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AdvaMed Written Testimony

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Medtronic, Inc.
On behalf of AdvaMed, thank you for the opportunity to provide written testimony to the Institute of Medicine’s Committee on Accelerating Rare Diseases Research and Orphan Product Development. My name is Susan Alpert, Senior Vice President, Global Regulatory Affairs, Medtronic, Inc. Medtronic is a global leader in medical technology – alleviating pain, restoring health and extending life for millions of people around the world. We serve physicians, clinicians and patients in more than 120 countries and employ more than 36,000 people worldwide.

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed’s members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent of the health care technology purchased annually around the world. AdvaMed members range from the smallest to the largest medical technology innovators and companies. Nearly 70 percent of our members have fewer than $30 million in sales annually.

**Introduction**

It is important to understand the device regulatory context with respect to rare diseases. The Orphan Drug Amendments of 1988 created the orphan products grant program. For this purpose, rare is defined as a prevalence of fewer than 200,000 patients in the United States. The related humanitarian use device program, authorized in the Safe Medical Devices Act of 1990, is a special product approval pathway to market for devices that treat or diagnose diseases and conditions that affect fewer than 4,000 patients per year in the United States, including pediatric populations and subpopulations. Although medical device companies are authorized to apply for grants under the orphan products program to support device research and development for rare diseases, device manufacturers can only use an HDE to treat rare diseases or conditions of less than 4,000 patients per year. An FDA-approved humanitarian use device is referred to as a Humanitarian Device Exemption (HDE).

In contrast to pre-market approval (PMA) requirements which necessitate that manufacturers demonstrate their products are both safe and effective, the review standard for HDEs requires manufacturers to demonstrate the safety of the device, the likelihood of effectiveness (termed
probable benefit), and to demonstrate that the device will not expose patients to significant or unreasonable risk. Device manufacturers are prohibited from making a profit on the marketing of HUDs although they are permitted to recoup the costs of research and development, manufacturing, packaging and distribution.

Importantly, to spur pediatric device development, the Food and Drug Administration Amendments Act of 2007 (FDAAA 2007) amended the humanitarian use device program to permit a device manufacturer to make a profit for HDE devices designed to meet a pediatric device need. FDAAA 2007 also created the Pediatric Device Consortia Grant Program under the FDA Office of Orphan Products Development (OOPD) to develop nonprofit consortia to facilitate pediatric medical device development.

Questions Posed by the Institute of Medicine
AdvaMed has specific responses to the questions below. Much of AdvaMed’s testimony focuses on pediatric device development issues because they are an important orphan “sub-population” and the issues involved in pediatric device development exemplify many of the challenges associated with orphan diseases and conditions.

Question One
What do you see as the major strengths and limitations of government policies to promote basic, translational, and clinical research to improve the health of people with rare diseases? What changes in government policies and procedures related to research funding or research infrastructure should the committee consider?

AdvaMed Response
AdvaMed has previously commented [e.g., comments to the National Institutes of Health (NIH)] that it is important to methodically collect data on unmet pediatric device needs including the number of patients with a particular disease or condition, age ranges, and current treatment and diagnostic options and health outcomes. At a recent FDA workshop on pediatric clinical trial design, pediatric cardiovascular physician panelists also pointed out that there are still many unanswered basic pediatric research questions. As the panelists 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, understanding the associated basic research questions related to unmet medical device needs should also be an important part of any data collection effort. A similar process should be utilized for orphan diseases although it is our understanding that the National Organization of Rare Diseases (NORD) has already collected or conducted a considerable amount of research with respect to rare diseases.

In addition to directed specialty evaluations, participants in previous NIH conferences devoted to pediatric device development issues have suggested that existing hospital discharge databases could assist in identifying specific device needs for pediatric patients. Efforts to collect pediatric data through the establishment of registries [e.g., the American College of Cardiology IMPACT Registry™ (IMproving Adult and Congenital Treatments)] may be another important source of such data.

AdvaMed believes the primary responsibility for data collection efforts of unmet orphan or pediatric medical device needs should reside with the NIH. Further, the responsibility for answering basic research questions associated with orphan or pediatric device needs should also be the responsibility of NIH. NIH is the only entity with the breadth and depth of knowledge, funding and resources to conduct such research. Once such data is collected and prioritized, it should be made public (e.g., through a public NIH website or clearinghouse or for registries, via the Agency for Healthcare Research and Quality’s proposal to create a registry of patient registries) to enable all interested stakeholders, including pediatric device consortia and device manufacturers to understand potential orphan and pediatric device development opportunities. It should also be noted that the pediatric research centers and consortia performing pediatric device research are ill-equipped to perform the types of rigorous clinical trials that support FDA clearance or approval. An educational effort by NIH and FDA needs to be undertaken.

It is also important to prioritize orphan and pediatric needs, perhaps based on criteria such as size of patient population, public health need, commercialization potential, or by targeting
needs that are cross-cutting in nature and provide benefits beyond one subpopulation. Prioritization of needs is important to help determine and assess basic pediatric research requirements that may be beyond the resources or financial scope of any one device company and that should be conducted by NIH. Such activities may for example include assessing existing biomaterials for their effects in pediatric populations; identifying new biomaterials that are safe and effective for use in pediatric populations; or assisting in the basic research and development of key, priority research questions or devices and their related clinical trials. The latter activities could significantly reduce the development costs linked with the small markets associated with many orphan and pediatric disease device needs – a key barrier to device development – thus enhancing chances that such devices would get to market.

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 orphan 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;
2. Help offset the tremendous expense associated with early orphan device research and development, thus enhancing commercialization opportunities for interested stakeholders such as device manufacturers or pediatric consortia; and
3. An enhanced technology transfer program between the relevant Institutes and the device industry could help assure the development and manufacture of the needed breakthrough medical devices.

Finally, AdvaMed also recommends that the NIH develop an office of orphan diseases and conditions including pediatric populations. Such an office would presumably be aware of ongoing orphan or pediatric research issues being conducted within each institute and could also serve an important coordinating function with stakeholders to ensure that priority needs
and research issues are being addressed. An office of this nature would 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 would make sure that ongoing NIH research of this nature received the needed attention by relevant stakeholder groups. Further, an NIH office that could delineate and prioritize orphan and pediatric device research and development needs would create a readily understood roadmap for Congressional authorizers and appropriators and other stakeholder advocates to improve congressional funding for new orphan device development projects.

**Question Two**

What do you see as the major strengths and limitations of policies governing the approval (or clearance) of medications and devices for the prevention, diagnosis, or treatment of rare diseases? What changes in government policies and procedures should the committee consider to accelerate the development and marketing of such products?

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 populations are well-served by this un-ending cycle. While it may not be feasible for all 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. AdvaMed has a number of recommendations below that are intended to help address this problem.
Small Market Sizes
A significant obstacle to orphan and pediatric device development is that the annual market associated with specific diseases and conditions may not be commercially viable (for either large or small device companies). Secondly, orphan diseases and conditions are difficult to study because they 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 to assure an adequately powered clinical trial and to meet FDA requirements.

General versus Specific Device Claims
FDA requirements for 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 Regulatory Models and Adaptive Clinical Trial Designs
To address small market issues, FDA must develop 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 (e.g., pediatric heart valves). 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\textsuperscript{1} 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 becoming 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 previously recommended a number of proposals (e.g., in comments to the NIH) that are reiterated below that are intended to make better use of existing FDA regulatory tools and enhance orphan or pediatric access to medical devices. Providing examples of these or other types of valid scientific evidence FDA is willing to consider in

\textsuperscript{1} FDA must take care not to reveal proprietary or trade secret or confidential commercial or financial information when sharing trial designs.
FDA guidance would be helpful to breaking down barriers to orphan and pediatric device development. Importantly, the proposals below retain the existing standard of reasonable assurance of safety and effectiveness.

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.

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 affect 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. 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:** 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 a reasonable assurance of safety and 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.

5. **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 a reasonable assurance of safety and 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.

**Development of Custom Device Guidance**

Section 520(b) of the FDCA and 21 CFR 812.3(b) provide for the manufacture of custom devices that are intended for use by an individual patient in response to a clinician’s order. AdvaMed recommends that FDA develop guidance for custom devices that expands the numbers for orphan and pediatric populations, a recommendation that was echoed by former Center for Devices and Radiological Health Director, David Feigal Jr, M.D., at a July 23, 2008 NIH pediatric device workshop. Custom guidance should clarify the number of devices manufacturers may customize for orphan or pediatric patients. In the ongoing pediatric dialogue, clinicians have repeatedly reported that they feel compelled to “jerry-rig” or modify existing devices to treat pediatric patients. Dr. Jon Abramson (representing the American Academy of Pediatricians) reiterated this point at the July 23 workshop.

While FDA has a custom device program intended to address this problem, manufacturers have been reluctant to participate because the rules are unclear and custom devices are limited to one or just a few patients. AdvaMed has heard from manufacturers that they, on occasion, are compelled to choose between complying with FDA requirements and pediatric patients’ needs with the knowledge and heavy burden that their decision to adhere to FDA requirements may result in a dire outcome for the child. Given that FDA’s formal definition of pediatric is from neonate to age 21, that so many different device sizes are required to treat this wide age range, and the small market sizes that may be associated with this wide size-
range, custom devices may be the only alternative for some medical devices. FDA guidance on custom devices that relaxed the current limitation on manufacturing just one or two custom devices and that specified the number of orphan or pediatric custom devices that could be manufactured and distributed would be helpful. Envisioned here is a special program for unique devices for very small orphan or pediatric populations or very early device modeling that could encourage development of these therapies.

**Improvements in the HUD/HDE Program**

As outlined in the Background section of our testimony above, 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. The language should state that prospective randomized controlled clinical trials generally will not be necessary to demonstrate probable benefit to
health, and that, consistent with FDA’s Least Burdensome policies, FDA and industry should consider non-clinical data, published literature, historical data and patient records, surrogate endpoints and statistical methods and evidence from experience with similar devices.

On a related point, during FDA-sponsored pediatric stakeholder meetings on pediatric device development in 2004, numerous participants pointed out that private insurers typically refuse to reimburse for pediatric HDEs reasoning that because HUDs can only be administered in facilities with properly constituted and functioning IRBs. Insurers assume the HDE must therefore be an investigational device that is not eligible for private insurer reimbursement. While payment issues are not within the normal purview of FDA, in this instance, inclusion of an additional Question and Answer in FDA’s HUD/HDE guidance that explicitly states that an HDE has FDA approval could be a useful addition to the guidance, assisting facilities and physicians in seeking reimbursement, improving patient access to needed HDEs, and importantly, helping patients avoid unnecessary out-of-pocket costs. For this reason, AdvaMed recommends that language be added to the guidance that explains that an HDE constitutes an explicit approval from FDA. Similarly, the Centers for Medicare and Medicaid Services (CMS) should have a process to cover and reimburse HDEs. Insurers frequently follow the lead of CMS with respect to coverage and reimbursement decisions.

**Orphan and Pediatric Ombudsman in the Center for Devices and Radiological Health**

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.
Question Six

Do you have other comments on the committee’s statement of task (attached) or additional concerns or suggestions related to strategies to accelerate research and development that are not covered by the preceding questions?

In addition to the proposals and comments outlined above, AdvaMed has a number of other recommendations to improve orphan and pediatric device development that would require statutory changes. Many of these programs would help offset the costs of orphan or pediatric device research and development and address small market size and commercialization risks. These are outlined below.

- 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 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 develop 510(k) or PMA devices for an orphan disease that affects 4,500 patients annually, yet because the population is only 500 patients over the 4,000 cap, it is ineligible for the HUD program.
Finally, AdvaMed 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 FDAAA 2007 pediatric HDE program. 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. Appropriate controls would be statutorily mandated including: (1) compliance with quality system, labeling, adverse event reporting, device tracking and postmarket surveillance regulations; (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 United States Food and Drug Administration would be required.

In closing, AdvaMed greatly appreciates the opportunity to testify to the Committee on Accelerating Rare Diseases Research and Orphan Product Development.