Report to Congress

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

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U.S. Department of Health and Human Services
Food and Drug Administration

Executive Summary

Background

The Medical Devices Technical Corrections Act of 2004 (MDTCA), Public Law 108-214, was enacted on April 1, 2004. Section 3 of this law requires the Secretary of Health and Human Services (HHS) to submit a "report on the barriers to the availability of devices intended for the treatment or diagnosis of diseases and conditions that affect children." The statute requires the report to include any recommendations of the Secretary "for changes to existing statutory authority, regulations, or agency policy or practice to encourage the invention and development of such devices." MDTCA requires the Secretary of HHS submit the report within 180 days of enactment (i.e., by September 28, 2004).

To prepare this report to Congress, the Food and Drug Administration (FDA) sought comment from interested parties, including consumers, researchers, healthcare practitioners, the device industry, and professional and trade associations through participation in a stakeholder meeting and by publishing a notice in the *Federal Register* requesting comment. FDA received 25 comments in response to the notice.[1] These comments are summarized below and available under Public Docket No. 2004N-0254 and at www.fda.gov/cdrh/pediatricdevices/comments.pdf.

Summary of the Comments

Unmet Medical Needs

Comments from clinicians and patient advocacy groups stressed the need for pediatric devices in several medical specialties, including pediatric cardiology, pulmonology, nephrology, orthopaedics, and surgery. Additionally, most of the comments from clinicians and organizations representing patients and physicians cited the widespread practice of modifying adult devices for pediatric use, the risks of that practice, and the need for data on long-term effects of device use as well as adverse events in children. The comments did not discuss whether modification of adult devices for use in children was successful in addressing the needs of pediatric patients in the specialties cited. Moreover, while the comments cited the need to prioritize unmet device needs, they did not address the fact that no commonly accepted definition of "unmet pediatric device need" exists. HHS believes that without a clear definition of this term, identifying the needs of pediatric patients cannot be fully accomplished.

Barriers to Pediatric Device Development

Commenters identified numerous potential barriers to the development, approval, and widespread availability of pediatric devices. However, they did not discuss the relative importance of those barriers or the urgency of addressing them in relation to the various unmet needs that were identified. For example, it is unknown what the relative contributions are of the

[1] Although 25 comments were received, FDA believes that comment # EC 6 was submitted to this docket in error.

small market for pediatric devices, insufficient reimbursement, difficulty in obtaining clinical data for FDA approval, and perceived increased liability associated with pediatric devices to the creation of unmet needs in this patient population. In addition, the barriers actually contributing to the existence of unmet needs may not be the same for each device. For example, the small market for a cardiovascular device may serve as the major disincentive to its development, whereas in another case, the need to submit clinical data to gain approval for a modification to an adult device may be the most significant deterrent to a manufacturer. Therefore, HHS believes there needs to be a better understanding of the links between each identified unmet need and the barriers to addressing it.

Fostering the Development of Pediatric Medical Devices

Many specific recommendations for fostering the development and availability of pediatric devices were submitted in response to the FR notice. The recommendations generally fall into the following categories: legislative actions; regulatory actions; funding for research and development; financial incentives; and enhanced information gathering and exchange. One of the most frequently proposed incentives was modifying the Humanitarian Device Exemption (HDE) provision, which relates to the marketing of medical devices that serve limited populations. There was general agreement among all groups of commenters that changes to the HDE provision, such as allowing profit-making and raising the limit on the number of patients who can be treated or diagnosed with such a device, would encourage the use of this marketing path. In addition, many commenters stressed the need for enhanced interaction and communication between clinicians, the device industry, and FDA as a mechanism for identifying and addressing unmet needs in the pediatric population.

Despite the number and breadth of the recommendations, however, HHS believes that further discussion and study are necessary to evaluate which proposals might be more, or less, effective in addressing the barriers to pediatric device development generally or which proposals might be more, or less, effective in facilitating the development of specific categories of pediatric devices (e.g., for pediatric cardiology). In addition, further evaluation is needed to better understand the impact the proposed incentives could have on various parties. While there was agreement regarding some proposals, there was disagreement between commenters on others. For example, some parties recommended mandatory pediatric device labeling for all products that might be used in children; however, this proposal was explicitly opposed by other stakeholders.

Conclusions

HHS concludes that it is premature to recommend any substantive policy changes, including administrative and legislative changes, at this time. Based on the complexity of the issues and the wide range of perspectives included in the comments, it is clear that further study is warranted to evaluate the scope of the unmet needs, the potential barriers to bringing new pediatric devices to market, and the most promising solutions to addressing these unmet needs. HHS believes that the next step is to conduct a systematic needs assessment to determine the scope of unmet device needs in the pediatric population. HHS agrees with the comment that such an effort should include all stakeholders and should encompass a wide range of pediatric diseases. Following this needs assessment, it may be easier to prioritize the needs and more fully

understand the role various barriers play in creating them. Such an understanding of unmet pediatric device needs and the barriers to the development of pediatric devices should facilitate the availability of new devices for this population.

Three of the recommendations made by commenters can be integrated into this needs assessment and prioritization process.

1) **Enhanced interaction and communication between pediatric clinicians and device manufacturers.** This recommendation from stakeholders would help identify the most pressing unmet pediatric device needs, promoting discussion of what modifications to existing adult devices would facilitate pediatric use, and generating ideas for new pediatric devices. Proposals to facilitate such communication included the development of workshops and closer communication links between representatives of pediatric clinicians and device trade associations as well as roundtable discussions including these parties, HHS, and other stakeholders. HHS will explore with all stakeholders possible venues for these interactions.

2) **Development of a network of children's hospitals and healthcare facilities with expertise in pediatric diseases and conditions.** While several commenters made this recommendation, HHS would like to point out that the National Institutes of Health (NIH) support numerous research networks for many childhood conditions, including the Children's Oncology Group, Neonatal, and Pediatric Critical Care networks, among others. Therefore, HHS intends to include a discussion of these research networks on the agenda for the interactions described above with interested stakeholders. These discussions would be aimed at evaluating the contributions of the existing research networks in identifying pediatric clinical study sites, recruiting children in clinical studies, and, where available, collecting data on the use of medical devices in pediatric populations. In addition, the need for forming new national networks of facilities (either real or "virtual") will be explored.

3) **Consideration of certain pediatric device issues by the Office of Pediatric Therapeutics or the Pediatric Advisory Committee.** This recommendation could enhance the premarket review of pediatric medical devices. HHS agrees that this promising suggestion warrants further discussion with our stakeholders.

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

I. Introduction

On April 1, 2004, the Medical Devices Technical Corrections Act of 2004 (MDTCA), Public Law 108-214, was enacted. This law provides technical amendments to the Medical Device User Fee and Modernization Act of 2002 (MDUFMA), which amended the Federal Food, Drug, and Cosmetic Act (FFDCA). Section 3 of Public Law 108-214 requires the Secretary of Health and Human Services (of the Department of Health and Human Services (DHHS)) to submit a "report on the barriers to the availability of devices intended for the treatment or diagnosis of diseases and conditions that affect children." The law requires the report to include any recommendations of the Secretary "for changes to existing statutory authority, regulations, or agency policy or practice to encourage the invention and development of such devices."

To prepare the report, the Food and Drug Administration (FDA) examined the following questions regarding medical devices intended to treat or diagnose diseases and conditions affecting children:

- Are there unmet medical device needs in the pediatric population?
- What are the potential barriers to the development of new pediatric medical devices?
- What can be done to facilitate the development of devices intended for use in the pediatric population?

MDTCA requires the submission of the report within 180 days of enactment (i.e., by September 28, 2004). This report is submitted to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives as required.

II. Background

The FFDCA categorizes devices into three classes based on the level of risk associated with the device and the level of controls needed to help ensure its safety and effectiveness. "General controls," such as registration and listing, good manufacturing practices, and adverse event reporting, apply to all devices.[2] Devices for which general controls alone are insufficient to provide a reasonable assurance of safety and effectiveness may also be subject to "special controls," such as additional performance standards, post market surveillance requirements, use of patient registries, and the dissemination of guidelines by FDA.

[2] There are, however, some devices that are exempted from certain general controls.

As discussed below, there are three main pathways by which devices go to market: Premarket Notification, Premarket Approval, and Humanitarian Device Exemption. Although not as common, some devices go to market through a Biologics License Application, so we have included a discussion of this process. In addition, FDA recently issued guidance on the type of data needed to support marketing of pediatric devices and the patient protection measures that should be followed during trials involving pediatric subjects.

A. Premarket Notification (510(k))

The largest premarket review program for medical devices is the Premarket Notification Program. Each year, FDA reviews approximately 4,000 such submissions. Under this program, a manufacturer submits a 510(k) to FDA to demonstrate that the device it plans to market is substantially equivalent to a legally marketed "predicate" device. A legally marketed predicate device may be a device that was legally marketed prior to May 28, 1976, the enactment date of the Medical Device Amendments of 1976 (i.e., a pre-amendments device), a device which has been reclassified from Class III into Class II or I, or a device that was found to be substantially equivalent to a device in one of the above categories through the 510(k) process. To support this determination, applicants provide descriptive data comparing the two devices and, when necessary, performance data. In approximately 10 percent of the 510(k)s reviewed by FDA, clinical data is needed to support the equivalency determination. Substantially equivalent devices are "cleared" by FDA for marketing.

B. Premarket Approval Application (PMA)

A PMA is the most stringent type of device marketing application and is reserved for Class III devices, which generally present the highest level of risk. Due to the level of risk presented by Class III devices, general and special controls alone are insufficient to assure the safety and effectiveness of these devices. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to give reasonable assurance that the device is safe and effective for its intended use(s). FDA reviews about 40-50 PMAs per year, and almost all of these applications are supported by clinical data.

C. Humanitarian Device Exemption (HDE)

The Safe Medical Devices Act of 1990 (SMDA) provided for a humanitarian device exemption to encourage the discovery and use of devices that are intended to benefit a relatively small number of individuals. This provision allows FDA to grant an exemption from the effectiveness requirements of a PMA if:

- The device is designed to treat or diagnose a disease or condition that manifests itself in fewer than 4,000 individuals in the United States;

- The device is not otherwise available, and there is no comparable device available to treat or diagnose the disease or condition; and
- The device will not expose patients to unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

Because the small patient population for which the device is intended cannot support full clinical trials, an HDE application need not contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended use(s). However, the application must contain sufficient information for FDA to determine that the device satisfies the safety and probable benefit to health standards described above. In order to do this, most HDEs are approved on the basis of preclinical animal and bench testing and either small clinical trials or clinical experience gained from marketing outside of the United States. FDA reviews approximately 5-10 HDEs each year.

In addition to the above limitations, devices granted a humanitarian exemption may only be used following approval by an institutional review board (IRB), except in emergency situations. Finally, manufacturers of devices approved for marketing under the HDE are only allowed to recoup the costs of research, development, fabrication, and distribution of the device.

D. Biologics License Application (BLA)

Some medical devices are considered biological products and are subject to FDA approval. A biological product is "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product … applicable to the prevention, treatment or cure of a disease or condition of human beings." (42 U.S.C. § 262(i)). Biological products are approved for marketing under section 351 of the Public Health Service Act (PHS Act), which requires individuals or companies who manufacture biologics for introduction into interstate commerce to hold a license for the products. Under section 351 of the PHS Act, FDA will grant such a license only if the sponsor presents valid scientific evidence demonstrating that the product is "safe, pure, and potent." (42 U.S.C.§ 262). However, because biological products also meet the definition of "drug" or "device" under the FFDCA, they are also subject to regulation under FFDCA provisions.

E. FDA Guidance on Pediatric Medical Devices

FDA most recently addressed premarket review of medical devices intended for pediatric patients when, on May 14, 2004, it issued a guidance entitled, "Premarket Assessment of Pediatric Medical Devices."[3] The guidance was published pursuant to MDUFMA, which contained several provisions intended to promote the development of safe and effective pediatric devices. In this guidance, FDA defined the age ranges for pediatric

[3] This guidance may be found on FDA's website at: www.fda.gov/cdrh/mdufma/guidance/1220.pdf

subpopulations, identified the types of information needed to provide reasonable assurance of the safety and effectiveness of medical devices intended for use in the pediatric population, and described the protections that sponsors should consider for pediatric subjects involved in device clinical trials.

Specifically, FDA clarified that it assesses the safety and effectiveness of devices for pediatric populations using the same bases, approaches, and processes used to assess devices for adults. In addition, the agency explained that it applies a least burdensome approach to the premarket review of pediatric devices just as it does for devices intended for adult populations.

The guidance also notes that certain adult devices may be inappropriate for pediatric use due to a variety of factors (e.g., patient size, growth, and development), or may require design changes or special labeling for pediatric use. Therefore, in order to ensure proper design, demonstrate safety and effectiveness in pediatric populations, and provide clear instructions for use, clinical data may be needed for certain pediatric devices. Those cases typically occur when:

- Pre-clinical data (e.g., bench or animal data) or clinical data obtained in adults are inadequate to establish safety and effectiveness in the pediatric population
- Pediatric data are needed to validate or verify design modifications
- Pediatric data are needed to develop an age appropriate treatment regimen

The agency also has clarified that where clinical data are needed, published reports and studies as well as actual use information may be utilized, if appropriate. In some cases, the inclusion of pediatric patients in the original clinical trials may result in adequate data collection to support marketing approval. Finally, FDA encourages sponsors of pediatric devices to take advantage of both informal and formal meetings with the agency to discuss investigational protocols and the least burdensome approach to obtaining marketing approval for their device.

F. Office of Pediatric Therapeutics and the Pediatric Advisory Committee

The Office of Pediatric Therapeutics (OPT) was created by Section 6 of the Best Pharmaceuticals for Children Act, Pub. L. 107-109 (January 4, 2002). The OPT was given a broad scope of responsibility and was statutorily directed to "be responsible for coordination and facilitation of all activities of the Food and Drug Administration that may have any effect on a pediatric population or the practice of pediatrics or may in any other way involve pediatric issues." The delegation from HHS to FDA incorporated the broad charge of responsibility. Although the OPT has focused on issues primarily related to drugs since its inception, certain cross-cutting issues, including ethical concerns, also impact the medical device program. It is anticipated that the OPT will continue to broaden its consideration of issues that have a more direct impact on the concerns associated with pediatric medical devices.

The Pediatric Advisory Committee (PAC) charter provides the committee with a broad responsibility similar to the OPT. The Committee advises and makes recommendations to the Commissioner of Food and Drugs regarding pediatric research; identification of research priorities related to pediatric therapeutics and the need for additional treatments of specific pediatric diseases or conditions; ethics, design, and analysis of clinical trials related to pediatric therapeutics; research involving children as subjects as specified in 21 CFR 50.54; and, other matters involving pediatrics for which FDA has regulatory responsibility including certain medical device issues.

III. What Has FDA Done to Gather Information on Pediatric Medical Device Issues?

A. *Federal Register* Notice

To prepare this report to Congress on the barriers to bringing pediatric devices to market, FDA sought comment from interested parties, including consumers, the medical device industry, researchers, healthcare practitioners, and professional and trade associations by publishing a notice in the *Federal Register(FR)*. On June 21, 2004, the agency published a notice entitled, "Possible Barriers to the Availability of Medical Devices Intended to Treat or Diagnose Diseases and Conditions that Affect Children"[4] (Public Docket No. 2004N-0254). In this notice, FDA summarized the new statutory provision and requested comments from the public on the following questions:

- 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?
- 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 pre-market process that would encourage clinical investigators, sponsors, and manufacturers to pursue clinical trials and/or marketing of pediatric devices?

In order to reach as broad an audience as possible, FDA and several non-governmental stakeholders informed their constituents of this request for comments. These outside parties included:

- Device manufacturers
- Medical device trade associations
- Clinical specialists in pediatrics and rare diseases
- Special government employees serving as pediatric experts for FDA

[4] This Federal Register notice (69 FR 34374) is available at http://www.fda.gov/OHRMS/DOCKETS/98fr/04-13872.htm.

- Members of organizations and associations with an interest in rare diseases and pediatrics
- Patient advocacy organizations
- Other government agencies
- Public members on FDA's contact listing database with an interest in pediatric issues.

During the 60-day comment period, FDA received 25 comments.[5] These are available under Public Docket No. 2004N-0254 and at www.fda.gov/cdrh/pediatricdevices/comments.pdf, and included comments from ten healthcare practitioners (one international), six healthcare professional organizations, two special health organizations, five device companies (one international), and one device trade association.

B. Stakeholder Meeting

On June 28, 2004, 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 hosted a meeting of stakeholders to discuss the development and availability of pediatric devices. Representatives from the clinical community, medical device manufacturers and trade organizations, federal agencies, biomedical technical societies, academia, and pediatric patient advocacy organizations participated in the meeting. FDA is grateful to the host organizations, especially the lead organization, the American Academy of Pediatrics, for its enthusiasm in planning and convening the stakeholder discussion.

The goal of the meeting was to identify unmet pediatric device needs, barriers to addressing those needs, and possible mechanisms for increasing the availability of pediatric medical devices. During the discussion, participants noted that while there clearly is an unmet need for certain therapeutic and diagnostic devices for pediatric populations, there is not a clear understanding of the scope of these needs, nor is there a mechanism for pediatricians, researchers, and manufacturers to share information about these needs. While unmet needs in various medical specialties were identified, some participants recognized that these needs seemed to fall into one of three categories. That is, the unmet pediatric needs include those cases where there is no device available to treat a pediatric indication, instances where off-label use of an adult device is being used to satisfy the need, or cases where there is a pediatric device available but it does not meet the specific needs of the particular population.

The participants also spent considerable time discussing the possible barriers to bringing new devices to market and the potential solutions to facilitating new pediatric device development. This discussion raised many complex issues, including the varying needs of pediatric subpopulations (neonates, infants, children, adolescents), the diversity of the device industry, the relatively short life cycle of devices compared to drugs, liability

[5] Although 25 comments were received, FDA believes that comment # EC 6 was submitted to this docket in error.

concerns for manufacturers and pediatricians, intellectual property considerations, the difficulty in conducting pediatric clinical trials, and reimbursement concerns.

Given the above, the group recognized that additional meetings would be needed to fully explore these issues and the potential solutions identified during the discussions. Several participants mentioned the need for additional information gathering and further discussion with the various stakeholders before proceeding with any legislative effort. As a result, several workshops were proposed to identify and prioritize the unmet pediatric needs as well as to explore possible solutions.

C. Congressional Briefing

On July 14th, 2004, FDA participated in a briefing of Congressional staffers on the issues surrounding access to and the development of medical devices. The attendees included representatives from NIH and FDA. FDA presented background information on its regulatory mechanisms for bringing new devices to market and discussed various aspects of the Orphan Products Program. Issues particular to pediatric device development, including the HDE Program, were also discussed. NIH provided an overview of various programs that are involved in fostering pediatric device development. Representatives from the various institutes and offices discussed specific programs and gave examples of pediatric device research programs that are funded by NIH. These included a decade-long program for the development of cochlear implants, which are now FDA approved, and a number of devices, still in the prototype stage, such as pediatric cardiac pumps and ventricular assist devices.

IV. Major Issues Concerning Pediatric Medical Devices – Summary of the Comments

A. Unmet Medical Needs for Pediatric Medical Devices

Commenters agreed that significant differences in the need for medical devices exist between children and adults as well as among pediatric subpopulations. Comments from clinicians and patient advocates demonstrate that they clearly believe that unmet pediatric medical device needs exist and that they should be addressed through the increased development of devices intended, and labeled, for pediatric use. However, medical device manufacturers commented on the need for a more systematic review and prioritization of "unmet pediatric device needs" and that the clinical community was in the best position to perform that function. Manufacturers stated that this was a critical first step towards enabling stakeholders, including device manufacturers and the government, to begin to address those needs. Manufacturers also commented that improvement in communication between clinicians and device manufacturers would help facilitate the development of devices targeted for the unmet needs identified by clinicians.

Comments from individual clinicians, organizations representing physicians, and patient advocacy groups described a number of disease states and organ systems where devices intended for pediatric use were either unavailable or unable to meet the current standard of care. The comments emphasized the device needs of pediatric cardiologists (e.g., devices for valvular heart disease, atrial and ventricular septal defects, stent placement), pulmonologists (e.g., inhalers designed for pediatric use), nephrologists (e.g., specialized central venous dialysis catheters), orthopaedic surgeons (e.g., bioabsorbable fracture fixation devices), and general surgeons (e.g., devices for laparoscopic and endoscopic procedures). Comments also stressed the need for medical devices to be tailored for specific pediatric subpopulations because their needs for devices may be different (e.g., certain devices may only be needed by some subpopulations, such as neonates or adolescents).

Commenters also emphasized that the lack of availability of devices labeled for pediatric use may require pediatricians or hospital staff to use adult devices "off-label" by modifying, "jury-rigging," or creating make-shift device solutions for pediatric patients. They said that the risks associated with off-label use are higher because there is less information available to the clinician and the patient about the safety and efficacy of such use. Clinicians, patient advocates, and physician organizations stressed the potential for adverse outcomes due to the unavailability of pediatric devices. They also cited the increased risks associated with using an adult device that has been modified for a pediatric indication when there is limited information about the new use. Commenters cited some specific concerns (e.g., increased tissue damage from the use of an adult endoscope, the need for more invasive surgery requiring greater sedation), but there was limited discussion of poor health outcomes that were directly related to off-label use of approved devices in children or whether any unmet pediatric device needs were being successfully addressed through off-label use. The success rate may be dependent upon clinical practice or the "definition" of success within pediatric subspecialties and may vary by pediatric subpopulation.

B. Possible Barriers to the Development of New Pediatric Devices

In the FR notice, FDA asked commenters to identify regulatory, clinical, economic, and legal issues that might inhibit the development and marketing of pediatric medical devices. Most commenters noted that there are many, often overlapping, potential barriers to the availability of new devices for children. Several respondents cited all of the above as contributing to the unmet needs in the pediatric population. Below is a summary of the barriers identified in the comments.

1. Regulatory Issues

- **Ambiguous device approval criteria** -- Many commenters indicated that the criteria for pediatric device approval are ambiguous, and some commenters expressed the belief that FDA is more conservative and requires more data for pediatric devices than adult devices.

- **FDA guidance is helpful but more is needed** -- Several commenters noted that FDA recently issued guidance on the premarket review of pediatric devices. They stated that if FDA followed the principles identified in the guidance, testing and approval of new devices could be facilitated. However, another commenter raised concerns about the strict limitations it believes FDA has used to define pediatric subpopulations in the guidance. Others commented that additional device-specific guidance is needed.

- **HDE process is restrictive and difficult to understand** -- Clinicians and industry noted these concerns, which are discussed in more detail below.

    - A key concern raised both at the June 28, 2004, meeting and in the industry comments is that the HDE applies only to those devices that address diseases or conditions that affect or are manifested in fewer than 4,000 patients. It was stated that this limit is arbitrary and overly restrictive.

    - Manufacturers and clinicians noted that IRBs are unclear about how to handle HDEs, and insurance companies may not cover their use because they are uncertain whether these devices should be treated as investigational or approved. Clinicians noted that IRBs question whether some of these devices are appropriate for off-label use.

    - Discussion at the June 28, 2004, meeting indicated a concern about the requirement for IRB review and questioned the value it adds to the use of the device. Further, manufacturers stated that IRBs find the request for review and approval confusing since FDA has already approved the device for marketing.

- **FDA does not allow use of off-label data** – Several comments noted that the agency does not allow the use of off-label data, collected retrospectively, to support marketing approval of new devices. The commenters cited the statutory requirement that informed consent be obtained in all device clinical trials as an obstacle to the development of new pediatric devices. While some commenters stated that changing the statute to allow IRBs to waive informed consent under certain circumstances would facilitate the collection of data to support new pediatric indications for adult devices, others argued against modifying the law to relax human subject protections for this vulnerable patient population.

- **Difficulty in collecting postmarketing data** -- At the June 28, 2004, meeting and in the written comments, manufacturers indicated that it is difficult to gather useful pediatric information through postmarket studies. Some companies fail to complete postmarket study commitments because

manufacturers have difficulty enrolling subjects in studies after similar or improved devices enter the market. Healthcare practitioners and parents may also not be aware of the process to report adverse events associated with the use of pediatric medical devices.

2. Clinical Trial Issues

- **Eligible pediatric population for clinical trials is small and clinically varied**-- Both clinicians and the device industry noted that the smaller number of eligible pediatric patients with specific clinical conditions and the clinical heterogeneity within the population makes it extremely difficult to conduct clinical trials needed to support marketing approval. Both clinicians and industry indicated that any requirement for randomized controlled trials for pediatric devices, when no such trials may have been required for the adult device, contributes greatly to this difficulty. A device trade association acknowledged that many pediatric medical devices have already gained market entry via the 510(k) process without the need for large, costly clinical trials.

- **Randomized, controlled trials are especially difficult** -- It was also noted that randomized controlled trials are often difficult to design in pediatric populations due to ethical and practical concerns of exposing children to risks that may be considered excessive, especially if the device being tested is thought to be a safer alternative. Some commenters felt that even non-randomized prospective clinical studies significantly delay access and impose high costs that manufacturers may be unable or unwilling to incur.

- **Reluctance to enroll children in clinical trials** -- A clinician noted that a reluctance to expose younger patients to clinical trial risks requires even more stringent guidelines for investigational device exemptions applications (IDEs) and more comprehensive education on informed consent for parents or guardians.

- **Informed consent and IRB requirements are too burdensome** -- Other commenters stated that the informed consent regulations for studies involving children are confusing and overly burdensome. Additionally, a healthcare professional organization stated that IRBs are excessively stringent in their review and they have difficulty in finding appropriate multi-specialty expertise to serve on their committees. In contrast, another commenter emphasized that the success in conducting pediatric drug studies demonstrates that clinical trials involving children can be designed to meet the human subject protection guidelines for this vulnerable patient population.

- **FDA's reluctance to accept alternative types of data** – Several industry commenters noted that even though FDA has two guidance documents available regarding the use of published literature, which acknowledge that clinical studies should not be necessary if there is no substantial change to the device or its application, there may be a potential reluctance for FDA to accept literature evidence in lieu of prospective clinical studies in pediatric device applications. Further, a clinician stated that this reluctance to accept literature is, in part, because FDA may not have the pediatric expertise needed to fully understand the nuances of pediatric subspecialty clinical needs and key technologies used in those subspecialties.

3. Economic Issues

- **Development costs for pediatric devices are prohibitive** -- The majority of commenters representing all groups indicated that the cost of developing pediatric medical devices is the most significant barrier to the development of new pediatric medical devices. The economic challenges noted include not only the limited size of the pediatric device market, but also that the return on the investment required to develop and test pediatric devices usually falls below the profit goals of most medical device companies.

  It was reported at the June 28, 2004, meeting that many small device manufacturers would incur prohibitive costs in order to hire the pediatric clinical expertise needed to develop devices for this population. Research and development costs as well as increased manufacturing and retooling costs for pediatric devices were also cited as significant barriers. Finally, companies often must make frequent changes to products and develop multiple sizes of the same product, all of which require additional testing, manufacturing changes, and regulatory activity.

- **Lack of understanding of the unmet needs** -- Several clinicians noted that there is a lack of understanding of the pediatric unmet needs by device manufacturers. They noted that there are many pediatric devices that do not work well but could be easily modified. Similarly, there are adult devices that could be modified for pediatric populations, but there is currently no easy way for clinicians to convey this information to the device industry.

- **No profit-making on HDEs** -- Industry and healthcare professional organizations identified the restriction on profit-making for HDEs as a key economic barrier to the development of pediatric devices. (Currently, a company is limited to recouping the research, development, fabrication, and distribution costs.) The requirement for an independent certified

public accountant to verify that no profit is being made was noted as a further deterrent for the use of this regulatory path.

- **Lack of patent exclusivity** -- It was also noted that there is no exclusivity in the marketing of medical devices, once approved.

- **Obtaining insurance coverage is difficult** -- Industry and healthcare practitioners cited the lack of reimbursement and the cost of obtaining billing codes as barriers to the development of new devices for children.

- **Liability insurance is expensive** -- Finally, the cost of additional product liability insurance, if available, was identified by the device industry as a major obstacle in bringing pediatric medical devices into clinical use.

4. Legal Issues

- **Off-label use of adult devices in pediatrics** – Several commenters stated that the current standard of care in many instances is to use adult (or approved) devices off-label in children and that this practice poses a potential barrier to the development of pediatric products because it may appear that there is no unmet need for that indication. Other comments recommended requiring mandatory labeling about pediatric use to help healthcare professionals select appropriate adult medical devices for pediatric use. However, a device trade association emphasized that requiring labeling for pediatric use would be a potential barrier, and in fact, detrimental to the development of medical devices for pediatrics. All categories of commenters agreed that off-label use of adult devices in children poses a significant liability risk to health care practitioners, institutions, and industry.

C. Fostering the Development of New Pediatric Devices

FDA recognizes that fostering the development, approval, and availability of devices for pediatric use will likely require the commitment of numerous stakeholders. Comments to the docket contained a number of recommendations that should help to facilitate the development and availability of devices intended and labeled for pediatric use. They fall into the categories of legislative actions, regulatory actions, funding for research and development, financial incentives, and enhanced information gathering and exchange.

1. Legislative Actions

- **Creation of a statutory presumption that devices indicated for adults should also be designed for and tested in pediatric populations** -- Clinicians and a patient advocacy group felt that an action, similar to the passage of the Pediatric Research Equity Act of 2002, could encourage pediatric device development. Device manufacturers disagreed, asserting

that such a requirement could actually decrease the availability of pediatric devices for two reasons: (1) the significant cost associated with the development, design, and clinical testing required for pediatric labeling, and (2) if pediatric labeling were required, then "general" labeling, which is typical for many 510(k) devices, would no longer be sufficient for pediatric use. This would make pediatric use off-label, thereby making such use ineligible for reimbursement by many insurers.

- **Removal of the profit restriction associated with HDEs** -- Clinicians, patient advocacy groups, and device manufacturers made this suggestion. The device manufacturers cited the regulatory burdens associated with the current requirement to prove that no profits were being made through the sale of HDE approved devices. Although agreeing with the suggestion, clinicians and patient advocates cautioned that removal of the restriction could result in windfall profits for device manufacturers, and therefore, steps should be taken to ensure that such a change would be limited to pediatric devices and would result in increased pediatric device development.

- **Modifications to the HDE statute, in addition to removing the profit-making restriction, include raising the limit on the number of patients who can be treated under the HDE, eliminating the requirement that there be no alternative device for the condition, and eliminating the requirement for IRB approval** – Several commenters asserted that the statutory limit on the number of patients who can be treated under an HDE should be raised to encourage manufacturers to pursue marketing under this authority. (No specific increase was cited.) In addition, companies stated that the requirement that no alternative device exist in order for an HDE to be approved is a deterrent and should be removed. The device industry and clinicians cited the IRB approval requirement as confusing and burdensome to them and the IRBs.

- **Allowing FDA to share information it has gained from other applications** -- A device manufacturer suggested that current law should be modified to allow FDA to make information involving biocompatibility of materials for pediatric products publicly available, so that the public is alerted to both problems and solutions. At the June 28, 2004, meeting, a similar proposal was made to allow public availability of safety and effectiveness data related to biocompatibility of materials used in pediatric devices.

- **Establishment of tax credits for pediatric device development** -- See discussion below under Funding.

- **Establishment of liability protections for manufacturers of pediatric devices** -- One manufacturer suggested passing legislation to reduce liability exposure of pediatric device manufacturers.

2. Regulatory Actions

- **Expedited premarket review by FDA for pediatric devices** -- Both clinicians and medical device manufacturers suggested that shorter premarket review would be an incentive to the development of pediatric devices and recommended either the establishment of an expedited review program for these products or more aggressive performance goals. One manufacturer recommended that either the Special 510(k) or *de novo* process[6] be modified to accomplish this.

- **Adoption of approval processes used in Europe** -- A clinician suggested that FDA adopt methods used in the European Union to approve devices. He cited limiting review to structural integrity and biocompatibility of the device, and allowing institutional review boards or ethics committees to recommend use of the device. A device manufacturer recommended that FDA accept/acknowledge the experience/approval of devices from other countries with recognized device regulation and design controls.

- **Revising and clarifying the requirements for submission of clinical data in support of pediatric devices** -- Clinicians, patient advocates, and medical device manufacturers recommended that FDA review what it considers to be "valid scientific evidence" to establish the safety and effectiveness of pediatric medical devices and that it adopt a "least burdensome approach" because it is difficult to recruit children for device studies and to conduct large, randomized clinical trials for pediatric devices. Specific examples were cited, including:

  (1) FDA should explore the use of different statistical methods, such as Bayesian analysis, when reviewing clinical data for pediatric devices.

  (2) FDA should determine if any clinical data should be submitted in cases where minor technical changes to an approved device (e.g., change in size) are needed for pediatric use, where there is significant experience using the device in adults, and where the disease for which it is indicated is similar in adults and children. One device manufacturer commented that, with regard to approved devices, clinical data in support of a pediatric indication should be submitted only when significant uncertainties and clinical risk are possible.

[6] Section 513(f)(2) of the FFDCA is commonly referred to as the "de novo" provision.

(3) FDA should consider allowing submission of studies involving fewer patients with longer follow up.

(4) FDA should consider allowing submission of published literature, data from registries and/or other post-market surveillance data, or even non-clinical studies to support an application for pediatric indications. The agency should also more readily accept clinical data collected outside the United States in support of pediatric indications.

Commenters recognized that new authorities to waive current informed consent requirements might be required to allow FDA to review information obtained from certain databases and from banked samples. However, one commenter, a clinician ethicist, cautioned against relaxing informed consent protections for children.

- **Stratify clinical data requirements by pediatric subpopulation** -- One device manufacturer suggested that any required clinical data to support a pediatric indication for an approved device should be less in certain pediatric subpopulations (e.g., adolescents) than in others (e.g., neonates).

- **Use labeling modifications and postmarket controls to reduce risk** -- One device manufacturer suggested that establishing user qualifications and restricting use of a device to qualified individuals and institutions could allow approval of more pediatric devices.

- **Use of clinical experts earlier in the process** -- Commenters suggested that using subject matter experts (e.g., pediatric cardiologists, orthopeadists) familiar with the use of devices in their area of expertise could help FDA and manufacturers identify criteria for device performance earlier in the development process.

- **Use of consensus standards in the review process** – A healthcare professional organization recommended that FDA rely on international standards developed by the American Society for Testing and Materials International (ASTM) as a mechanism for reducing premarket review times.

- **Changes to allowable study designs** – Clinicians made two suggestions: (1) that FDA allow clinical trials without placebo arms to be submitted in support of pediatric device applications, where appropriate, to facilitate patient recruitment, and (2) that studies be designed to accurately reflect clinical use (e.g., study pediatric inhalers with spacers because they are used with spacers in clinical practice).

- **FDA should specifically allow a single institution to conduct clinical trials on more than one device for the same indication** -- This

comment, made by a clinician, cited the potential for clinicians to rapidly develop experience and understanding of multiple products, thereby increasing the likelihood that each of the products being tested would be used more safely and effectively once approved.

- **Consideration of certain pediatric device issues by the Office of Pediatric Therapeutics or the Pediatric Advisory Committee** -- Clinicians and patient advocacy groups commented that the OPT and PAC have been very successful in fostering pediatric drug development and labeling and that these entities could help achieve the same for pediatric devices.

- **Issue guidance to clarify existing regulations related to informed consent and other protections for children participating in clinical trials** -- Clinicians and advocacy groups made this recommendation; however, one commenter, a clinician ethicist, cautioned against relaxing informed consent protections for children.

3. Funding for Research and Development

- **Increase in government funding for pediatric devices** – A number of clinicians, patient advocates, and device manufacturers suggested expanded government funding for the design and development of pediatric devices. Specific suggestions included: (1) legislative changes to establish tax credits and/or guaranteed, low interest rate loans, (2) expansion of current grant programs from the National Institute of Child Health and Human Development (NICHD) and the National Institute for Biomedical Imaging and Bioengineering (NIBIB), and (3) public-private partnerships to create funding streams.

4. Financial Incentives

- **Removal of the profit restriction associated with the HDE** – See above under Legislative Actions.

- **Expedited coverage, coding, and payment determinations by the Centers for Medicare and Medicaid Services (CMS)** – A device trade association suggested that expedited review decisions by FDA coupled with faster reimbursement decisions by CMS 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 would provide a financial incentive for the development and marketing of pediatric devices.

5. Enhanced Information Gathering and Exchange

- **Creation of a Pediatric Research Network for devices** – Device manufacturers suggested the establishment of a network of children's hospitals and other entities that could assist with conducting clinical trials and recruiting patients might facilitate the performance of clinical trials.

- **Performance of a comprehensive needs assessment for pediatric devices, including prioritization of those needs, with subsequent communication to and collaboration with device manufacturers** -- Device manufacturers commented that the clinical community was in the best position to perform a needs assessment and prioritization of unmet needs in the pediatric population. Clinicians, patient advocates, and device manufacturers all agree that sharing this information over a Web site or through workshops and roundtables, similar to the FDA-sponsored *in vitro* diagnostic (IVD) Roundtable, could be useful in identifying opportunities to develop new pediatric devices or modify existing devices for pediatric use, as well as to promote collaboration and joint efforts to resolve device related issues.

- **Including a list of devices approved for pediatric indications on the FDA Pediatric Devices Web site –** At the June 28, 2004, meeting, it was suggested that listing devices approved for pediatric indications on FDA's Web site would be useful to healthcare providers.

- **Creation of a system to identify and track devices intended for pediatric use and adult devices intended for conditions that also occur in children** – Clinicians and patient advocates suggested that the MDUFMA requirement to exempt pediatric devices from user fees could be used to generate such a list. The list could also be used to identify devices that require minimal changes or testing to obtain a pediatric indication.

V. Discussion and Recommendations

The need to improve health care outcomes and the quality of life for children is of paramount importance to the public health. In many cases, the availability of medical devices intended and labeled for use in children can assist in achieving these goals. If such devices are not being developed, approved, and made widely available, appropriate steps should be taken to remedy the situation. However, based on the complexity of the issues and the wide range of perspectives included in the comments and information received, it is clear that further study is warranted to determine the scope of unmet needs, the potential barriers to bringing new pediatric devices to market, and the most promising solutions to addressing these unmet needs.

Discussion

In order to sort through these difficult issues, identify the most important barriers to pediatric device availability, and craft appropriate, targeted solutions to address those barriers, it is crucial that a systematic effort be undertaken to gather information concerning unmet pediatric device needs. All the commenters agree that such an effort should include all stakeholders and should encompass a wide range of pediatric diseases. One of the first steps needed in this effort is to arrive at a common understanding and definition of "unmet pediatric device needs" to ensure the comparability of information obtained from different stakeholders.

FDA recently issued guidance defining "unmet medical need" in the context of criteria for designation of a drug to a fast track development program.[7] In that guidance, FDA defined an unmet medical need as "a medical need that is not addressed adequately by an existing therapy." The guidance went on to differentiate those situations where "there is no available therapy for the condition" from those situations where "there is available therapy for the condition." In the former situation there is always an unmet medical need while in the latter situation the new drug must show some clinical benefit (e.g., improved clinical outcomes, reduced toxicity) as compared to existing treatments.

FDA issued supplementary guidance to further define "available therapy" for drugs and biologics.[8] In this second guidance, FDA states "available therapy (and the terms existing treatments and existing therapy) should be interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions."

As noted above, these definitions are currently limited to drug and biological products. Moreover, the applicability of these definitions to pediatric device development or to any other situation has not been studied. However, they may serve as a starting point for discussion when:

- There is an adult medical device available which does not meet the needs of children
- There is a pediatric medical device available, but it is not appropriate for the pediatric sub-population in need
- There is no medical device available for the condition

HHS believes that defining "unmet pediatric device need" is an important issue that needs to be addressed and that a common understanding of "unmet pediatric device need" can provide a framework for further analysis of "unmet needs" within pediatric subspecialties. Then, a systematic needs assessment should be conducted so that the

[7] The guidance entitled, "Guidance for Industry; Fast Track Drug Development Programs – Designation, Development, and Application Review" (issued July 2004) is available at: www.fda.gov/cber/gdlns/fsttrk.pdf

[8] The guidance entitled, "Guidance for Industry; Available Therapy" (issued July 2004) is available at: www.fda.gov/cder/guidance/5244fnl.pdf

scope of the unmet needs can be fully understood. After conducting a needs assessment, it may be easier to prioritize those needs and more fully understand the role various barriers play in creating them. Such an understanding of unmet pediatric device needs and the barriers to the development of those devices will facilitate crafting solutions that are appropriate for, and targeted to, removing or minimizing those barriers.

Recommendations

Based on the foregoing discussion, HHS concludes that it is premature to recommend any substantive policy changes, including administrative and legislative changes. Instead, HHS recommends further study of the issues discussed in this report.

HHS believes that the first step in resolving this complex issue is for all stakeholders to participate in the development of a common understanding of "unmet pediatric device needs" and to systematically gather information about those needs. A pediatric patient advocacy organization has offered to hold several meetings of stakeholders in the fall of 2004 and the winter of 2005 to discuss many of the issues raised in this report. FDA plans to actively participate in those meetings and intends to explore the need for broader public participation in this process.

The next step in the process should be the development of a consensus of all stakeholders, including HHS, concerning both the prioritization of those unmet needs as well as which barriers to pediatric device development should be addressed first. Following these analyses, HHS will need to work with clinicians, patients, industry, and other stakeholders to determine which solutions are most promising for addressing particular unmet pediatric device needs. HHS will either publish these findings for public comment or present them for public discussion at an advisory committee meeting.

This will be a difficult task requiring the participation and focus of all stakeholders. For example, prioritizing device needs across a range of illnesses must take into account the prevalence, severity, and currently available treatments for those illnesses. In addition, identifying the most important barriers to device development will likely require a specialty by specialty or disease by disease analysis.

HHS believes that three of the recommendations made by the commenters should be integrated into the needs assessment and prioritization process.

1) **Enhanced interaction and communication between pediatric clinicians and device manufacturers.** During both the stakeholder meeting and in written comments, this recommendation was suggested to help identify the most pressing unmet pediatric device needs, promote discussion of what modifications to existing adult devices would facilitate pediatric use, and generate ideas for new pediatric devices. Proposals to facilitate such communication included the development of workshops and closer communication links between representatives of pediatric clinicians and device trade associations as well as roundtable discussions including these parties, HHS, and other stakeholders.

HHS intends to explore this suggestion with the clinical and device communities as well as other interested stakeholders to discuss possible venues for these interactions.

2) **Development of a network of children's hospitals and healthcare facilities with expertise in pediatric diseases and conditions.** While several commenters made this recommendation, HHS would like to point out that NIH supports numerous research networks for many childhood conditions, including the Children's Oncology Group, Neonatal, and Pediatric Critical Care networks, among others. Therefore, HHS intends to include a discussion of these research networks on the agenda for the interactions described above with interested stakeholders. These discussions would be aimed at evaluating the contributions of the existing research networks in identifying pediatric clinical study sites, recruiting children in clinical studies, and, where available, collecting data on the use of medical devices in pediatric populations. In addition, the need for forming new national networks of facilities (either real or "virtual") will be explored.

3) **Consideration of certain pediatric device issues by the Office of Pediatric Therapeutics or the Pediatric Advisory Committee.** This recommendation could enhance the premarket review of pediatric medical devices, and HHS agrees that this promising suggestion warrants further discussion with our stakeholders.

As the above process moves forward, HHS will continue to work with Congress and keep its interested members updated on our progress in addressing this important public health issue.