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The FDA Review Process for Cardiac Medical Devices in Children: A Review for the Clinician

Christopher S. Almond, MD, MPH*

*Department of Cardiology, Children's Hospital Boston; Department of Pediatrics, Harvard Medical School, Boston, MA

Abstract

Pediatric medical devices play a vital role in the treatment of children with cardiovascular disease. Most cardiac medical devices used in children today are used off-label where the risk-benefit of devices has not been well characterized. Pediatric medical devices face a variety of challenges to FDA approval related in large part to the small target population, heterogeneity of the patient population and ethical considerations of device testing in children. While relatively few cardiac devices have received FDA approval in children, the number of devices navigating the approval process successfully is growing. Most pediatric device approvals are being granted through the humanitarian device exemption (HDE) pathway, which is designed for rare diseases making it suitable for devices treating congenital heart disease. This review summarizes the FDA review process for pediatric medical devices as it continues to evolve in response to the unique challenges of understanding device performance in the pediatric population.

INTRODUCTION

High-risk medical devices play an essential role in the treatment of children with cardiovascular disease[1–12]. Contemporary examples include balloon catheters, endovascular stents, atrial septal defect occluders, pacemakers, defibrillators, prosthetic heart valves, and ventricular assist devices. Along side refinements in surgical and medical practice over the past twenty years, medical devices have contributed significantly to reducing the overall burden of morbidity and mortality observed in children with cardiac disease[8].

The United States Food and Drug Administration

The United States (US) Food and Drug Administration (FDA) is tasked by Congress with oversight of all medical devices sold in the US[13]. For a medical device to be marketed in the US, it must meet certain regulatory requirements which essentially establish that the device is safe and effective for use in humans to treat a specific condition (i.e. indication)[14]. In adults, the safety and effectiveness of a medical device is typically determined by a large randomized clinical trial such as the REMATCH trial for the Thoratec XVE® Left Ventricular Assist Device[15], the MADIT-CRT trial for resynchronization-ICD devices[16] and the TAXUS and SIRIUS trials for Paclitaxel and Sirolimus drug-eluting coronary stent[17] s[18], . By contrast in children where cardiac disease is rare[8], large randomized trials are

Corresponding Author: Dr. Christopher Almond, Department of Cardiology, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115. Phone: 617-355-6329, Fax 617-734-9930. christopher.almond@childrens.harvard.edu.

generally considered infeasible[19–21]. Furthermore, because of the tiny market for pediatric devices where research and development is expensive, there is little financial incentive for companies to invest in the development of pediatric medical devices[21]. Thus pediatric clinicians are frequently left to adapt adult-sized devices to their pediatric patients where size or growth considerations may make it awkward or impossible and where the risk-benefit profile is often uncertain[22].

The problem of off-label use in pediatrics: Lack of risk-benefit data

The vast majority of medical devices used in children today are used off-label, or outside the population/purpose where the device's safety and efficacy profile has been evaluated in prospective studies and FDA-approved[6,21,22]. Perhaps the best example of this in pediatrics are biliary stents, which were studied and FDA-approved for adults with biliary tract obstruction due to malignancy[23], and are commonly implanted off-label in the pulmonary arteries and ductus arteriosus of children[24] despite little original data on their safety in the heart or circulatory system. While off-label use is entirely legal and considered a vital part of clinical practices in pediatrics, off-label use frequently suggests that important safety data may be lacking. Thus instead of device-related safety concerns being characterized prospectively during the course of a monitored clinical trial, safety problems may only come to light if adverse events are voluntarily reported by industry or centers sufficient to raise a red flag. This was the case of the PRECISE® RX Transhepatic Biliary Stent whose stent system was recalled by the FDA for use in the circulatory system after it was found to introduce air to the patient, which resulted in stroke, coma or seizures in at least nine patients[25]. Even so, because no reliable data exists on the total number of cases (denominator) where the device has been used in the vascular system—or the total cases of air emboli given reporting is voluntary—it is virtually impossible to know what the true level of risk is or whether the risk is meaningfully different from similar balloon devices or delivery systems.

Understanding the FDA approval process for pediatric medical devices

Because of the desire to reduce off-label device use in children, as well as the need to secure FDA approval for promising new devices for children, there has been growing interest among pediatric clinicians in understanding the FDA approval process for pediatric medical devices. While the FDA process often seems well understood by industry and adult cardiologists who have extensive experience with medical devices, it is often viewed as a mysterious black box to pediatric cardiologists and surgeons who have had significantly less exposure to the device approval process. Therefore, the specific aim of this review is to provide an overview of the FDA review process for cardiac medical devices in children, and to highlight some of the challenges and opportunities that are likely to lie ahead.

THE FDA REVIEW PROCESS FOR PEDIATRIC CARDIAC MEDICAL DEVICES

In general, the FDA evaluates the safety and efficacy of pediatric medical devices using the same regulatory pathways available to adult devices. In short, this process generally involves two steps (A) Pre-clinical testing (i.e. bench or animal testing) to clear the device for testing in humans, and (B) Clinical testing (i.e. human studies) to evaluate the risk-benefit profile of the device in humans for treating a specific condition. Data from both steps are combined to support FDA approval of a medical device. This review focuses primarily on the FDA review process for high-risk or class III medical devices that receive the greatest scrutiny (table 1).

Inside the FDA: The Office of Device Evaluation: Division of Cardiovascular Devices

From an organizational standpoint, cardiac medical device applications are submitted to the FDA through the Office of Device Evaluation's (ODE) Division of Cardiovascular Devices (DCD) at the Center for Devices and Radiological Health (CDRH). Within the DCD, applications are processed through one of five cardiovascular branches, which include (1) Circulatory support and Prosthetic Devices, (2) Pacing, Defibrillator and Leads, (3) Cardiac Electrophysiology and Monitoring Devices, (4) Interventional Cardiology Devices, and (5) Peripheral Vascular Devices. Each application is assigned a lead reviewer within one of these 5 branches who is tasked with coordinating review activities including reviews from biomedical engineers, physicians/surgeons, epidemiologists, biostatisticians, among others. In the event the applications is referred to an FDA Advisory Panel for an approval recommendation, the lead reviewer often takes primary responsibility for coordinating the FDA's Panel presentation.

Pre-clinical studies

FDA typically requires a series of bench and animal tests to characterize the reliability, durability and biocompatibility of cardiac devices prior to testing in humans. Because cardiac devices vary considerably in purpose and functionality (e.g. balloon catheter used once versus a pacemakers used for years or even decades), testing requirements vary considerably for each type of cardiac device. For this reason, the FDA has developed device-specific guidances describing the types of pre-clinical testing necessary for a range of devices. Combination medical devices, such as transcatheter valves that retain properties of both vascular stents and artificial valves, have unique testing requirements that combine testing requirements of both device types. Biomedical engineers, rather than physicians, typically coordinate most of the pre-clinical testing of medical devices, although clinical input is necessary to inform testing requirements.

Clinical studies

Once a medical device has completed pre-clinical testing it is eligible for human testing. Clinical testing is required for approval of most but not all high-risk medical devices approvals. For example, the Debakey Ventricular Assist Device *Child* was approved without a clinical trial in children on the grounds that the risk-benefit profile of the pediatric pump could be extrapolated from the adult version of the pump. In general, however, because cardiac medical devices typically carry higher risks to patients, cardiac medical devices are less frequently exempted from the clinical trial requirement.

PMA (Pre-Market Application) Pathway

The Pre-Market Application (PMA) pathway is the most commonly used regulatory pathway for approval of new class III (high-risk) medical devices in the US. The PMA pathway is appropriate for medical devices intended to treat relatively common medical conditions such as coronary artery disease and congestive heart failure. PMA approval typically requires a large clinical study or randomized trial designed to demonstrate a reasonable assurance of safety and effectiveness, the legal threshold for PMA approval. Following FDA approval, the device may be sold for profit in the US. Examples of devices that have received PMA approval include the Heartmate II VAD for bridge-to-transplant, Sirolimus-eluting stents for treatment of coronary disease, and the St. Jude's Medical Trifecta Aortic Valve. To date, no cardiac devices intended specifically for children have received PMA approval although cutting balloons for the treatment of resistant pulmonary artery stenosis is currently under review for PMA approval[26].

HDE (Humanitarian Device Exemption) Pathway

The Humanitarian Device Exemption (HDE) pathway is used far less frequently in the US, however it is intended for devices that treat rare conditions (<4,000 cases per year) making it appropriate for most devices treating congenital heart disease. While not legally required, HDE approval usually necessitates a clinical study such as a single-arm clinical study with historical controls or objective performance criteria in order to demonstrate the devices is associated with “probable benefit” (as opposed to “effectiveness” as required for PMA approval) in addition to a reasonable assurance of safety. In contrast to PMA-approved devices, HDE-approved devices may not be sold for profit in the US *except* for pediatric devices as of legislation passed in 2007 (Pediatric Medical Device Safety and Improvement Act). Examples of pediatric cardiac devices that have received HDE approval include the Medtronic Melody® Transcatheter Pulmonary Valve in 2010, the Berlin Heart EXCOR® Pediatric VAD for bridge to transplant in 2011, and the CardioSEAL® Septal Occluder for Fontan fenestration closure and treatment of complex VSDs (1999).

510(k) Pathway

The 510(k) pathway is the single most commonly used pathway for FDA clearance of medical devices in the US accounting for as many as 4,000 device approvals per year (or >10 per day). It is restricted primarily to class II or moderate risk medical devices such as cardiac monitors or pulse oximeters. To receive FDA clearance, the device maker must demonstrate that the device is ‘substantially equivalent” to an existing FDA-approved (“predicate”) device. In most cases (>85%), this can be accomplished without additional human testing and on the basis of pre-clinical testing alone. Examples of pediatric cardiac devices that have been FDA-approved using the 510(k) pathway include Infant Cardiac Array MRI coils, Medtronic Unipolar Pediatric Temporary Pacing Catheter, and the Quadrox Pediatric Diffusion Membrane Oxygenator.

Federal Advisory Panels

In certain cases, the FDA may elect to refer a medical device application to a Federal Advisory Panel for an approval recommendation. These hearings, which are open to the public and usually scheduled over one day, allow an independent panel of approximately two dozen invited experts to review the safety and efficacy data for a device and make a non-binding recommendation to the FDA for approval or non-approval. In the past two years, both the Melody® Transcatheter Pulmonary Valve and the Berlin Heart EXCOR® Pediatric VAD received FDA approval after review by a Federal Advisory Panel. Reasons a device may be referred to a Federal Advisory Panel include situations where a device’s risk-benefit is unclear, where there is substantial public interest in a particular device, or a device is novel in its field and is likely to change clinical practice significantly.

Cardiac Medical Device Approvals for Children

Altogether, the total number of high-risk cardiovascular medical devices approved for use in children is small. Starting in 2007 the FDA began tracking the annual number of FDA-device approvals in children (PMA and HDE) and to categorize them according to (A) whether a pediatric population suffers from the same disease a device is intended to treat in adults, and (B) whether the device was studied/labeled specifically for pediatric populations. In the FDA’s first report from 2008, there were a total of 29 high-risk medical devices that won FDA approval (27 PMAs, 2 HDEs) of which roughly half (N=14) were classified as cardiovascular devices. Of these, 9/14 (71%) devices were approved for conditions where a pediatric population suffers from the same disease (e.g. Heartmate II for bridge-to-heart transplant in patients with advanced heart failure); however none was labeled specifically

for children. Table 2 summarizes the primary cardiovascular devices approved/ labeled specifically for children under the HDE regulation since 1999.

Barriers to FDA approval of pediatric medical devices

Pediatric medical devices have faced a variety of barriers to FDA approval that are specific to the pediatric population. These include small sample size, significant population heterogeneity (e.g. patient age and size requiring multiple device sizes to be evaluated in some cases, as well as congenital heart disease itself because of the wide diversity of anatomic subtypes present), limited financial incentive for device makers (including a specific prohibition against profit-making for HDE approved devices), ethical challenges related to high-risk medical device testing in a vulnerable population such as children (e.g. randomizing), difficulty in establishing equipoise in the minds of families and clinicians, and logistical challenges such as the recruitment and follow-up of patients with a rare disease across the US and Canada or internationally. Opportunities to expand FDA approvals for existing adult devices used off-label in children has historically been hampered by the lack of organized national device databases (i.e. post-approval registries), inconsistent reporting of adverse events, and an inability to track individual devices and patient outcomes/adverse events over time and across regions.

Initiatives to expand pediatric device development

Over the past several years, the FDA has worked to identify and address barriers associated with bringing new pediatric devices to market through collaborative partnerships with a variety of stakeholders including the academic pediatric community, the American Academy of Pediatrics, the National Organization for Rare Diseases (NORD), American Heart Association, the American College of Cardiology, industry and Congress. Three major legislative developments impacting pediatric device developing include: (1) 1997 legislation creating the HDE regulatory pathway permitting medical devices for rare diseases to be approved without enrolling a large clinical trial, (2) a 2004 Report to Congress entitled “Barriers to the Availability of Medical Devices Intended for the Treatment or Diagnosis of Diseases and Conditions that Affect Children” outlining unmet device needs in children and working plans to address those needs, and (3) 2007 legislation entitled “the Pediatric Medical Device Improvement and Safety Act” which included several provisions that (A) permits pediatric device makers to generate a profit for HDE device approvals in children, (B) establishes a pediatric device consortium to facilitate device development across pediatric medical centers, (C) tasks the FDA, NIH and Agency for Healthcare Research and Quality to work together to expand opportunities for pediatric device research, and (D) facilitates data collection opportunities for devices already used in children (e.g. post-market registries such as IMPACT and INTERMACS) in an effort to clarify their risk-benefit profile of approved and off-label devices more systematically.

Also important has been the work in the area of trial design that has explored innovative trial design strategies for pediatric devices to maximize small sample sizes, the use of objective performance criteria or performance goals for comparisons, increased use of propensity matching of historical control groups, expanded use of prospective clinical registry data, and considering a shift in emphasis for data collection towards the post-market setting if post-market data collection can be made more reliable and comprehensive than it is currently. This, combined with novel programs such as MedSun (Medical Product Safety Network) designed to improve the quality and reliability of adverse event reporting post-approval, as well as better tracking of individual devices and patients over time through the Unique Device Identifier (UDI) initiative, are working to address the challenges despite limitations inherent in the pediatric population. These ideas have been discussed over the past several years in a series of public and private FDA workshops on the regulatory process for

pediatric devices hosted by FDA[20,27–29], FDA guidances and publication of white papers on the regulatory process as it pertains to children [30,31], agency participation in post-approval pediatric devices databases[32] such as the ICD Registry[33], IMPACT Registry[34], and INTERMACS Registry[35], and recruiting pediatric experts to participate in the regulatory activities of the agency[31,36,37].

Conclusion

In summary, pediatric medical devices play a vital role in the treatment of children with cardiovascular disease. Most cardiac medical devices used in children today are used off-label where the risk-benefit of devices has not been well characterized. Pediatric medical devices face a variety of challenges to FDA approval related to the small target population, heterogeneity of the patient population and ethical considerations of testing high-risk devices in children. While relatively few cardiac devices have been FDA approved in children, the number of device approvals seems to be growing. Emerging opportunities to expand post-market surveillance may play an important role in improving the quality of risk-benefit data available for existing medical devices used in children.

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Table 1

FDA Risk-Classification of Medical Devices

	Risk to patients	Examples
Class I	Low	Bandage, scalpel
Class II	Moderate	Cardiac monitor, pulse oximeter, catheter
Class III	High	VAD, ICD, pacemaker, prosthetic valve

FDA, Food and Drug Administration; VAD, ventricular assist device; ICD, implantable cardiac defibrillator

Table 2

Pediatric cardiac medical devices FDA-approved through the Humanitarian Device Exemption (HDE) Pathway*.

Device	Year	Company	Population/Indication	Supporting Clinical Data
Berlin Heart EXCOR® Pediatric Ventricular Assist Device (H100004)	2011	Berlin Heart, Inc	Children ≤16 years with class IV heart failure and listed for transplant in cardiogenic shock or slow progressive decline despite optimal support	Multi-center single arm cohort study (N=48) compared to retrospective cohort of children supported with ECMO and safety OPC. Supplemental data from compassionate-use implants (N=156).
Medtronic Melody® Transcatheter Pulmonary Valve and Ensemble Transcatheter Valve Delivery System (H08002)	2010	Medtronic, Inc	Pediatric and adult patients with original RVOT conduit ≥16 mm with dysfunctional RVOT conduits with a clinical indication for intervention due to PR>moderate or PS> 35 mm Hg	Multi-center single arm cohort study (N=90) of children and adults (ages 7–44 years); Supplemental data from OUS implants (N=68) also reviewed.
Debakey VAD Child Left Ventricular Assist system (H03003)	2004	Micromed Technology, Inc	Children age 5–16 years with BSA 0.7–1.5 with class IV heart failure refractory to medical therapy and listed for heart transplantation	None
Contegra® Pulmonary Valved conduit (H20003)	2003	Medtronic, Inc	Children <18 years requiring RVOT reconstruction due to pulmonary stenosis, TOF, Truncus Arteriosus, TGA-VSD, Pulmonary Atresia	Multi-center, prospective single arm cohort study (N=237) compared to homograft controls drawn from the literature.
Shelhigh Pulmonic Valve Conduit Model NR-4000 with “No- React®” Treatment (H980007)	1999	Shelhigh, Inc.	Infants or children up to age 4 years of age requiring replacement of a dysfunctional or absent pulmonary artery (TGA, TOF, Truncus Arteriosis, Pulmonary Atresia, or replacement for accelerated conduit failure)	European clinical experience which included 70 patients (47 were infants)
CardioSEAL® Septal Occlusion System (H990005)	1999	Nitinol Medical Technologies, Inc.	Children and adults with complex VSDs warranting closure due to size but cannot be closed with standard surgical trans-atrial or trans-arterial approaches because of location.	Single-center experience of 53 patients (median age 4 years) with complex VSDs
CardioSEAL® Septal Occlusion System (H990004)	1999	Nitinol Medical Technologies, Inc.	For the treatment of children and adults with complex single ventricle physiology who have undergone a fenestrated Fontan palliation procedure and require closure of the fenestration.	3-center experience of 67 patients (median age 7 years) implanted for Fontan fenestration closure

OPC, objective performance criteria; ECMO, extra-corporeal membrane oxygenation; OUS, outside the United States; RVOT, right ventricular outflow tract; TOF, Tetralogy of Fallot; TGA-VSD, transposition of the great arteries with ventricular septal defect; VAD, ventricular assist device; VSD, ventricular assist device

*CardioSEAL and Amplatzer septal occluders were also originally HDE-approved for PFO closure however HDE approval was subsequently withdrawn by the FDA when the disease population affected was estimated to be >4,000 cases per year.