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2004 N-0254



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

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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, "Premarket 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