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# Pathways to Approval of Pediatric Cardiac Devices in the United States: Challenges and Solutions

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## KEY WORDS

cardiac devices, medical devices, device approval, pediatric cardiology

## ABBREVIATIONS

FDA—Food and Drug Administration  
IDE—investigational device exemption  
PMA—premarket approval  
HDE—humanitarian device exemption  
HUD—humanitarian use device  
OPC—objective performance criteria  
PG—performance goal  
OUS—outside the United States

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## abstract

Patients treated by pediatric interventional cardiologists and cardiac surgeons often have unmet medical device needs that pose a challenge to the current regulatory evaluation and approval process in the United States. In this report we review current US Food and Drug Administration regulatory processes, review some unique aspects of pediatric cardiology and cardiac surgery that pose challenges to these processes, and discuss possible alternate pathways to cardiac device evaluation and approval for children. Children deserve to benefit from new and refined cardiac devices and technology designed explicitly for their conditions. *Pediatrics* 2009;124:e155–e162

The fields of pediatric interventional cardiology and cardiac surgery have grown rapidly during the past 2 decades. These specialties provide infants and children with innovative transcatheter and surgical therapies that often are the result of adapting medical devices that were developed and approved for use in adult patients with acquired cardiovascular disorders. In some instances, device modifications are routinely conducted in real time in the cardiac catheterization or operating room suites. Rarely, cardiac devices have been developed, evaluated, and approved specifically for treatment of children with congenital heart disease. The way in which cardiovascular devices are designed, evaluated in clinical studies, and submitted for regulatory approval has remained a considerable challenge for the field.

Unmet cardiovascular device needs in the pediatric population occur when a needed device does not exist or when a device exists for a different (typically adult) indication but must be modified or used in an off-label fashion for children. An example of a needed device that does not exist is a transcatheter pulmonary artery flow restrictor, which could benefit many children who currently must undergo surgical pulmonary artery banding. Examples of existing devices that are used in children for unapproved indications include biliary stents (which are routinely used in children for pulmonary artery stenosis and coarctation stenting), angioplasty balloons (which are used to dilate valves and vessels in unapproved locations), and peripheral vascular occlusion coils (which are used for transcatheter closure of the ductus arteriosus). None of these existing devices have been engineered for or formally approved as safe and efficacious for the common pediatric indications to which they are applied.

In this article we address the topic of cardiac device approval from the perspective of pediatric cardiology and cardiac surgery. We include a review of the current regulatory processes that exist in the United States, the challenges faced with the care of the diverse and complex

patients with congenital heart disease, and possible novel strategies for enhancing the review and approval processes for cardiac devices intended for use in children. Children deserve to benefit from advances in medical device technology in the same way that adult patients have benefited for years. Without exception, however, any change in review processes for pediatric cardiac devices cannot be made at the cost of patient safety or welfare.

### **THE CURRENT FOOD AND DRUG ADMINISTRATION DEVICE-APPROVAL PROCESSES**

The US Food and Drug Administration (FDA) is responsible for oversight of all medical devices sold in the United States. Before a medical device can be shipped across state lines, either for use in a clinical study or for sale, certain FDA regulations must be met. Most medical device manufacturers are quite familiar with these regulations and the processes that will allow marketing of their devices. However, to many practicing physicians, these regulations and processes may seem mysterious and convoluted.

How can a physician legally use a medical device to treat or diagnose a patient? If the device has been “cleared” or “approved” for marketing, the physician can use the device freely. That is, the physician can use the device for the types of patients and in the manner described in the labeling (ie, as stated in the indications-for-use statement in the instructions for use). Alternatively, the device may be used in a different manner or for a different indication (ie, off-label) if the physician believes that this approach would be in the best interest of a particular patient. However, if the device has not been cleared or approved for marketing, the physician can only use the device under special circumstances, most commonly under a protocol approved by the FDA

known as an investigational device exemption (IDE). The IDE can be regarded as a “contract” between the physician and the FDA that specifies the terms under which the device can be used legally.

To determine if a device can be “cleared” for marketing, the FDA regulates medical devices by using a risk-based approach, assigning each device type to a regulatory class. Class I devices are simple devices that pose a low risk to patients, such as certain handheld surgical instruments (eg, scalpels, retractors). The great majority of these devices do not require prospective FDA review to begin marketing (ie, they are considered “exempt” from the need for a marketing application); the only requirement is that the manufacturer and manufacturing facility be registered with the FDA. Class II devices are considered to pose a moderate risk to patients, and many of these devices will require the submission of a marketing application to the FDA before marketing the product. Examples of class II devices include guide wires, infusion catheters, and patient monitors. These marketing applications are called 510(k)’s, after the section of the law that described them. The 510(k) application should demonstrate that a new device is “substantially equivalent” in terms of intended use and device performance to an already marketed device (sometimes referred to as “noninferiority”), which means that the new device must be at least as safe and effective as a similar device already on the market. In most instances, only bench testing and, in certain cases, animal studies are required; only 10% to 15% of 510(k)’s require clinical data. When a 510(k) application has successfully demonstrated substantial equivalence, the application is said to be “cleared.”

Class III devices pose the highest risk

to patients and include devices such as septal and vascular occluders, coronary stents, and ventricular assist devices. The majority of these devices will require a premarket approval (PMA) application before marketing. PMAs require bench, animal, and clinical data to demonstrate that there is a reasonable assurance of safety and effectiveness when the device is used as intended. The clinical data to support a PMA application are typically obtained under an IDE protocol. The protocol gives specific directions about how a device is to be used, and how data are to be obtained, and should be designed to collect information that is sufficiently interpretable such that reasonable safety and effectiveness can be inferred. After the clinical protocol has been completed, the data are analyzed and presented to the FDA to support a PMA application. Before a PMA can be approved, a manufacturer will also undergo a manufacturing inspection to demonstrate that the device can be manufactured with consistently high quality.

Class III devices can also reach the market through a humanitarian device exemption (HDE). The HDE program was established to ensure availability of devices for the diagnosis or treatment of conditions that affect fewer than 4000 patients in the United States per year. Because the number of patients potentially available to participate in a clinical trial is small, the HDE regulation provides an exemption from the requirement to show effectiveness. An HDE can be approved if the device has been shown to provide a reasonable assurance of safety and probable benefit. A manufacturer who wishes to pursue an HDE must first show that the number of patients with the disease or condition who would be treated with the device is fewer than 4000 in the United States per year. Devices that qualify on this basis will re-

ceive a humanitarian use device (HUD) designation. Once the HUD designation has been granted, the HDE can be submitted to gain approval for marketing. Although an HDE allows for less clinical data collection than a PMA, there are disadvantages as well. A manufacturer cannot ship an HDE-approved device to a hospital or clinic until its institutional review board has given approval for its use. Until recently, the manufacturer was also prohibited from making a profit from the sale of a device that possessed HDE status; only the costs of research and development could be recovered in the sale price. Recent legislation (see below) has lifted this restriction so that pediatric devices approved for marketing under an HDE can now be sold for profit.

As discussed above, a device can be marketed if it is the subject of a cleared 510(k), an approved PMA or HDE, or is exempt from the requirement for a marketing application. However, it is common in pediatrics for devices to be developed by individual users or to be available in other countries before it is marketed in this country. The FDA makes provisions allowing limited use of unapproved devices in some of these settings. If the device is being studied under an IDE, a physician may request the use of the device through the manufacturer or sponsor of the IDE for a patient who does not meet the clinical study criteria. The FDA will ask that certain provisions be followed for the patient's protection but, in the majority of cases, will grant these requests for "compassionate use." The patient-protection measures include appropriate informed consent from the patient or patient's guardian, approval of the institutional review board, and the concurrence of an uninvolved physician. If a device is not being studied under an IDE, the prescribing physician can apply directly to the FDA to obtain approval to use the de-

vice. If the application is approved, the FDA will require the same patient-protection measures described above to be in place.

Some devices are subject to further study after marketing approval, a process known as "postapproval" or "postmarket" studies. Postmarket studies can provide data to further refine initial understanding of device performance. Such studies may provide additional insights into appropriate patient selection, training of physicians, and practical issues such as device performance in patients with multiple comorbidities. In addition, the Safe Medical Devices Act requires reporting of adverse events and significant device malfunctions to the FDA for any device, even those that are not subject to formal postapproval studies. Additional information for reporting requirements may be found at [www.fda.gov/cdrh/medsun/about.html](http://www.fda.gov/cdrh/medsun/about.html). To facilitate identification of gaps in device availability for pediatric indications, the FDA has established a formal postmarket surveillance partnership with clinical sites, known as KidNet ([www.fda.gov/cdrh/medsun/about.html](http://www.fda.gov/cdrh/medsun/about.html)). This site provides a venue for institutions involved in pediatric care to record circumstances in which acceptable pediatric devices were unavailable and in which adult devices needed to be substituted or modified.

### RECENT LEGISLATION

In 2007, Congress passed the Pediatric Medical Device Improvement and Safety Act (Pub L No. 110-85) as part of legislation to amend the Food Drug and Cosmetic Act. In passing the act, Congress identified the need for improved access to pediatric medical and surgical devices as well as needed improvements in postmarket safety monitoring of existing devices used in children. As mentioned above, the act removed the profit prohibition on devices ap-

proved through the HDE pathway for "the treatment or diagnosis of a disease or condition that occurs in pediatric patients" (Pub L No. 110-85, §303[a]), which allows device producers to make a profit on devices used in fewer than 4000 children. The act also created new mechanisms for pediatric device development through the creation of nonprofit consortia to stimulate innovation.

In the postmarket setting, the act granted new authority to the FDA to extend the current limit of 36 months for postmarket studies of class II or III devices if needed for children and to require postmarket studies as a condition of approval. Finally, Congress instructed the FDA, the National Institutes of Health, and the Agency for Healthcare Research and Quality to develop a plan for expanding pediatric medical device research and development. On July 23, 2008, the 3 federal agencies conducted the Pediatric Medical Devices Stakeholders' Workshop to gain input on the plan, which is expected to be presented to Congress soon.

### CHALLENGES FROM PEDIATRIC CARDIOLOGY AND CARDIAC SURGERY

The fields of pediatric cardiology and cardiac surgery share characteristics, distinct from their counterpart specialties in adult medicine, that pose unique challenges to the development and approval of cardiac devices for children. First, congenital cardiac defects are relatively uncommon and include a diverse array of anatomic subtypes. For example, moderate-to-severe congenital cardiac defects that require therapy occur with an estimated total prevalence of only 6 per 1000 live births.<sup>1</sup> The relatively small number of patients affected with any given congenital cardiac defect makes it difficult to design a traditional ran-

domized clinical trial that is adequately powered. From an industry perspective, virtually all congenital cardiac defects can be considered “orphan” disorders that occur in small patient populations with a relatively limited market potential for any given device.

A second challenge to the development of cardiac devices specifically for children exists because pediatric cardiovascular anatomy presents a wide range of anatomic sizes which, in turn, require a demanding range of device sizes. Unlike adult valves, ventricles, and great vessels which have a relatively narrow range of normal dimensions, pediatric cardiovascular anatomy grows significantly from birth to young adulthood. For example, cardiac valve diameters increase threefold from birth to adulthood. The normal aortic and pulmonary valve annulus diameters increase from 7 to 22 mm and from 8 to 26 mm, respectively, from birth to adolescence.<sup>2</sup> To be suitable for children of all ages, semilunar valve prostheses with diameters that range from 7 mm for newborns to the more familiar adult dimensions should be available; however, in current practice, the smallest approved semilunar valve prosthesis measures 16 mm in diameter. The changes in cardiac chamber volume that occur with growth are even more pronounced, as illustrated by the increase in normal left ventricular diastolic volume from ~10 mL in the newborn to 150 mL in the adult.<sup>3</sup> Clearly, the engineering challenges are substantial if a ventricular assist device is to benefit patients of all ages and sizes. Table 1 demonstrates the wide range of “normal” dimensions (ie, z value = 0) for representative cardiovascular structures for newborns, children, and young adults.

A third challenge to the development of pediatric cardiac devices relates to

the substantial somatic growth that occurs during childhood. Any cardiac device implanted into the cardiovascular system of a growing child must be able to accommodate the child’s future growth while remaining safe, effective, and intact. Atrial or ventricular septal occlusion devices implanted in a child are known to be compatible with future cardiac growth because the cardiac septa grow “around” the endothelialized devices. However, a semilunar or atrioventricular valve prosthesis implanted into a small child will often become too small and, therefore, hemodynamically obstructive as the child grows. Ventricular-arterial conduits or great artery grafts of appropriate dimension and capacity for a child but lacking growth potential will become diminutive, and need replacement, as the child grows. Similarly, ventricular assist devices of suitable size for children may be outgrown, making the concept of “destination therapy” for long-term circulatory support impracticable when using a single implanted device. All of these considerations related to somatic growth impart substantial design and engineering challenges for device developers who aim to provide devices that can be maintained long-term in growing children.

Finally, remarkable durability is required of pediatric cardiac devices because in pediatrics a patient’s life expectancy is typically measured in decades. In reality, this is in marked contrast to adult cardiovascular medicine, in which patient longevity is often

described in months or several years. A muscular ventricular septal defect device that is implanted in a 6-month-old infant must remain intact on the ventricular septum for 70 or 80 years. The prospect, and indeed the expectation, that pediatric cardiac patients may survive for many decades demands unique long-term durability from the cardiac devices implanted in them.

### OFF-LABEL USE OF DEVICES

Because of the challenges to device design and approval posed by the relatively uncommon cardiovascular defects of children, the off-label use of devices approved for other patient populations (typically adults) and indications has become a routine, accepted practice in pediatric cardiology (Table 2). For example, the large majority of stents implanted in pediatric interventional procedures are biliary stents used off-label to treat vascular stenoses within the pulmonary arterial tree, aorta, and large veins. Approved medical devices can be used legally off-label by pediatric practitioners if this use is judged by the physician to be medically appropriate and in the patient’s best interest. However, the off-label practice itself has important disadvantages. First, a device used off-label will not have been subject to the FDA approval process to provide reasonable assurance of safety and effectiveness for this patient population or for the specific pediatric indication. This absence of formal evaluation and approval can cause

**TABLE 1** Mean Dimensions (z Value = 0) of Normal Cardiovascular Structures in Newborns, Children, and Young Adults

Cardiovascular Structure	Newborn	Child (6 y old)	Adult
Aortic valve diameter, mm	7	14	22
Pulmonary valve diameter, mm	8	16	26
Mitral valve diameter, mm	10	19	28
Aortic root diameter, mm	10	15	30
Right pulmonary artery diameter, mm	6	12	18
Left ventricular diastolic volume, mL	10	50	150

Data were derived from refs 2 and 3.

**TABLE 2** Approved Medical Devices That Are Commonly Used for Off-Label Pediatric Indications

Device	Labeled Indications	Off-Label Pediatric Applications
Stents	Biliary tree stenosis Coronary artery disease	Pulmonary artery stenosis Coarctation of the aorta Systemic vein stenosis
Embolization coils	Arteriovenous fistula	Patent ductus arteriosus
Dilation balloons	Pulmonary valve stenosis Peripheral vascular disease	Aortic valve stenosis Pulmonary artery stenosis Coarctation of the aorta
Cutting balloons	Arteriovenous dialysis fistula stenosis	Pulmonary artery stenosis
Radiofrequency perforation wire	Atrial transseptal puncture	Pulmonary valve atresia

difficulties for pediatric practitioners who may be required to make decisions about device use on the basis of insufficient information, or who may be subject to medical malpractice claims if their judgment is questioned. Second, a medical device that is used for an off-label indication may be deprived of important industry research and development to improve device performance for that pediatric condition. Because early generations of a device used off-label for pediatric indications may not have had sufficient data to support such use, device enhancements for pediatric indications and approval of these later-generation devices may be difficult or impossible. Finally, the off-label use of devices tested in adults to treat pediatric conditions creates some special challenges for the pediatric device-approval process. In some instances, considerable information about how a device may perform in children can be extrapolated from safety and efficacy information derived from adults. In other instances, however, this information may not be useful because of differences in pediatric anatomy, physiology, and pathophysiology. Determinations about when use of adult information is appropriate are not straightforward and can complicate the design of studies in pediatric patients.

### POSSIBLE SOLUTIONS: NOVEL APPROVAL PATHWAYS

Many pediatric cardiologists and cardiac surgeons recognize the problems in achieving safety and efficacy standards for devices used in the care of patients with congenital heart disease. Safety standards require that the probable benefits from use of the device outweigh the probable risks. Reasonable assurance of effectiveness is established when it can be determined, on the basis of valid scientific evidence, that in a significant portion of the target population the use of the device for its intended purpose and conditions of use will provide clinically significant results.

The FDA is committed to the least burdensome principle throughout the regulatory process of medical devices and will assist in the design of trials that will produce clear and interpretable data. Randomized, controlled clinical trials (RCCTs) are considered the gold standard for such clinical trials but are costly, technically challenging, long, and arduous. In small pediatric populations the RCCT may not be statistically possible, and patients or families may refuse to accept randomization. Table 3 lists several alternatives to the use of the RCCT which may be applicable to the evaluation of pediatric cardiac devices, and a brief discussion of each alternative is presented below.

### Objective Performance Criteria and Performance Goals

One alternative is the use of objective performance criteria (OPC) or performance goals (PGs) in the evaluation of medical devices during the regulatory approval process. The essence of an OPC or PG is that the metrics to be used to evaluate whether a device meets criteria for approval are specified in advance and are not obtained as a part of an IDE study. OPCs or PGs are often expressed as a rate.<sup>4,5</sup> Thus, the OPC or PG is used as a replacement for a traditional randomized control group and serves as a benchmark, or minimally acceptable value using a pass/fail approach, to determine if a particular device application is ultimately approved for marketing.

The estimate for an OPC or PG is necessarily derived from historical data. The development of an OPC is a more formal process than that for a PG, requiring pooling of data across previously published studies by using a formal meta-analysis or similar approach. Ideally, historical trials should provide patient-level data including clinical outcomes and patient characteristics. Pocock<sup>6</sup> described 5 requirements for valid historical controlled studies:

1. Control group receives the precisely defined treatment in a recent study.
2. Criteria for eligibility, workup, and evaluations must be the same.
3. Prognostic factors are completely known and the same in both groups.

**TABLE 3** Possible Pathways to Device Approval for Pediatric Cardiology (Alternatives to Randomized Clinical Trials)

Use of OPC or PGs
Extrapolation from existing data in studies of adult patients
Use of registry data
Enhanced postmarket surveillance
Use of data generated OUS

4. No unexplained indications leading one to expect different results.
5. Differences in prognostic factors are insufficient to explain observed differences in outcome.

Rigorous and scientifically valid methodologies have been developed and used in the derivation of any OPC for use in the medical device-approval process. An OPC must be derived from recognized and generally complete historical data sets and be the product of appropriate statistical modeling and analytical techniques. Nonrandomized comparison data using propensity scoring may also be a mechanism for achieving well-matched patient groups.<sup>7</sup> There should also be a designated provision for periodically evaluating and updating the OPC on the basis of more recent experience and data.

PGs are developed when less historical information is available. A scientific or clinical rationale must be outlined for the selection of studies on which the PG is based, including adjustments for differences in populations or other aspects of the studies, in comparison to the proposed methodology that will be used in the IDE study. Given the less robust data and analysis that contribute to the development of a PG, an OPC is the preferred control for a nonrandomized trial. Nevertheless, PGs may provide an important alternative, especially for therapies for which off-label device treatment is routine (eg, numerous pediatric cardiac interventions), which makes randomized studies using surgery or medical therapy as a control difficult to conduct.

OPCs have been used in the regulatory approval process in the past, and multiple ongoing studies use PGs. OPCs have been used frequently in the study of prosthetic heart valves. A more recently developed set of OPCs was used during the approval process for a transcatheter occluder device for

patent ductus arteriosus. These OPCs were developed, in part, by using comparisons to published surgical data<sup>8</sup> and to the PDA Coil Registry.<sup>9</sup> Currently, 2 occluder devices are approved for atrial septal defect closure. Additional approvals for atrial septal occlusion may be facilitated by development of appropriate PGs. Similarly, stents to treat pulmonary artery stenosis or coarctation of the aorta could have appropriate PGs developed on the basis of published results, which could be used in conjunction with data from robust long-term registries to follow patients who have had a pulmonary artery or aortic stent implanted.

### Extrapolation From Existing Data in Studies of Adult Patients

Generally, the use of data obtained from adult patients to inform decisions regarding device safety and efficacy in children is of limited applicability because of differences in patient growth and longevity and functional differences between devices for coronary disease and congenital heart disease. The option of developing a medical device for pediatric use that has features similar to an adult device represents a potential pathway for device design and approval, but safety evaluation would require a separate trial to determine device safety in children. Some special-function catheters (imaging or therapeutic) for adult use may be applicable for infants and children when manufactured in sizes appropriate for pediatric use. Prosthetic cardiac valves may represent another class of devices for which performance data from adults might be extrapolated to pediatric applications. Ideally, sponsors should include their approach to assessment of performance in pediatric patients at the time of IDE application for adult devices that ultimately may be used in children as well.

### Use of Registry Data

This route is a similar approach to the use of PGs described above, because it relies on application of historical data as a surrogate for data obtained from a more traditional contemporaneous control group. However, this mechanism depends on the existence of rigorous registry data that include a thorough capture of adverse events. An example of such a registry is the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). This registry was developed with the support of the Department of Health and Human Services, the National Heart, Lung, and Blood Institute, and the FDA. Some notable features of this registry include the use of sequential patient enrollment, a well-defined data set, independent clinical evaluations, well-designed clinical report forms, and a commitment to minimize the amount of missing data.

Prospective databases have the potential to provide important clinical data supporting expansion of “labeled” indications for cardiovascular devices. Databases currently enrolling patients with congenital heart disease who undergo cardiac catheterization include the Mid-Atlantic Group of Interventional Cardiology (MAGIC), Congenital Cardiac Catheterization Project on Outcomes (C3PO), and Congenital Cardiovascular Interventional Study Consortium (CCISC). Generally, these databases are too limited in scope or were inaugurated too recently to provide primary data sets to support FDA review and approval of new applications for existing cardiovascular devices. However, over time, these registries do have potential to contribute valuable clinical data sets for devices that are used or implanted in children outside approved indications; the inclusion of longitudinal follow-up data are a key component of any registry data set intended to support the expansion

of “labeled” indications to pediatric applications. An example of such a registry is the current CCISC registry of patients having surgery, angioplasty, or stent therapy for coarctation of the aorta. This prospectively collected data set has defined patient inclusion and exclusion criteria as well as recommended follow-up intervals, evaluations, and studies. Neither specific angioplasty balloon catheters nor specific stents are mandated, but acute and longitudinal data are captured on all patients, effectively collecting data about all of the currently used (on-label and off-label) surgical and catheter-based treatment strategies for coarctation. Thus, the CCISC is building individual sets of data about several devices and has potential to support FDA review and approval of new pediatric cardiovascular indications for these devices.

An important additional development is the recent creation of a congenital heart disease registry, the Improving Pediatric and Adult Congenital Treatment (IMPACT) registry, funded by the American College of Cardiology Foundation through the National Cardiovascular Data Registry (NCDR) program. The IMPACT registry will aim to assess the prevalence, demographics, management, and outcomes of patients undergoing diagnostic catheterization and catheter-based interventions for congenital heart disease. Importantly, it will include a robust capture of catheterization-related adverse events. The registry plan involves a pilot phase limited to 10 centers collecting acute catheterization data only, with rapid expansion to allow participation of all dedicated pediatric cardiac catheterization facilities. In its final implementation phase (year 4), the registry plan involves recruitment of ~300 centers known to provide catheterization services for congenital heart disease and to include longitudinal data collection

to assess the longer-term efficacy and safety of selected procedures and devices. A broad data set will be derived that includes essentially all interventional procedures that are currently being performed. Building on the successful use of adult NCDR registries to obtain information for regulatory purposes, it is an explicit goal of the IMPACT registry to provide a vehicle to facilitate device approval for pediatric indications.

### Enhanced Postmarket Surveillance

Historically, FDA approval of PMA applications for cardiovascular devices has included substantial postmarket surveillance plans. In some cases, however, sponsors have not adequately complied, and the FDA has lacked either the mechanisms or willingness to enforce the plans. This has placed indirect pressure on the FDA to “raise the premarket bar” by requiring sponsors to provide premarket studies with more data and more follow-up of patients. Conceivably, the pressures in this situation could be reversed if sponsors were to comply more fully with postmarket surveillance plans. If postmarket surveillance were enhanced, the FDA might accept safety and efficacy data from smaller pivotal studies with shorter follow-up periods to qualify devices for conditional approval and to permit sales of the devices for pediatric conditions. These devices could be eligible for final or unconditional approval after the agreed postmarket studies are completed and demonstrate acceptable safety and efficacy outcomes.

The approval in 2006 of the Gore Helex septal occluder (W.L. Gore & Associates, Inc, Flagstaff, AZ) is an example of this approach by the FDA. The pivotal study of the Helex reported on a device arm that enrolled 143 patients with technical success in 119 patients. One-year follow-up outcomes were re-

ported for only 105 patients. This study was considerably smaller than the pivotal study on the Amplatzer septal occluder (AGA Medical Corporation, Plymouth, MN), which reported on a device arm with more than 300 enrolled patients. The FDA, however, provided Gore with approval conditioned on further characterization of the long-term safety and effectiveness of the Helex occluder. An additional 250 patients must be followed for 5 years, and at least 80% of these patients must be available for 2-year follow-up. Annual reports and a final report to the FDA will be required.

### Use of Data Generated Outside of the United States

Clinical data generated outside the United States (OUS) may be submitted for FDA review in support of PMA applications. These data may also comprise part or all of the pivotal study data. Not surprisingly, the FDA requires that the quality and verifiability of such clinical data meet the same standards as required from data generated in the United States. In the past, OUS data have not typically been of sufficient quality to allow immediate device approval in the United States. Substantial preliminary mechanical and animal testing is required before allowing initial human clinical studies. However, high-quality OUS data from well-controlled and monitored studies could provide support in the setting of limited preclinical or equivocal animal data, or could take the place of a US feasibility study. Global studies in which data are gathered from US and OUS clinical sites according to a single protocol could also be considered to provide a reasonable alternative to pivotal US-only studies. For these studies, it will be important to be aware of and plan to address potential population or clinical practice differences that might affect the study outcome. When

considering such efforts, the FDA has strongly suggested early and frequent interaction with the agency to ensure appropriate development of such high-quality OUS and global studies.

## CONCLUSIONS

The design, development, evaluation, and approval of cardiac devices for children pose significant challenges to industry processes and to regulatory pathways originally intended for de-

vices developed to benefit adult patients and their conditions. These challenges relate to the relatively small population of children with cardiovascular disease, and to the unique aspects of the pediatric cardiovascular system and the disorders that affect it. We have reviewed the current FDA regulatory processes, reviewed some unique aspects of pediatric cardiology and cardiac surgery that pose challenges to these processes, and dis-

cussed possible alternate pathways to device evaluation and approval. Children deserve to benefit from new and refined cardiac devices and technology designed explicitly for their conditions. As the medical community, industry, and the FDA work together to enhance the pathways to approval of cardiac devices for children, all parties must also remain vigilant to safeguard the safety and autonomy of these most vulnerable patients.

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