that the threshold number of patients necessary to qualify for a humanitarian devices exemption should be re-examined. The current threshold of 4,000 patients was arrived at arbitrarily, and we believe it is unduly restrictive. The "orphan" market for drugs is defined at 130,000 patients per year, and while we do not have data demonstrating the appropriate market for devices, we believe the appropriate threshold for medical devices should be significantly higher than it is currently. To reiterate once more, there are safeguards within the HDE statutory framework to ensure safety and ensure inappropriate use. These safeguards would not be mitigated by establishing a higher threshold population.

2. Pediatric Device Research Network

There are many institutions across the United States, that are dedicated, at least in part, to treating diseases and conditions that affect children. Establishing a network of institutions that could assist sponsors of medical technology in recruiting patients for clinical trials during the approval process, would be very helpful to those manufacturers who seek to address the needs of pediatric populations. This network could also be helpful with data coordination and publication of peer-reviewed data.

3. Grants

There are a number of programs within FDA and NIH to assist those who are developing products for a small patient population. We recommend that as part of its report, FDA identify which programs could be most useful in encouraging the development of pediatric products, and suggest new programs to Congress if those currently existing are not sufficient. Grants can reduce the costs of those who wish to develop products for children, and, if they are large enough, there are enough of them, and their existence is well known, they will assist in the goal of developing more pediatric products.

4. Historical Data

We believe that historical data is always valuable in the approval process and should be utilized wherever possible, particularly in pediatric populations where the number of patients is so small and controls are difficult to establish. In these circumstances, historical data can and should be used to compensate for the complexities of collecting clinical trial data given the underlying reality of a small patient population.

5. Use Of Information

Many medical technologies are used today for off-label purposes, particularly in treating small patient populations. Physicians often collect significant data regarding the safety and effectiveness of off-label uses. Unfortunately, the law constrains FDA in considering data gained from off-label use in product approval applications. We recommend that FDA undertake a legal analysis of these constraints to determine if they can be removed. To the extent that a statutory change is required, we recommend that FDA propose legislation to Congress to permit the utilization of such data with appropriate safeguards to ensure against abuse by manufacturers. Utilizing such data can significantly expedite the approval of new conditions of use for important technologies, particularly for small patient populations.

Further, current law prohibits FDA from sharing information it has gained from other applications. We believe that there is a strong case for major long-term reform regarding the use of information. In the short term, we recommend that steps be taken to permit FDA to share information regarding any issues which arise involving biocompatibility of materials for pediatric products. The public needs to be alerted to both problems and solutions.

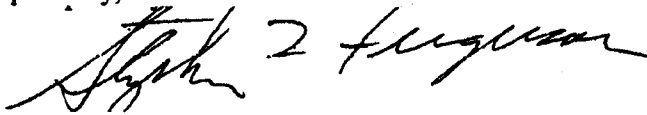
Ms. Joanne Less
August 13, 2004
Page Five

Several of the changes we have recommended will require legislative action. Congress will need to amend the provisions of the Federal Food, Drug, and Cosmetics Act governing the humanitarian device exemption and perhaps improve programs offering grants. It will also need to provide funding at appropriate levels for these programs. It will probably be necessary to make statutory changes to establish a pediatric network and to broaden the use of information as well. We respectfully urge FDA to recommend such changes in its report to Congress later this year.

We are very grateful for the opportunity to offer our thoughts on this very important subject, and we commend the agency for making the significant effort to analyze issues affecting children and medical technology. America's children truly are its future, and they deserve nothing but the finest medical care.

Thank you again for consideration of our comments.

Respectfully,

A handwritten signature in black ink, appearing to read "Stephen L. Ferguson". The signature is written in a cursive style with a large initial "S" and "F".

Stephen L. Ferguson

Comments from Medical Device Trade Associations

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AdvaMed

Advanced Medical Technology Association

August 20, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0254 -- Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children; Request for Comments

Dear Sir/Madam:

AdvaMed, the Advanced Medical Technology Association, submits these comments in response to FDA's request for comments regarding possible barriers to the availability of medical devices intended to treat or diagnose diseases and conditions that affect children.

AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems, ranging from the largest to the smallest innovators and companies. AdvaMed's more than 1,200 members and subsidiaries manufacture nearly 90 percent of the \$75 billion in health care technology products purchased annually in the United States, and more than 50 percent of the \$175 billion purchased annually around the world. AdvaMed members range from the smallest to the largest medical technology innovators and companies. Nearly 70 percent of our members have fewer than \$30 million in sales annually.

GENERAL COMMENTS

AdvaMed was first approached by the American Academy of Pediatricians about their concerns regarding pediatric device availability in the summer and fall of 2000. At that time, we offered to meet with pediatric clinicians and stressed the importance of gaining a better understanding from pediatric clinicians about devices for which there was not appropriate pediatric access. For this reason, AdvaMed was pleased to participate in the June 28, 2004 meeting co-hosted by FDA, the American Academy of Pediatrics, the Elizabeth Glaser Pediatric AIDS Foundation, the National Association of Children's Hospitals and the National Organization for Rare Diseases to discuss ways to improve the availability of

pediatric devices. A tremendous amount of ground was covered during the day-long meeting, and we believe participants left the meeting committed to working together to finding practical solutions.

The pediatric coalition has subsequently outlined a series of meetings to further identify pediatric device issues and define potential opportunities. AdvaMed looks forward to continuing this important dialogue which is in its initial stages and we are committed to working with FDA, pediatric representatives and other important stakeholders to develop appropriate incentives and regulatory mechanisms to encourage appropriate pediatric device development.

It is important to note, however, that several of the examples of pediatric device needs that were raised during the June 28th meeting highlight technological challenges that face both adult and pediatric patients (e.g., premature calcification of tissue heart valves and non-invasive diagnostic testing) for which comprehensive solutions have not yet been identified. Others present long-term technological challenges that will require considerable investments in research and development and significant breakthroughs in materials, tissue engineering, design and engineering (e.g., prosthetic internal bone fixation devices that can be lengthened as a child develops without invasive surgery or prosthetic valves that "grow" with the patient).

With respect to prosthetic devices that grow with the child, considerable advances have been made in this area. Some pediatric prosthetic devices that minimize invasive surgeries and allow the prosthetic device to be lengthened as the child develops are in fact, already on the market. One such device, marketed via the 510(k) review process, is an expandable implant that can be made longer internally simply by passing an electromagnetic field over the device for a few minutes during a doctor visit. It has been used in children between the ages of 5 and 14.

While there are numerous challenges to pediatric device development, we would also like to emphasize that there are many devices already on the market that:

- are used extensively in pediatric patients,
- were developed specifically for pediatric populations, or
- were specifically redesigned for pediatric populations.

These include, among others: syringes with the greater dose accuracy required for some pediatric medications and medication delivery systems that are less invasive (such as nasal or intradermal delivery devices); incubators, respirators and warming blankets; glucose meters; enteral pumps; pediatric spinal fixation systems, downsized fracture fixation hardware, and total joint prostheses that can be lengthened; diagnostic cardiac catheters, therapeutic cardiac catheters, vascular grafts, pacemakers and heart valves; septal defect closure devices and hydrocephalic shunts (including those with anti-microbial coatings); tracheal stents; cochlear implants; and diagnostic tests that are specific for diseases that more frequently afflict children (e.g., rotavirus tests) and diagnostic assays with pediatric indications including

Albumin BCG & BCP, Alkaline Phosphatase, Amylase, Calcium, Carbon Dioxide, Cholesterol, Creatinine, Glucose, Magnesium, TIBC, Total Protein, Urea, Uric Acid and Urine Protein/CSF.

Many of these have been approved via the 510(k) review process – without the need of large, costly clinical trials.

RESPONSES TO QUESTIONS

In our responses below, we outline challenges to pediatric device development as well as some initial thoughts on potential solutions. We look forward to working with the relevant stakeholders to further refine these solutions or to identify additional solutions.

CHALLENGES TO PEDIATRIC DEVICE DEVELOPMENT

- 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?***

While we can provide an opinion regarding unmet medical device needs in the pediatric population, the medical device industry is not in the best position to articulate the needs of clinicians involved in the treatment of pediatric populations. The needs in this area must be articulated by the clinical community. AdvaMed reiterated this message at the recent June 28th meeting with pediatric representatives and we strongly endorse what we believe was a key conclusion from the June 28th meeting, namely: *the need for pediatric specialty societies to identify and prioritize pediatric device needs so that we all can begin to understand the nature and extent of the problem.*

Identification of unmet needs by pediatric specialty groups is the critically important first step that will enable medical device manufacturers and other relevant stakeholders to begin to address specific pediatric device needs. In addition, some mechanism must be developed that allows clinicians to communicate such needs to device manufacturers and others.

- 2. What are the possible barriers to the development of new pediatric devices? Are there regulatory hurdles? Clinical hindrances? Economic issues? Legal Issues?***

From an industry perspective, there are a number of challenges to pediatric device development. Although some of the challenges to pediatric device development are within the purview of FDA, many of them are not. The challenges include:

- Difficult to identify pediatric device needs
- Small company nature of the medical device industry
- Technical barriers associated with the unique requirements of pediatric populations
- Lack of commercial viability because of small market size of pediatric populations
- FDA regulatory and data requirements result in costly clinical studies

- Perception of increased liability profile associated with pediatric device use
- Achieving adequate reimbursement is difficult
- Complicated Nature of the Humanitarian Device Exemption (HDE)
- Mandatory pediatric device labeling would limit pediatric device availability

The challenges listed above are described below.

A. Pediatric Device Needs Must be Clearly Identified

As mentioned above, a significant challenge to improving pediatric device development is to begin appropriately identifying, characterizing and prioritizing pediatric device needs and gaps. Medical device innovation relies heavily on clinician input both for initial ideas as to needed technologies and to improve products which already exist. Unlike drug development, the device innovation process is highly iterative. Modifications are made constantly over time in response to user needs and the emergence of new technological capabilities. The average life-cycle for many advanced medical technologies is short, approximately 18 months. Frequently, improvements to the product, based on input from practicing clinicians, are already beginning to be incorporated into the next generation of the device before the first generation device is launched.

A strong dialogue between manufacturers and the clinician users is essential to device development. Although relationships between individual pediatric practitioners and device manufacturer representatives may be good, there is nevertheless a clear need to strengthen overall interactions and communications between the representatives of pediatric clinicians and a broad array of device manufacturers to help set priorities and policies that will facilitate action.

B. Nature of the Device Industry Presents Unique Challenges

Unlike the drug industry, 80 percent of medical device companies have fewer than 50 employees. Further, most devices are designed for specialty procedures with "niche product lines" and revenues of less than 100 million dollars.¹ Start-up device companies rely heavily on venture capitalists – who demand a return on investment – to finance product research and development until viable revenue streams are achieved. For these reasons, overly burdensome statutory or regulatory mandates can easily overwhelm both the financial and human resource capabilities of small device companies.

In addition, patent protections – extensions of which provide potent incentives for drug companies – are often successfully challenged or are easily designed around by device companies. For example, in the device arena, several different companies may hold competing patents on the same technology (e.g., pacemakers) with the same intended use in the same population. In contrast to a drug patent for a unique chemical entity, device patents are typically held for a specific design attribute or material – not the device as a whole.

¹ The Wilkerson Group, Inc. *Forces Reshaping the Performance and Contribution of the U.S. Medical Device Industry* (Health Industry Manufacturers Association, June 1995), p. 11

C. Technical Barriers Associated With Pediatric Populations

There are numerous technical challenges associated with developing devices for pediatric populations. For example, not all devices function in the same manner when manufactured in the sizes needed for pediatric indications. Secondly, the dynamic rate of change in size and, in some cases, the shape of the anatomy of pediatric patients can limit the applicability of devices intended for long-term use such as permanent, weight-bearing implants. In addition, the selection of materials used in devices for pediatric indications must take into account the different susceptibility of the young to physical and chemical agents, as compared to that of adults. Metabolic and hormonal changes may also need to be considered in material selection. The lifetime burden of exposure to agents must also be considered. These factors can limit the range of materials from which devices for pediatric applications can be fabricated, greatly complicating already difficult design challenges. These are just some examples of the issues that must be addressed when designing or adapting medical devices for the pediatric population.

Other technical issues manufacturers must consider as they develop pediatric devices include the array of sizes needed to meet pediatric needs, the likelihood of patient compliance with limitations imposed by the medical device and the ability to anticipate the activity level and forces imposed by patients who may not be able or willing to exercise significant self-control. All of these factors can add significant research and development costs.

The nature of proving safety and effectiveness in pediatric populations is also different in devices than it is in drugs. This is not to say that many drugs don't require testing and/or reformulation for use in pediatric populations. However, for many devices, significant and added expense will be incurred to demonstrate the safety and effectiveness of the device in pediatric populations. For example, separate animal testing in younger and/or smaller animals, along with the documentation and verification of the data for each separate model may be required. Retooling or different manufacturing lines from those used for adult devices are certain to be required for many pediatric devices/models.

D. Unique Challenges Associated with the Small Market Size of Many Pediatric Populations

It cannot be stated definitively until pediatric specialty and subspecialty groups identify and characterize pediatric device needs (including, if possible, the number of pediatric patients requiring the device(s) on an annual basis) whether a given device will be commercially feasible. However, it is likely that for many pediatric device needs, the annual market will not be commercially viable for either large or small device companies. While all companies must deal with the tremendous costs associated with the research, development, manufacture and marketing of devices relative to the potentially small pediatric device market, small device companies must also deal with the pressures associated with venture capital financing.

According to the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality, there were 36,417,565 hospital stays for adults and there were 6,351,345 stays for children in 2000. Of the children, 2,850,254 were normal newborns.² This leaves 3,501,901 stays for children for other reasons, about 9.6% of the adult population. If anything, costs associated with pediatric device development will be higher for some of the reasons enumerated above, yet manufacturers will in most cases be developing the device for a far smaller market.

In addition, while the American Academy of Pediatrics has taken the critically important step of advocating inclusion of pediatric patients in clinical trials to ensure that children share equally in treatment and diagnostic gains, there are nevertheless, serious societal obstacles to children participating in clinical trials. These include the understandable reluctance of many parents and guardians to subject their child(ren) to unproven treatments – unless there are no other options – as well as the negative repercussions associated with any anticipated, unanticipated or unforeseen serious or life-threatening adverse events or deaths. For these reasons, companies may find it difficult to recruit children to clinical trials. Because of the small populations involved, companies may also find it difficult to recruit enough children to assure an adequately powered clinical trial.

To overcome such challenges, it may be necessary to develop incentives that are linked to the commercially viable adult indications for devices.

E. FDA Regulatory and Data Requirements Discourage Pediatric Device Development

A number of AdvaMed members reported that FDA data and regulatory requirements necessitated large pediatric clinical studies or would require multi-year, multi-hospital studies with long-term results monitoring – sometimes more than was required for the original adult claim. Challenges include accruing sufficient clinical trial participants over a reasonable timeframe and within a manageable number of investigational sites to meet FDA requirements. For small pediatric patient populations, the costs associated with conducting such trials may never be recouped.

Several AdvaMed members also reported that for some pediatric conditions, the many co-morbidities associated with the condition made it extremely difficult to prove definitively the effectiveness of the device. They expressed the concern that a clinical trial of a device that diagnosed or treated such a condition would likely experience many adverse events related to the co-morbidities making it difficult to assess the therapy under evaluation. Consequently, it would be hard to generate enough data to establish safety and effectiveness using the traditional means. In addition, the number of pediatric participants required to generate enough safety and effectiveness data for such a trial would be overwhelming and tremendously expensive.

² <http://www.arhq.gov/HCUPnet>

F. Perception of Potential Liability Risks Associated with Pediatric Device Use

The same conditions that have led to decreased availability of affordable malpractice insurance for pediatric surgeons has effects for device manufacturers. The perception exists that the emotional nature of the pediatric device litigation could lead to higher awards. The perception also exists that there may be an increased risk of liability associated with clinical trials involving pediatric conditions with many co-morbidities and congenital anatomic anomalies.

G. Challenges Achieving Adequate Device Reimbursement

Medical device companies face particularly serious challenges in achieving adequate reimbursement for their products. Even for devices targeting older Americans, it can take 15 months to 5 years to get Medicare reimbursement. In addition, the Medicare processes for coverage, coding and payment are all separate and uncoordinated and can require companies to "successfully negotiate multiple, distinct and complex processes to obtain adequate payment for a single device. Each process can take years to complete."³ Companies must frequently negotiate similar processes with the approximately 1,300 private payers in the U.S.

Achieving adequate coverage, coding and payment is particularly difficult for small companies that do not have the expertise or resources needed to negotiate the complex processes associated with coverage, coding and payment with numerous payers.

These problems are compounded in the Medicaid program – a key program for ensuring health care for children in low-income households – where each State separately establishes the services and procedures that will be covered under its Medicaid program. Medicaid is generally the payer of last resort and is among the lowest of payers.

H. Humanitarian Device Exemption (HDE) Program is Highly Complex and In Need of Simplification

The Safe Medical Devices Act of 1990 (SMDA) authorized the humanitarian device exemption program. The program is intended to create incentives for the development of devices for patients with diseases or conditions that affect or are manifested in less than 4,000 patients per year (i.e., orphan diseases or conditions). Humanitarian use devices (HUDs) are exempt from FDA effectiveness requirements but must still be deemed safe by FDA.

The FDA has approved six pediatric humanitarian use devices since it issued the final rule implementing the SMDA provision in 1996 including: the left ventricular assist device (February 2004) for use in certain pediatric patients age 5 to 16; a pulmonary valved conduit (November 2003) for certain pediatric patients under age 18; a pulmonic valve conduit

³ The Lewin Group, Inc. *The Medicare Payment Process and Patient Access to Technology* (The Advanced Medical Technology Association, 2000), pp. 1-2.

(September 1999) for certain pediatric patients up to age 4; a urinary stimulator (December 1997); a fetal bladder drainage catheter (September 1997) for fetuses age 18 to 32 weeks; and a fetal bladder stent (February 1997) for fetuses age 18 to 32 weeks. FDA has approved another 10 HUDs for both pediatric and adult indications, and 18 for adults only. Since the program was fully implemented in 1996, FDA has approved a total of 16 pediatric or pediatric/adult HUDs over 8 years. It is not clear whether this is because industry has submitted few applications or because FDA has approved so few.

There are several requirements that present challenges to companies in securing HUD approval:

- The HDE application must include "documentation, with appended authoritative references, to demonstrate that the device is designed to treat or diagnose a disease or condition that affects or is manifested"⁴ in less than 4,000 patients per year.
- In order to get an HUD approval, FDA must determine that there is "no comparable device, other than another HUD approved under the HDE regulation or a device being studied under an approved investigational device exemption . . . available to treat or diagnose the disease or condition."⁵
- For any charges over \$250.00 associated with the approved HUD device, the applicant must "obtain a report by an independent certified public accountant, or . . . an attestation by a responsible individual of the organization, verifying that the amount does not exceed the cost of research, development, fabrication and distribution."⁶
- The manufacturer must also ensure that the HUD is "only used in facilities having an Institutional Review Board (IRB) constituted and acting in accordance with 21 CFR Part 56."⁷ Importantly, the IRB must review and approve the HUD before it is used and is also responsible for continuing review of the HUD. Although informed consent is not legally required, "most HDE holders . . . have developed patient labeling that incorporates information to assist a patient in making an informed decision about the use of the device."⁸

Given the tremendous costs associated with retooling manufacturing to produce a device or an array of devices with a pediatric indication, the 4,000 patients or less per year limitation and the limitation on profit are significant disincentives to using the program.

Further, while manufacturers are not overly concerned about the IRB review requirement, IRBs find the request for review and approval confusing since FDA has already approved the HUD.

⁴ Humanitarian Device Exemptions (HDE) Regulation: Questions and Answers; Final Guidance for Industry, p. 3.

⁵ *Ibid.*, p. 3-4.

⁶ *Ibid.*, p. 4.

⁷ *Ibid.*, p. 5.

⁸ *Ibid.*, p. 6.

AdvaMed members also report that insurers frequently refuse to pay for HUDs on the grounds that the device has not been found safe and effective by FDA. The requirement to have IRB approval raises the awareness levels of insurers and ensures closer scrutiny with an increased chance that the HUD-related claims will be denied. In short, reimbursement systems have not kept pace with regulatory processes for HUDs. HUDs are approved by FDA and should be appropriately reimbursed by insurers.

I. Mandatory Pediatric Device Labeling

AdvaMed disagrees with the proposal for mandatory pediatric device labeling which has been floated to improve pediatric device development. This proposal presents a serious concern for industry. Assuming that the shared goal is to increase, rather than decrease the number of devices available to pediatric populations, we believe that mandatory pediatric labeling would do the opposite. Many devices used for pediatric populations are on the market with general labeling. Mandating pediatric labeling for such devices, many of which are 510(k)'d, would make pediatric use of such devices off-label and thus ineligible for reimbursement. The end result would be fewer devices available for pediatric populations.

Further, while much larger drug companies may be able to "afford" such mandates, the smaller and more competitive device industry can ill afford such mandates. A study conducted in 2000 found that drug prices for one 12-month period increased by 4.1 percent while device prices for 21 categories showed an overall decrease of 0.8%. Twelve product categories for the period showed price decreases while 5 product categories had price increases of less than 1%. None of the device categories outpaced the Consumer Price Index (CPI) which was 3.4 percent for the 12-month period.⁹ Many companies would be unable to handle the financial burden of producing a great deal of additional data or testing for pediatric indications, and would be forced to remove products from the market. Indeed, mandatory pediatric device labeling could easily put many device companies out of business. We believe this would result in fewer rather than more pediatric devices.

POTENTIAL SOLUTIONS

- 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?***

As mentioned above, while some of the challenges to pediatric device development are within the purview of FDA, many of them are not. Thus, some of the potential solutions outlined below would involve FDA and others would require the involvement of other important stakeholders.

⁹ The Lewin Group, Inc. *The Medicare Payment Process and Patient Access to Technology* (The Advanced Medical Technology Association, 2000), pp. 36-37.

The solutions listed below are preliminary in nature and will require additional refinement, thinking and discussion. AdvaMed is committed to engaging in a dialogue with our members to identify other potential solutions and to achieve consensus support for some or all of the potential solutions outlined below.

We also look forward to working with all of the relevant stakeholders to discuss and improve the potential solutions mentioned here or to discern additional solutions.

A. Identification and Communication of Pediatric Device Needs

As mentioned above, it is critically important that pediatric specialty groups begin the process of identifying and prioritizing pediatric device needs and begin communicating those needs to the medical device industry and other stakeholders. A formal mechanism – such as an appropriately managed and updated web-based site – is needed to communicate and share these needs.

In addition, as part of this communication, the adoption of common terminology with respect to the age ranges of pediatric subgroups is necessary. A starting place for discussion may be FDA's guidance document, "Pre-market Assessment of Pediatric Medical Devices."

B. Enhanced Communications between Pediatric Clinicians and Device Manufacturers

As noted, the dialogue between manufacturers and clinicians is essential to device innovation and development. In addition to the broad communication of pediatric device needs, there appears to be a need to enhance and strengthen interactions and communications between pediatric clinicians and device manufacturers. Improved communication between pediatric clinicians and device companies could facilitate modifications to existing devices for pediatric use and generate ideas for new pediatric devices.

Among other suggestions, improved communications could be achieved through the development of workshops, closer communication links between the national representatives of pediatric clinicians and AdvaMed, and professional roundtables including industry and clinical associations, FDA and other important stakeholders. One potential model for such roundtables is the FDA-sponsored IVD Roundtable which meets quarterly and includes all the relevant stakeholders. The IVD Roundtable provides stakeholders with an opportunity to discuss problems and resolve issues.

C. Fast-Tracked FDA Review and Approval and Coverage, Coding and Reimbursement of Devices

There are numerous challenges associated with the development of pediatric devices. These include, among others:

- accruing sufficient pediatric clinical trial participants,
- enhanced risk of adverse events associated with certain pediatric conditions,
- tremendous costs associated with the research, development and manufacture of such devices and the simultaneous reality of small market size in many instances,

- increased liability profile associated with pediatric clinical trials and device use
- difficulties associated with device reimbursement, and
- an inability to recoup all of these costs due to small pediatric markets.

In the Food and Drug Administration Modernization Act of 1997, the drug industry was provided with a powerful incentive to develop drugs for pediatric use – a six-month extension on patent exclusivity for the drug as a whole (i.e., the extension is not limited to the much smaller pediatric indication for the drug but applies to both adult and pediatric indications). The extended patent exclusivity provides drug manufacturers with significant resources that are above and beyond the higher costs associated with pediatric drug development.

As noted above, this specific incentive will not be effective for device manufacturers and could in fact, be detrimental in the medical device environment. However, a program to provide comparable incentives for the device industry is needed. Such a program might include expedited FDA review and approval and expedited CMS coverage, coding and reimbursement for the related adult indications of a pediatric device or for the adult indication of another device manufactured by the same company when there is no corresponding adult indication related to the pediatric device or if the adult device is already in the market. AdvaMed is exploring other potential incentives with our members and we hope to be able to provide additional thoughts in the near future.

D. Improved Funding for Research and Development of Breakthrough Pediatric Devices

Based on a few of the examples of pediatric device needs of which we are currently aware, a new paradigm for research and development may be needed. Several of the examples cited at the June 28th meeting presented long-term technological challenges requiring breakthroughs in underlying science, materials, design and engineering. To overcome such technological challenges, tremendous resources will be needed – in some cases, more than industry will likely be able to muster, especially given the constraint of small market sizes associated with pediatric devices. Increased R&D funding from the National Institute of Child Health and Human Development (NICHD) and the National Institute for Biomedical Imaging and Bioengineering (NIBIB) or other relevant Institutes, targeting specific pediatric device needs would serve several purposes.

First, it would spur the basic research needed for areas where breakthrough devices are desired. Secondly, such funding could help offset the costs of device manufacturer R&D and help to demonstrate feasibility, thus reducing commercialization risk. Finally, an enhanced technology transfer program between the relevant Institutes and the device industry could help assure the development and manufacture of the needed breakthrough medical devices, assuming the basic research yields returns.

E. Improvements to the HDE Program

During discussions on the Medical Devices Technical Corrections Act (MDTCA), AdvaMed proposed a lifting of the profit restriction contained in the HDE program. The requirement to have an independent, certified public accountant or attestation by a responsible individual in the organization that the amount charged does not exceed the cost of research, development, fabrication and distribution is a serious disincentive for manufacturers to use the program. We again recommend that the profit restriction be lifted.

Additionally, for pediatric device needs, there should be no restriction on the required number of patients or on whether comparable devices already exist.

Finally, we would encourage the inclusion of health insurers in stakeholder discussions to seek consensus and agreement on the need to adequately cover and pay for HDE-approved technologies.

F. Explore Types of Data Acceptable to FDA as Valid Scientific Evidence to Demonstrate Safety and Effectiveness as it Applies to Pediatric Device Studies

Further dialogue is needed on what constitutes valid scientific evidence to establish safety and effectiveness given the challenges associated with pediatric device studies. In general, a least burdensome approach should be utilized. For example:

- Statistical methods and modeling (such as Bayesian statistics) should be further discussed and explored as alternatives for some pediatric data requirements.
- Consideration should be given to whether devices that have already been commercialized for adults should be required to demonstrate effectiveness in pediatrics through required randomized clinical trials, especially when the disease and its progression are the same in adults and pediatric populations. In some instances, the endpoints used and approved in the original PMA for the adult population may be appropriate, thus allowing the pediatric study to demonstrate effectiveness using an equivalence study. Consideration should be given to ensure that such studies demonstrate safety and effectiveness but without being so large that they are not likely to be done.
- FDA has recently granted PMA approvals for several devices using only published literature to demonstrate safety and effectiveness. In many instances, pediatric clinicians have used legally marketed devices off-label for years and have published their clinical experience in peer-reviewed journals. To expedite the PMA or PMA supplement approval process, FDA should consider whether clinical and commercial safety and effectiveness data from the originally approved patient population, coupled with an analysis of the published off-label literature would be sufficient to support a marketing application for pediatric use.

- Pediatric patient files contained in public or private registries, children's hospitals or other facilities (e.g., large implanting centers) provide a rich source of clinical data that could constitute valid scientific evidence to establish safety and effectiveness without having to conduct prospective randomized control clinical trials. However, as discussed below, for the most part, such data is currently not available for use by device manufacturers because of the informed consent issue.

G. Use of Existing Submission Mechanisms to Add Pediatric Indications to Marketed Devices Presenting Minimal Risk

Greater use of existing submission mechanisms, such as Special 510(k)s and de novo review to add pediatric claims to marketed devices may also be helpful for appropriate devices. In some instances, specific guidance on how to apply these tools to pediatric indications for appropriate devices may need to be developed.

H. Provide FDA with Discretionary Authority to Waive Informed Consent for Pediatric Device Studies

FDA regulations governing human subject consent provide the ability to waive consent in extremely narrow circumstances. Providing FDA with discretionary authority to waive consent with respect to banked samples and databases would remove an important challenge to pediatric device development and in fact, to device development as a whole.

Under current regulations governing protection of human subjects for research conducted by FDA or federal entities such as the National Institutes of Health, IRBs may waive assent for children if "the capability of some or all of the children is so limited that they cannot reasonably be consulted or the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit and is available only in the context of the clinical investigation" (21 CFR 50.55(c)). 45 CFR 46.408(a) of the Health and Human Services Policy for Human Subject Protection provides a similar waiver of assent. Nevertheless, parental consent is still required even if the assent of the child is waived (see 46.408(b) and 21 CFR 50.55(e)). In practice, waivers are only granted for HDE devices and minimal risk studies such as blood draws or questionnaires.

FDA's inability to waive consent requirements for banked samples or databases provides significant challenges for device manufacturers. For example, in the diagnostic test arena, FDA requires informed consent for studies that use unidentified or banked samples. Even though the unidentified or banked blood, urine or other samples may be comprised solely of samples from a children's hospital and the diagnostic test may be for a pediatric condition or disease, the company may be prohibited from using the data to obtain a pediatric indication because it failed to obtain informed consent.

Similar issues apply with respect to patient information contained in databases. Pediatric patient files in public or private registries, children's hospitals or other facilities (e.g., large implanting centers) could provide a rich source of clinical data. However, for the most part,

such data is currently not available for use by device manufacturers because of the informed consent issue.

I. Enhanced Tax Incentives for Pediatric Device Development

A significant obstacle to pediatric device development is the associated research and development costs. As discussed above, challenges include accruing sufficient clinical trial participants over a reasonable timeframe and within a manageable number of investigational sites to meet FDA requirements. A significantly enhanced R&D tax incentive program for pediatric device development would help companies manage such costs. Such a credit should apply to any company research associated with pediatric devices including associated pre-clinical and clinical study costs. The credit should also apply to any pediatric devices developed through the HDE program.

J. Continue the Existing Exemption From User Fees for Pediatric Device Submissions

The Medical Device User Fee and Modernization Act (MDUFMA) established a user fee program for medical devices in return for improved FDA review times. The Act included an exemption from PMA and 510(k) user fees for any pediatric device submission. This exemption should be continued.

K. Pediatric Research Networks

Given the broad diversity of devices – there are more than 3,000 distinct, major product lines, and approximately 84,000 individual products – careful thought and consideration should be given to whether the establishment of a network of children's hospitals and other facilities or clinics with particular expertise in diseases and conditions that affect children would be workable. However, for priority areas, such a network or networks might be valuable in helping to recruit children for studies and to assure enough participants to gather statistically relevant data. Such networks could also help in conducting some research and publishing studies, especially in those instances where the population is so small that it is unlikely to be commercially feasible.

In closing, AdvaMed is committed to working with FDA and other stakeholders to finding practical solutions and incentives to encourage pediatric device development.

Sincerely,



Tara Federici
Associate Vice President
Technology & Regulatory Affairs