

VIEWPOINT

AMERICAN PEDIATRIC SOCIETY

Lessons From Drugs to Devices

A Pediatric Perspective

Kolaleh Eskandanian, PhD, MBA, PMP
Children's National Health System, Washington, DC.

Michael Klein, MD
American Pediatric Surgical Association, Deerfield, Illinois; and Children's Hospital of Michigan, Detroit.

Peter C. W. Kim, MD, PhD
Children's National Health System, Washington, DC.

Children have medical device needs that are considerably different from adults. Designing devices for children requires considerations such as growth and development, anatomical and physiological differences, hormonal influences, and activity level. The challenges also include small markets, minimal financial incentives, and regulatory issues. Often, the lack of available devices for children forces clinicians to use an adult device off label or to improvise. Off-label use may be the only option, but such use can bring risks of serious adverse events that could be avoided if there were more US Food and Drug Administration (FDA)-approved pediatric devices.¹ To address very similar issues related to orphan drugs, the US Congress passed the Orphan Drug Act in 1983 to provide incentives for industry investment in orphan drugs. It was not until 2007 that a somewhat analogous act, the Pediatric Medical Device Safety and Improvement Act, became public law. This Viewpoint suggests that incentives in forms of legislation and availability of grant programs have greatly facilitated the development of orphan drugs. Although there are inherent differences in drug and device development pathways, there are lessons to be learned. The Table illustrates that, in contrast to drugs, there are very few incentives available to stimulate investment in pediatric devices.

What has been clearly demonstrated by pediatric drug development is that financial incentives, modernized regulatory pathways, and availability of federal grants stimulate pediatric research. The Orphan Drug Act provided 3 major incentives: (1) 7-year market exclusivity to sponsors of approved orphan drugs; (2) tax credit of 50% of the cost of clinical trials; and (3) federal grants for clinical testing of new therapeutics for rare diseases. Pharmaceutical companies generally believe the Orphan Drug Act was a success. Between 1983 and May 2010, the FDA approved 353 orphan drugs and granted orphan designations to 2116 compounds. As of 2010, there is an approved treatment for 200 of the roughly 7000 officially designated orphan diseases. The financial rewards to pharmaceutical companies have been remarkable. Between 1997 (passage of the FDA Modernization Act) and 2012, the additional 6 months of exclusivity drove more than \$71 billion in incremental revenue.² Between 1997 and 2014, 185 drugs were granted pediatric exclusivity. This, in turn, translated into 211 label changes as an outcome of pediatric trials.³ Increasingly, pharmaceutical companies have been establishing divisions to focus on the development of orphan drugs.

While legislations have provided drug developers with incentives to pursue pediatric drug research, the Pediatric Medical Device Safety and Improvement Act of

fers device manufacturers little incentive to develop devices specifically for children or to develop smaller versions of adult devices for the relatively small numbers of children who might benefit from them.^{4,5} The testing and approval of high-risk medical devices in children younger than 18 years remain extremely uncommon. Between January 1, 2008, and December 31, 2011, among the 22 medical devices approved through the premarket approval—the regulatory pathway for higher-risk class III devices—only 1 device was indicated for use in patients younger than 18 years, and few pediatric patients were exposed to the devices before market availability.⁶ In fiscal year 2013, the FDA approved 1 device under the Humanitarian Device Exemption—a pathway to market for devices intended for rare diseases—but this approved device did not include a pediatric indication. In the same fiscal year, the FDA approved 38 premarket approval applications. Of those, 11 were approved for a treatment, diagnosis, or cure of a disease or condition that occurs in children, but only 8 were indicated for a pediatric population.

There are successes related to pediatric device development that should be used to demonstrate that federal grant programs and improved regulatory pathways work and that more should become available to promote pediatric device development. In 2004, a story in the *New York Times*⁷ catalyzed the demand in the United States for the EXCOR Ventricular Assist Device (VAD) as a bridge to heart transplantation in children with end-stage heart failure. Unlike adults who have access to a wide variety of reliable FDA-approved long-term VADs, children have limited options. Today, thanks in large part to the Humanitarian Device Exemption pathway and the FDA Orphan Products Grants Program, the Berlin Heart EXCOR Pediatric VAD has emerged as an alternative to extracorporeal membrane oxygenation, a method with a dismal success rate, for bridging children to transplantation. This device received Investigational Device Exemption approval in 2007, which allowed for the start of a multicenter study in the United States, and received Humanitarian Device Exemption approval in 2011. To date, in the United States alone hundreds of children have benefited from its superior functionality.

In conclusion, policy makers should use examples such as the EXCOR VAD to increase grant programs and orphan-like incentives to pediatric device developers. In September 2014, the FDA announced 15 awards worth more than \$19 million as part of its Orphan Products Grants Program—no medical device was in that list. Set-aside grants for pediatric devices will remedy this. We applaud the advocacy work of the 21st Century Cures bill, which includes provisions that pediatric diseases re-

Corresponding Author: Kolaleh Eskandanian, PhD, MBA, PMP, Children's National Health System, 111 Michigan Ave NW, M7779, Washington, DC 20010 (keskanda@childrensnational.org).

Table. Legislations and Incentives to Improve Pediatric Product Development

Legislation and Incentive	Pediatric Drugs	Pediatric Devices
Orphan Drug Act (enacted in 1983) Includes provisions for tax incentives, enhanced patent protection and marketing rights, clinical research subsidies, creating a government-run enterprise to engage in research and development	+	-
Best Pharmaceuticals for Children Act (enacted in 2002) Extended the provision from the 1997 FDA Modernization Act offering an additional 6 mo of patent exclusivity for on-patent drugs being tested for pediatric use	+	NA
Pediatric Research Equity Act (enacted in 2003) Requires new drug applications and biologics licensing applications to contain a pediatric assessment unless the applicant has obtained a waiver or deferral	+	-
Pediatric Medical Device Safety and Improvement Act (enacted in 2007) Eliminates the profit restriction on devices approved under the Humanitarian Device Exemption and authorizes appropriations for grants to nonprofit consortia to facilitate the development, production, approval, and distribution of pediatric medical devices	NA	+
Food and Drug Administration Safety and Innovation Act (enacted in 2012) "Breakthrough therapy" designation assists drug developers to expedite the development and review of new drugs with preliminary clinical evidence that indicates the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases; the analogous program for devices is the Expedited Access Pathway for certain medical devices that demonstrate the potential to address unmet medical needs for life-threatening or irreversibly debilitating diseases	+	+
Rare Pediatric Disease Priority Review Voucher Program Priority review vouchers are awarded to sponsors of certain rare pediatric disease drugs	+	-
FDA Orphan Products Grants Program Goal is to encourage clinical development of products for use in rare diseases or conditions	+	+

Abbreviations: FDA, US Food and Drug Administration; NA, not applicable; +, currently exists; -, could be applied from drugs to devices.

main a priority. Under this new bill, we encourage policy makers to give proportional attention to pediatric device development. We also acknowledge the FDA's recent draft guidance on leveraging existing clinical data for extrapolation to pediatric uses of medical devices as a positive step to stimulate development of pediatric de-

vices and to promote labeling for safer device use in children. These positive developments should also be coupled with the formation of a coalition of the government, device industry, academia, and start-ups to promote creation of pediatric divisions within device companies.

ARTICLE INFORMATION

Published Online: September 8, 2015.
doi:10.1001/jamapediatrics.2015.1932.

Conflict of Interest Disclosures: None reported.

Additional Contributions: Mark Batshaw, MD, Children's National Health System, Washington, DC, provided critical reading of the manuscript; he received no compensation.

REFERENCES

- Hamburg M. Keynote address. Talk presented at: Second Annual Pediatric Surgical Innovation Symposium; October 24, 2014; Washington, DC.
- Armstrong W. Pharma's orphans. *Pharmaceutical Executive*. May 1, 2010. <http://www.pharmexec.com/pharmas-orphans>. Accessed January 15, 2015.
- Aumock N, Smith J, Townsend S. Do incentives drive pediatric research? http://www.mckinsey.com/~/media/McKinsey/dotcom/client_service/Public%20Sector/Regulatory%20excellence/Do_incentives_drive_pediatric_research.ashx. Accessed March 21, 2015.
- Field MJ, Boat TF. *Rare Diseases and Orphan Products: Accelerating Research and Development*. Washington, DC: National Academies Press; 2010.
- Ulrich LC, Joseph FD, Lewis DY, Koenig RL. FDA's pediatric device consortia: national program fosters pediatric medical device development. *Pediatrics*. 2013;131(5):981-985.
- Hwang TJ, Kesselheim AS, Bourgeois FT. Postmarketing trials and pediatric device approvals. *Pediatrics*. 2014;133(5):e1197-e1202.
- Grady D. Tubes, pump and fragile hope keep a baby's heart beating. *New York Times*. August 22, 2004. <http://www.nytimes.com/2004/08/22/science/22heart.html>. Accessed July 20, 2015.