February 5, 2014

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

Re: Docket No. FDA–2013–N–1073: Complex Issues in Developing Medical Devices for Pediatric Patients Affected by Rare Diseases; Public Workshop; Request for Comments

Dear Sir or Madam:

On behalf of AdvaMed, the Advanced Medical Technology Association, we are pleased to submit these comments in response to the Food and Drug Administration’s (FDA’s) Federal Register request for comments on “Complex Issues in Developing Medical Devices for Pediatric Patients Affected by Rare Diseases.”

The Advanced Medical Technology Association (AdvaMed) is the world’s largest trade association representing medical device and diagnostics manufacturers. AdvaMed's member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed has more than 400 member companies, ranging from the largest to the smallest medical technology innovators and manufacturers. AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. The Association promotes policies that foster the highest ethical standards, rapid product approvals, appropriate reimbursement, and access to international markets.

AdvaMed commends FDA for holding the January 8, 2014 public workshop on “Complex Issues in Developing Medical Devices for Pediatric Patients Affected by Rare Diseases.” We believe the workshop was very productive and that much constructive interaction occurred at the workshop.

AdvaMed provides responses to many of the questions posed in the Federal Register Notice in addition to a number of other comments and recommendations below.

A. Current Clinical Practice

1. The current use and practice trends of medical devices in rare disease pediatric populations. For example, how much off-label use occurs? How much modification and adaptation of existing adult devices occurs?
Although we do not have information on how much off-label use occurs or how much modification and adaptation of existing adult devices occurs to treat pediatric patients, clinicians have routinely reported at FDA and the National Institutes of Health (NIH) public workshops on pediatric device development issues that they feel compelled to “jerry-rig” or modify existing devices to treat pediatric patients. We are very supportive of the FDA/NIH Needs Assessment Project that was reported on at the workshop because we believe the assessment could begin to capture and characterize unmet pediatric and rare disease device needs. We believe questions such as off-label use and modification or adaptation of existing adult device questions including the questions in C.1 of this Federal Register notice, should be included in the needs assessment.

In our comments to the December 5, 2012 docket associated with the FDA’s Public Workshop on Use of Scientific Research Data to Support Pediatric Indications for Devices, we noted that at an October 2009 FDA Workshop on Pediatric Clinical Trial Design, pediatric cardiovascular physician panelists pointed out that there are still many unanswered basic pediatric research questions. As the physicians noted, failure to answer or address certain basic pediatric research issues resulted in corresponding challenges in the FDA regulatory process (e.g., making it difficult for manufacturers and FDA to select and agree on appropriate surrogate or other clinical trial endpoints). Thus, FDA should consider whether there is an opportunity to query stakeholders participating in the pediatric device needs assessment whether there are related basic research questions that also need to be answered.

We recognize that this initial assessment will likely be unable to comprehensively identify all pediatric device needs and all scenarios related to off-label use or modification of existing devices but it is a critically important start. The assessment findings should help serve as a roadmap to understanding common research and development, and regulatory challenges that exist across disease conditions or device types and will also help to prioritize pediatric and rare disease device development. Identification of common challenges could assist with the development of potential solutions. We would anticipate that the initial assessment will serve as a foundation on which to build and add information to over time.

B. HUD/HDE

1. Is there any confusion about the designation process for HUDs or the application process for HDE’s? Where have barriers been encountered in the HDE marketing pathway, and how can they be mitigated? Please provide examples of any specific issues, how frequently they occur and suggestions to constructively address these barriers.

AdvaMed commends the FDA for the release of the revised guidance on HDEs, dated July 8, 2010. We believe that once companies begin exploring the HUD/HDE process they are able to readily understand the framework for the HUD designation process and the separate HDE process. However, we believe companies may generally be unaware that the HUD/HDE process exists as a potential pathway to market. AdvaMed is currently working with the Office of Orphan Products Development to help publicize the HDE pathway but we would encourage
FDA to continue efforts to highlight the HDE pathway as a potential regulatory pathway especially in basic descriptions and presentations of the pathways to market (i.e., 510(k), PMA, De Novo, HDE, etc.).

With respect to barriers in the HDE marketing pathway, AdvaMed has previously commented in numerous docket comments that companies face challenges in meeting FDA’s requirements for demonstrating probable benefit. We believe this challenge still exists and makes it hard for companies to consider using the HDE regulatory pathway to market. We have recommended that FDA add to existing guidance to clarify the level of evidence needed to meet the probable benefit standard.

Section 520(m)(2)(C) of the Food Drug and Cosmetic Act (FDCA) establishes the standard for FDA approval of HDE applications, specifically that “the device will not expose patients to an unreasonable or significant risk of illness or injury” and that “the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternate forms of treatment.” This is clearly a different standard than the premarket approval (PMA) requirement of reasonable assurance of safety and effectiveness which typically requires full-scale prospective randomized clinical trials because you cannot reasonably conduct such a trial in small populations. However, FDA has provided no general guidance to manufacturers regarding the type or level of evidence that must be developed to demonstrate that an HDE meets the probable benefit standard. This lack of guidance ultimately hinders the use of the HUD program as a pathway to market for devices that treat or diagnose diseases and conditions that affect fewer than 4,000 patients, including pediatric populations and subpopulations. Further, without clear FDA guidance, demands for evidence can continue to drift upward, until they begin to resemble the expectations for a PMA filing, as has been reported by some manufacturers.

For this reason, AdvaMed recommends that FDA develop general guidance on appropriate types and levels of data necessary for HDE approval. Such guidance should provide examples of what FDA believes are the appropriate types and levels of data needed to demonstrate probable benefit. AdvaMed believes that prospective randomized controlled clinical trials generally should not be necessary to demonstrate probable benefit to health, and that FDA should consider non-clinical data, published literature, historical data and patient records, surrogate endpoints and statistical methods and evidence from experience with similar devices.

With respect to barriers to utilizing the HDE pathway, AdvaMed has previously recommended in numerous comments to the docket that FDA be provided flexibility on the HDE cap. As we learned at the January 8, 2014 workshop, there was no significant scientific evidence behind the 4,000 patient HDE cap in the original HDE legislation. AdvaMed believes that because there continues to be so little information on the size of certain orphan and pediatric populations associated with specific conditions (due among other reasons to the lack of data on unmet pediatric device needs), it is unknown what affect applying the general HDE population cap of 4,000 to children’s devices may have on the availability of devices to treat pediatric conditions. AdvaMed recommends that the Secretary be given authority to selectively raise the cap for specific conditions when FDA determines the health of orphan or pediatric patients requires an
increase in excess of the annual distribution number – based on medical, demographic and scientific information provided by a petitioner. As an example, it is unlikely manufacturers will be incentivized to develop devices for an orphan disease that affects 4,500 patients annually and is under full PMA requirements, yet because the population is only 500 patients over the 4,000 cap, it is ineligible for the HDE program.

2. **Please comment on Institutional Review Board issues that arise for HDEs that are indicated for pediatric rare diseases.**

AdvaMed commends the FDA for clarifying in the existing HDE guidance, dated July 8, 2010, that an HDE device is indeed an approved device and not investigational. AdvaMed has previously noted in docket comments that numerous participants in pediatric stakeholder meetings in 2004 pointed out that private insurers typically refuse to reimburse for pediatric HUDs. The statute requires that HUDs can only be administered in facilities with properly constituted and functioning IRBs. Insurers thus assume the HDE must therefore be an investigative device that is not eligible for private insurer reimbursement. As a result, many times, costs associated with HUDs are out-of-pocket for patients.

AdvaMed conducted a very small, informal survey of members on this topic. Our members reported that for most HDEs, obtaining reimbursement is a significant undertaking for the physician, hospital, patient and manufacturer, requiring multiple prior authorization requests, appeals and conversations with insurer medical directors and that the process can take several months. Members also reported that the reimbursement challenges typically do not dissipate over the product’s lifetime. Members reported that they believed the reason for denial of reimbursement of HDEs related both to the requirement for IRB review as well as the HDE approval standard of safety and probable benefit. They also reported that some clinicians never offer HDEs to patients because of the effort involved in obtaining reimbursement. We believe the additional questions and answers that have been included in FDA’s “Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff – Humanitarian Device Exemption (HDE) Regulation: Questions and Answers” are very helpful in clarifying the role of IRBs with respect to HDEs and HUDs and may help address some of the reimbursement challenges associated with HDEs by helping to clarify that HDEs are legally marketed devices. We would note, however, that several stakeholders suggested potentially removing the requirement for IRB review at the January 8 workshop. If such a proposal were advanced, AdvaMed would review it and consider supporting it as this could potentially remove one of the challenges to use of existing HDEs and encourage development of other HDE products.

**D. Clinical Trials**

1. **What are the most challenging barriers in the process of designing protocols for devices used to treat/diagnose rare pediatric diseases?**

As we have commented before in numerous docket comments, pediatric and orphan diseases and conditions are difficult to study because patients with the affected conditions are few and are
widely dispersed making it extremely difficult to accrue sufficient numbers of clinical trial participants over a reasonable timeframe and within a manageable number of investigational sites and to assure an adequately powered clinical trial to meet FDA requirements. AdvaMed has a number of recommendations below that are responsive to small market size and failure to overcome regulatory barriers to on-label use. A related and significant obstacle to pediatric device development, especially for devices ineligible for HDE, is that the annual market associated with specific diseases and conditions may not be commercially viable (for either large or small device companies).

2. **What are unique challenges in identifying appropriate endpoints for protocols for devices used to treat/diagnose rare pediatric diseases?**

As noted above, at an October 2009 FDA Workshop on Pediatric Clinical Trial Design, pediatric cardiovascular physician panelists pointed out that there are still many unanswered basic pediatric research questions. As the physicians noted, failure to answer or address certain basic pediatric research issues resulted in corresponding challenges in the FDA regulatory process (e.g., making it difficult for manufacturers and FDA to select and agree on appropriate surrogate or other clinical trial endpoints). The needs assessment should help identify areas and conditions where devices are needed. Once that occurs, the appropriate specialty groups, in conjunction with FDA and relevant patient groups may be able to agree on appropriate endpoints – with the understanding that as more information and evidence is gained, endpoints may change over time. We would note, however, that FDA should not change endpoints during the course of a particular sponsor trial.

4. **How can new registries be developed or current registries be leveraged to provide robust data on the safety and effectiveness of pediatric medical devices to support premarket approval and clearance, and/or enhance postmarket surveillance activities related to pediatric medical devices?**

Some devices approved for use in adults may be used off-label in pediatric patients as practice of medicine. In some cases, the products have been on the market for many years and become the standard of care and are commonly covered by third party reimbursement. In cases like this, designing a protocol for a prospective trial to obtain FDA approval or clearance can become a major undertaking especially if the clinical trial is required to be randomized. Physicians and parents tend to opt out of participating in these studies and the studies end early with low enrollment rates. AdvaMed believes that enrolling pediatric patients in post-market real world registries would provide a means to support the clinical data necessary to support marketing applications.

Additionally, AdvaMed has previously developed a number of recommendations which have been submitted to various FDA dockets over the years that are intended to help improve device development for pediatric and orphan populations and subpopulations. One of those includes the recommendation that FDA develop new regulatory pathways to accommodate device development for small populations and subpopulations. As an example of one new regulatory approach that could be developed, AdvaMed has proposed that small confirmatory clinical trials
could be combined with Bayesian statistical approaches or postmarket approaches such as registries to demonstrate or monitor effectiveness. An article that outlines such an approach entitled *A new paradigm for obtaining marketing approval for pediatric-sized prosthetic heart valves* was recently published in The Journal of Thoracic and Cardiovascular Surgery. FDA commentary endorsing the approach accompanied the published article.

AdvaMed is also aware of the American College of Cardiology IMPACT Registry™ (IMproving Adult and Congenital Treatments) which may be a source of pediatric data.

E. Pediatric Needs Assessment

1. Describe the parameters that should be used in determining priority areas of development of devices, including both therapeutic and diagnostic devices, in pediatric rare diseases.

AdvaMed has long advocated that data on unmet pediatric device needs must be methodically collected including the number of patients with a particular disease or condition, age ranges, and current treatment and diagnostic options and health outcomes. As mentioned above, we believe questions such as off-label use and modification or adaptation of existing adult device questions including the questions in C.1 of this Federal Register notice, should be included in the needs assessment. FDA should also consider whether there is an opportunity to query stakeholders participating in the pediatric device needs assessment whether there are related basic research questions associated with pediatric diseases and conditions that also need to be answered.

Once the needs assessment has been conducted, a variety of criteria could be established to help determine priority areas of device development including:

- Is the disease or condition well-characterized and understood and is there consensus on potential clinical trial endpoints or surrogates?
- Can patient groups assist FDA, clinicians and sponsors in determining the benefit-risk calculus for the disease or condition and the related device?
- Can effectiveness data or safety data (where appropriate) be extrapolated between different device sizes, between adult and pediatric populations or between different pediatric subpopulations?
- Can pediatric clinical outcomes data from real world patient registries be used to support expansion of the age limit in a supplemental product submission to FDA?
- Is information available on the incidence and prevalence of the disease or condition?
- Is there an existing device that could be modified?

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• Is there an interested sponsor or consortium to support the product submission to FDA?
• Does a 510(k) for an adult device exist that could serve as a predicate for the pediatric device?
• Can well-documented case histories or historical controls help minimize the use of surgical interventions where a less invasive device has already been established as the standard of care?
• Can adult data serve as the control for investigational pediatric devices when the adult device has become the standard of care?

2. What is the best approach to conduct needs assessments of medical devices required for use with pediatric rare diseases?

AdvaMed supports the current needs assessment plan to define an unmet need as “When there are no approved devices for the treatment or diagnosis of a disease or condition or when a novel device could provide a significant clinically meaningful advantage over existing approved devices.” We are aware of situations in which patients (both pediatric and adult) are either unable to tolerate existing approved drugs or the drugs are ineffective for certain subpopulations. We also support the planned scope – evaluating needs across a broad spectrum of diseases/body systems and focusing on device needs rather than barriers to development. We understand that for Paperwork Reduction Act or other reasons, FDA may be constrained to rely primarily upon focus group interviews and we are supportive of that. However, we believe FDA should also reach out to specialty societies such as SCAI, AAOS, AAP, AANS, patient groups such as NORD or the National Health Council (NHC), and others to see if they would be willing to circulate a common survey to their memberships. Although device manufacturers are not likely to have significant information on device needs, AdvaMed is more than willing to circulate any common survey that is developed to its membership to help share knowledge on pediatric and rare disease device needs.

F. Device Related Issues for Diagnostic Devices

1. What are medical device related issues that need to be addressed for development of diagnostic medical devices?

A significant obstacle to using the HDE process for development of diagnostic devices for rare diseases is the HDE requirement to demonstrate the number of patients that would be subject to diagnosis by the device, rather than the number of individuals affected or manifesting the rare disease. Unlike other medical devices, where a demonstration by authoritative references that the disease or condition affects or is manifested in fewer than 4,000 people in the United States per year, for a diagnostic device, it is necessary to demonstrate by authoritative references that the number of patients per year who would be tested by the device is fewer than 4,000. Because such data is generally unavailable, the identification and presentation of authoritative references to support this requirement essentially renders the HDE process unavailable for diagnostic devices. In short, if a diagnostic test was developed to diagnose patients with a condition that manifests in 4,000 people or less per year, it is quite likely that physicians would prescribe the test more than 4,000 times a year in order to diagnose those with the referenced rare disease. To address this limitation, we recommend
removing this requirement and requiring the same demonstration of diagnostic devices as is required for other medical devices.

**G. Advancing Development**

1. **What incentives could help advance the development of diagnostic and therapeutic medical devices to treat pediatric rare diseases?**

Given the small market size related to pediatric and rare diseases and the costs and challenges associated with conducting trials and other studies related to pediatric and rare diseases, a key objective should be to find ways to reduce the costs associated with device research and development in these areas. The suggestions below are intended to help offset the costs of orphan or pediatric device research and development and address small market size and commercialization risks. They include:

- A strong orphan and pediatric device research and development tax credit program,
- A tax credit for orphan and pediatric HDEs similar to the tax credit that currently exists for orphan drugs,
- Minimization of governmental costs associated with developing products for orphan and pediatric populations such as restrictions on user fees,
- Expedited FDA clearance or approval of orphan or pediatric device applications, and
- Clear pathways for reimbursement once such products are cleared or approved.

AdvaMed also recommends the creation of an orphan/pediatric ombudsman in the Center for Devices and Radiological Health (CDRH). Currently, no one person or entity within CDRH has either the responsibility or the expertise to assist and counsel manufacturers or other interested stakeholders in how to utilize existing regulatory pathways (510(k), PMA or HDE) to achieve on-label indications for orphan and pediatric diseases and conditions. This individual could also serve as the liaison with an NIH Office of Orphan and Pediatric Diseases and Conditions. An ombudsman would help assure sponsors of pediatric/rare disease devices that there would be an entity to assist them as they encounter the inevitable challenges that are to be expected in the regulatory clearance and approval pathways involving sensitive populations. Whoever is selected for the ombudsman position should be a senior level individual who can assist in brokering disagreements that may arise between reviewers and sponsors.

3. **What are potential private resources (e.g., registries, industry, or patient advocacy groups) that could be tapped to advance the development of medical devices for rare diseases in the pediatric population?**

We believe patient groups for rare disorders may potentially have a lot of information to share including information that could assist with data collection on device needs. These groups may also be able to assist with helping to determine the benefit-risk calculus associated with regulatory data requirements. FDA may also want to reach out to universities who may be interested in conducting detailed assessments of needs associated with particular device types. The bio-design programs in some universities already conduct this type of activity so may be interested in participating.
4. What are potential improvements or changes that can be made to FDA guidance, regulations, or current science in order to help develop and improve medical devices to address the needs of the pediatric population affected by rare diseases?

A key challenge in orphan and pediatric conditions and diseases is that failure to overcome certain regulatory or other barriers to on-label use consigns certain devices and the diseases and conditions they treat to an unending cycle of “jerry-rigging” or off-label use. As a result, data that could be used to improve device research and development, obtain on-label indications, or improve patient outcomes is never collected. It is not clear that orphan or pediatric populations are well-served by this un-ending cycle. While it may not be feasible for all pediatric and orphan diseases or conditions and their associated devices, a concerted effort must be made to find ways to break this cycle and enable companies and clinicians to begin to obtain and to collect the data that will allow devices for orphan and pediatric diseases and conditions to be on-label. A related issue is the understandable desire to be able to answer all the questions related to a particular device submission for pediatric or rare diseases. Unfortunately, that will be an unattainable objective for many pediatric and rare disease submissions given the small populations involved and unanswered questions that may exist on basic research questions related to the disease or condition. In this context, the comment made by Ms. Christy Foreman, Director of the Office of Device Evaluation, suggesting that all parties may have to be willing to accept a level of uncertainty with respect to these devices, is critically important. We are unlikely to obtain the certainty in data in devices developed for pediatric and rare diseases that is currently achievable in adult devices. However, over time, more data and information can be obtained to guide data objectives and data gathering (e.g., appropriate endpoints, etc.).

AdvaMed has a number of recommendations below that are responsive to small market size and failure to overcome regulatory barriers to on-label use.

**General versus Specific Device Claims**

FDA requirements for limited and very specific claims and their associated data can be an important barrier to device development for small and dispersed orphan and pediatric populations. For example, FDA may require 100 patients in each pediatric age group to demonstrate device safety and effectiveness. FDA should consider and allow for more general claims to enable device approval. Subsequent condition of approval requirements, such as requirements for a registry, could then be used to ascertain whether there are particular issues associated with specific age ranges.

**New Adaptive Regulatory Models and Adaptive Clinical Trial Designs**

To address small market issues, FDA must develop adaptive regulatory models and adaptive clinical trial designs that take into consideration the reduced sample sizes associated with orphan diseases and conditions. For example, FDA could approve certain devices based on smaller confirmatory trials in conjunction with a long-term registry requirement either for an individual device or for certain device types. This would enable the collection of essential data to better understand patient outcomes and provide FDA with better data for future device approval decisions. Related to this, to facilitate pediatric device development by interested stakeholders (e.g., manufacturers or pediatric consortia), FDA should post on its webpage, examples of
adaptive clinical trial designs\(^3\) that have already been successfully used to obtain on-label orphan or pediatric indications.

**Valid Scientific Evidence Other Than Well-Controlled Trials**

Section 513(a)(3)(A) of the Federal Food Drug and Cosmetic Act and 21 CFR 860.7 give FDA authority to utilize valid scientific evidence other than well-controlled trials. Importantly, the standard of reasonable assurance of safety and effectiveness is the same no matter what type of scientific evidence is required. While FDA relies on many types of valid scientific evidence (other than well-controlled trials) in other areas, it is our sense that FDA has been reluctant to take advantage of this statutory authority in the case of pediatric devices.

FDA should be encouraged to make better use of all forms of valid scientific evidence which could help address the problems associated with the extremely small numbers of orphan or pediatric patients that are afflicted with any one condition or disease state. For example, what may have evolved as the pediatric standard of care may be off-label (e.g., a minimally invasive procedure supersedes a surgical procedure and becomes the standard of care). Doctors will be reluctant to randomize pediatric patients to a surgical control arm if the minimally invasive procedure is the standard of care. Parents will also be reluctant to have their child participate in such trials. In this instance, an FDA requirement to randomize pediatric patients to the surgical procedure creates a barrier that prevents the off-label use of the device from ever becoming on-label. Where numerous articles document the effectiveness of a particular off-label use of a device and it has become the standard of care, FDA should be encouraged to develop mechanisms that make use of this data.

AdvaMed has a number of recommendations that are intended to make better use of existing FDA regulatory tools and enhance orphan or pediatric access to medical devices. To help break down barriers to orphan and pediatric device development, FDA should provide examples of these or other types of valid scientific evidence in FDA guidance. Importantly, the proposals below retain the existing standard of reasonable assurance of safety and effectiveness although some of the recommendations may be applied to the HUD standard of safety and probable benefit.

1. **Proposal:** Where appropriate, FDA should use objective performance criteria (OPCs), historical controls or well-documented case histories as endpoints to show probable benefit or to demonstrate effectiveness.

   **Background:** Reliance on well-documented case histories and historical controls would take advantage of the existing literature, respond to the extremely small numbers of orphan or pediatric patients with any one condition (which makes it difficult to run statistically valid clinical trials in a timely fashion – as one person put it “20 years of literature vs. years to put together a control group”) and help minimize the use of surgical interventions as the control where devices have been established as the standard of care.

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\(^3\) FDA must take care not to reveal proprietary or trade secret or confidential commercial or financial information when sharing trial designs.
2. **Proposal:** Extrapolation of clinical data between different sizes of the same device based on engineering testing and other non-clinical data.

**Background:** Currently, FDA requires clinical evidence on the full range of device sizes for a particular device and it can be difficult to assemble enough patients at either end of the size ranges to be valid. It is often extremely challenging to get significant data on the smallest and largest sizes. This proposal would allow the use of non-clinical and bench data as well as the potential to do post-market clinical work to approve the full range of sizes.

3. **Proposal:** Reliance on non-clinical data for modifications of devices specifically approved for pediatric patient populations, when such modifications are unrelated to changes in intended use and do not effect safety.

**Background:** Modifications made to an already cleared or approved device to improve its performance or safety require that the device be cleared or approved again. For devices, much of the data about a product’s function can be established non-clinically (e.g., relying on animal, bench and/or reliability testing). Every time a minor modification is made (e.g., material changes or minor design changes), FDA often requires that the device be cleared or approved again. The requirements for clinical data in the modification process create a challenge and limit improvements for pediatric devices. Due to the barriers associated with gathering clinical data for pediatrics (small populations, widely dispersed populations, parental unwillingness to have children participate, timeliness, etc.), the intent of this provision – for devices specifically approved for pediatric use – is to enable use of engineering and bench testing, rather than clinical testing for minor device changes when the changes are not related to changing the intended use of the device and do not effect safety. FDA has the flexibility to do this – and allows it for adult devices – but should be specifically encouraged to do so in the case of pediatric products.

4. **Proposal:** Broader use of Medical Device Advisory Committees to make recommendations to FDA on establishing clinical evidence (other than randomized, controlled clinical trials) for devices that have become the standard of care but are being used to treat pediatric patient populations off-label. A panel meeting would allow appropriate stakeholders (e.g., manufacturers, patient support societies, pediatric societies) to present relevant information to the appropriate committee.

**Background:** FDA’s Advisory Committees review and evaluate data on the safety and effectiveness of marketed and investigational devices and make recommendations for their regulation. Advisory Committees function as an advisor to the Commissioner of Food and Drugs on regulatory matters that could help in advancing the development and approval of medical devices for pediatric and rare diseases. Specifically the Advisory Committees can provide a pediatric perspective during reviews of premarket approval applications (PMA) and PMA Supplements, 510(k)s and HDEs; reviews of guidelines and guidance documents; recommendations regarding exemptions of certain devices from the application of portions of the Act;
and can respond to requests from the agency to review and make recommendations on specific pediatric issues or problems concerning the safety and effectiveness of devices. Advisory Committees may also make appropriate recommendations on issues relating to the design of clinical studies regarding the safety and effectiveness of marketed and investigational devices. This proposal would assist FDA in better understanding the clinical use of medical devices being used off-label that have over time become the standard of care and establish an acceptable level of clinical safety and effectiveness evidence necessary to satisfy marketing approval.

5. **Proposal:** The acceptance of 510(k) devices intended for adult populations with the same use as a pediatric device as predicates for the 510(k) pediatric device.

   **Background:** Similar to the language proposed in the FDAAA 2007 pediatric device law which allows FDA to use adult data to support effectiveness in pediatric populations and to extrapolate data between pediatric populations, FDA has authority, where the course of the disease or effect of the device is the same in adults and in pediatrics, to use the adult 510(k) device as a predicate for the pediatric device. Doing so would be responsive to the extremely small numbers of pediatric patients – particularly of a given age range – with any one condition (which makes it difficult to run valid clinical trials in a timely fashion) and would help limit the number of children exposed to surgical controls. FDA could still require a clinical trial for a 510(k) device but the trial would be smaller and pediatric access to the device would be faster.

6. **Proposal:** The acceptance – as an appropriate control for investigational pediatric devices – of devices intended for use in adult populations when such devices provide the only device-related means for treating, diagnosing or preventing diseases or conditions in pediatric patients and have become the standard of care for such patients.

   **Background:** Similar to the language proposed in the new pediatric device law which allows FDA to use adult data to support effectiveness in pediatric populations and to extrapolate data between pediatric populations, FDA has authority to utilize as the control for studies under the Investigational Device Exemption process, devices that are not approved for pediatric use but that are already being used in pediatric populations. This would enable the adult data on already approved devices or these devices themselves to serve as the “control” for the pediatric trial, responding to the limited number of pediatric patients available for pediatric trials and reducing the number of children exposed to a surgical control.

**Proposal of a Compassionate Use Orphan/Pediatric Device Provision**

AdvaMed also recommends the creation of a New Compassionate Use Orphan/Pediatric Device provision to be applied in situations where even the HUD pathway makes little sense. As mentioned above, clinicians have repeatedly reported that they feel compelled to “jerry-rig” or modify existing devices to treat pediatric patients. Rather than having pediatric clinicians across the country individually jerry-rig devices during surgery, AdvaMed proposes a well-regulated mechanism to provide device access for super-small, orphan or pediatric populations that are not
likely to be served by the HUD program, the FDAAA 2007 or the FDASIA 2013 pediatric HDE programs. AdvaMed recommends that FDA be required to develop regulations that would allow manufacturers to distribute no more than 100 unapproved devices annually for patients when such patients are afflicted with diseases or conditions that affect too few patients annually to justify the expense necessary to achieve an approved device under the HUD program. As applicable, based on risk, appropriate controls would include: (1) compliance with quality system, labeling, complaint handling, medical device reporting (i.e., adverse event), unique device identifier (UDI) labeling and data submission requirements, and device tracking and postmarket surveillance regulations (if appropriate); (2) device promotion would be limited to medical professionals and no claims of safety or effectiveness could be made; (3) the manufacturer would be required to notify the Secretary upon the first shipment of such a device; (4) maintenance of records of each shipment of such a device; (5) limitation of distribution to prescription use only; (6) institutional review board approval would be required for each use of such a device; and (7) informed consent prominently informing the patient and the patient’s parent or legal guardian that the device is not approved by the Food and Drug Administration would be required.

Utilize Existing Government Funding and Programs More Efficiently
There is a significant need to utilize government funding in more efficient ways to address questions that are faced by all developers of orphan or pediatric-focused technologies. Although the deficit may make it challenging to significantly increase funding for rare and pediatric research, better coordination of existing or future research at the National Institute of Child Health and Human Development (NICHD), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute for Biomedical Imaging and Bioengineering (NIBIB) or other relevant Institutes that target specific orphan or pediatric device needs could:

1. Help spur the basic research needed for areas where breakthrough devices are desired; and
2. Help offset the tremendous expense associated with early orphan and pediatric device research and development, thus enhancing commercialization opportunities for interested stakeholders such as device manufacturers or pediatric consortia.

An enhanced technology transfer program between the relevant Institutes and the device industry could also help assure the development and manufacture of the needed breakthrough medical devices.

NIH Office of Orphan and Pediatric Diseases
AdvaMed also recommends that the NIH Office of Rare Diseases Research ensure that it is aware of ongoing rare or pediatric research issues being conducted within each institute so it can serve an important coordinating function with stakeholders to ensure that priority needs and research issues are being addressed. This office can be an automatic touch point for interested parties and stakeholders. For example, pediatric stakeholders attending FDA co-sponsored pediatric stakeholder meetings in 2004 learned – many for the first time – that the National Heart, Lung and Blood Institute (NHLBI) was developing a number of left ventricular assist device (LVAD) prototypes for commercialization, an important pediatric cardiovascular priority.
Such an office will make sure that ongoing NIH research of this nature receives the needed attention by relevant stakeholder groups. Further, this office can delineate and prioritize rare and pediatric device research and development needs to create a readily understood roadmap for stakeholders or for Congressional authorizers and appropriators and stakeholder groups to advocate for improved congressional funding for new rare and pediatric device development projects.

In closing, AdvaMed greatly appreciates this opportunity to provide our thoughts and recommendations to FDA on pediatric device development issues.

Sincerely,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs