

## HEALTH POLICY STATEMENT

# 2017 ACC/AAP/AHA Health Policy Statement on Opportunities and Challenges in Pediatric Drug Development: Learning From Sildenafil



Developed in Collaboration With the U.S. Food and Drug Administration

### Writing Committee Members

Craig A. Sable, MD, FACC, FAHA, *Chair*\*†  
D. Dunbar Ivy, MD, FAAP, FACC, FAHA, *Vice Chair*\*

Robert H. Beekman III, MD, FAAP, FACC\*  
Helene D. Clayton-Jeter, OD‡  
Kathy J. Jenkins, MD, MPH, FAAP, FACC, FAHA§  
William T. Mahle, MD, FAAP, FACC, FAHA†  
William R. Morrow, MD, FAAP, FACC§  
Mary Dianne Murphy, MD, FAAP‡||  
Robert M. Nelson, MD, PhD, FAAP‡

Geoffrey L. Rosenthal, MD, PhD, FAAP, FACC§  
Norman Stockbridge, MD, PhD‡  
David L. Wessel, MD, FAAP, FAHA†

\*American College of Cardiology Representative. †American Heart Association Representative. ‡U.S. Food and Drug Administration Representative. §American Academy of Pediatrics Representative. ||Retired from the U.S. Food and Drug Administration during the development of this statement.

*The STARTS-1 and -2 trials (Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension) and subsequent 2012 U.S. Food and Drug Administration (FDA) product labeling for sildenafil use in pediatric patients with pulmonary hypertension highlight many of the challenges to the development and approval of medications for children. This experience served as the impetus for direct collaboration between FDA representatives and the Joint*

*Council on Congenital Heart Disease (JCCHD) (representing the pediatric cardiology leadership of the American College of Cardiology, the American Heart Association, and the American Academy of Pediatrics) to improve communication and realign missions with regard to pediatric drug trials. These discussions led to the joint FDA/JCCHD development of this statement, which describes the current environment and identifies possible future directions for reducing barriers to pediatric drug trials.*

This document was approved by the American College of Cardiology Clinical Policy Approval Committee, the American Academy of Pediatrics Board of Trustees, and the American Heart Association Science Advisory and Coordinating Committee in March 2017, and by the American Heart Association Executive Committee in April 2017.

Author and peer reviewer relationships with industry (RWD) pertinent to this document are disclosed in [Appendixes 1 and 2](#), respectively. Additionally, to ensure complete transparency, authors' comprehensive healthcare-related disclosure information—including RWI not pertinent to this document—is available [online](#). The ACC disclosure policy for clinical document development is also available [online](#).

The American College of Cardiology requests that this document be cited as follows: Sable CA, Ivy DD, Beekman RH 3rd, Clayton-Jeter HD, Jenkins KJ, Mahle WT, Morrow WR, Murphy MD, Nelson RM, Rosenthal GL, Stockbridge N, Wessel DL. 2017 ACC/AAP/AHA health policy statement on opportunities and challenges in pediatric drug development: learning from sildenafil. *J Am Coll Cardiol* 2017;70:495-503.

This article has been copublished in. *Circulation: Cardiovascular Quality and Outcomes*

Copies: This document is available on the World Wide Web sites of the American College of Cardiology ([www.acc.org](http://www.acc.org)), American Academy of Pediatrics ([www.aap.org](http://www.aap.org)), and American Heart Association ([professional.heart.org](http://professional.heart.org)). For copies of this document, please contact the Elsevier Reprint Department via fax (212) 633-3820 or e-mail [reprints@elsevier.com](mailto:reprints@elsevier.com).

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American College of Cardiology. Requests may be completed online via the Elsevier site (<https://www.elsevier.com/about/our-business/policies/copyright/permissions>).

## BACKGROUND

---

There are many challenges to the development and approval of medications for children. The STARTS-1 and -2 trials, which are described briefly in the next section, highlight many of the challenges in pediatric trial design and approval of medications for children, especially those with rare diseases. Through a series of conversations between the FDA and JCCHD that had their origin around review of the effect of the STARTS-1 and -2 trials and subsequent regulatory response on clinical practice, it became clear that better communication and alignment of goals surrounding pediatric drug trials were needed. This paper serves as unique opportunity to bring leaders of the pediatric cardiology community and FDA together as 1 voice.

Fewer than 50% of drugs approved for use in the United States have sufficient data to support labeling for dosing, safety, and efficacy in children (1,2). Several studies estimate at least 40% and up to 100% of hospitalized children are prescribed at least 1 medication that is used “off-label” (3-6). Lack of approved medications for children limits evaluation and dissemination of safety and efficacy data. Although randomized clinical trials have shaped advances in care of adults with cardiovascular disease, there are many challenges to relying solely on randomized clinical drug trials to address the unique needs of children (7). Application of alternative study designs needs to be part of the roadmap toward more inclusive labeling of pediatric drugs.

Within pediatric cardiology, the scope of the problem is highlighted in a 2008 report by Pasquali et al. (8). This study used the Pediatric Health Information System database to query over 30,000 records of hospitalized children with cardiovascular disease; 78% received at least 1 off-label medication, and 31% received more than 3. The most commonly used off-label medications were furosemide, epinephrine, dopamine, lidocaine, and milrinone. A 2013 report from a single-center cardiac intensive care unit (82 patients over 3 months) found that 94% of patients received at least 1 (median 4/patient) off-label medication; 36% of all drugs prescribed were off-label (9).

Data from pediatric clinical trials often need to be interpreted in light of the small and heterogeneous study populations, lack of control of patient-specific variables, and often retrospective nature that may make data replication more challenging. Of the small number of published pediatric cardiology clinical drug trials, many have inconsistent results and conclusions, compared with those in adults (10-14). Several factors contribute to this, including the possibility that a drug that works in adults may not work in children. Further challenges include: 1) the rarity, heterogeneity, and ill-defined natural history

of pediatric diseases; 2) the lack of established research infrastructure; 3) ethical issues specific to pediatric research; 4) the lack of formulations suitable for infants and children (e.g., oral liquid, chewable tablet); 5) the need for more precise pharmacokinetic dosing data; 6) poorly designed dose-response assessments; 7) the lack of clinical equipoise; and 8) the use of surrogate or composite endpoints (1). The lack of appropriate endpoints to evaluate the effect of disease from the neonate to the adolescent creates an additional challenge (15).

Steps are being taken to close the gap between data on adults and data on children and to meet the demand for pediatric clinical trials (7). As described in the following text, Congress established—and, in 2012, permanently reauthorized—the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act (BPCA). In 2010, the National Institute of Child Health and Human Development established the Pediatric Trials Network, an alliance of clinical research sites cooperating in the design and conduct of pediatric clinical trials. The National Heart, Lung, and Blood Institute established the Pediatric Heart Network in 2001 in an attempt to narrow the knowledge gap in pediatric cardiovascular diseases (16); to date, over 300 peer-reviewed publications have resulted from Pediatric Heart Network-sponsored studies, including drug trials in children with single-ventricle physiology (14), Kawasaki Disease (11), and Marfan syndrome (12).

With continuous development of new medications, and a lack of data on outcomes with those currently available, there is a need to formulate new tools for pediatric clinical trials and alternative study designs to overcome identified barriers. Open communication between clinician-scientists and the FDA is a key strategy for success. This paper highlights the need for cooperation in describing the current state and direction of pediatric research and the regulatory environment as it pertains to the development of cardiovascular drugs.

## SILDENAFIL CASE STUDY

---

The STARTS-1 trial was the first randomized, double-blind, placebo-controlled, and dose-ranging parallel group study of a pulmonary hypertension drug in children (17). The primary efficacy endpoint was the percent change from baseline in peak oxygen consumption during cardiopulmonary exercise testing after 16 weeks in developmentally able children, with main secondary endpoints of change from baseline in mean pulmonary artery pressure and pulmonary vascular resistance index by cardiac catheterization in all patients. The trial did not meet its primary endpoint—the placebo-adjusted percent change in peak oxygen

consumption ( $p = 0.056$ ). Compared with placebo, the combined sildenafil cohort had improved pulmonary vascular resistance index but not mean pulmonary artery pressure. After the 16-week study period, patients in the low-, medium-, and high-dose groups continued sildenafil treatment with their originally assigned dose (the STARTS-2 trial) (18), and patients in the placebo group were randomized to low-, medium-, or high-dose therapy. By 2 years, there was a trend for an increase in mortality in the high-dose group. By 3 years, the hazard ratio for mortality was 3.95 (95% confidence interval: 1.46 to 10.65) for high- versus low-dose therapy. These findings raised significant concerns that chronic sildenafil therapy may be associated with dose-related mortality in children with pulmonary hypertension.

The results of the STARTS-2 trial are difficult to interpret for several reasons: the trial did not include a placebo group; doses of sildenafil changed during the STARTS-2 trial; patients requiring additional pulmonary hypertension therapy were withdrawn from STARTS-2; children were not censored once withdrawn from the study to add therapy or because of withdrawal of consent, but continued to be followed; and the mortality signal was not consistent across weight groups or etiologies. Subsequent data analysis revealed that most patients who died had idiopathic/heritable pulmonary hypertension and worse-than-median STARTS-1 baseline hemodynamic values.

Resulting labeling highlighted the findings and concluded—in a warning, not a contraindication—that “use of REVATIO, particularly chronic use, is not recommended in children.”

As noted earlier, this medication warning was the impetus for leaders within the congenital heart disease community to reach out to the FDA to understand the current regulatory environment and consider opportunities to increase cooperation with clinician-scientists to ensure a successful strategy for pediatric drug development.

## CURRENT REGULATORY ENVIRONMENT

The federal government promotes pediatric studies of products through 2 laws and 1 regulation. The Pediatric Research Equity Act (19), promulgated as a regulation in 1998 and as legislation in 2003, requires studies in children when a new drug or new use is to be studied in adults, provided a similar condition exists in children and other criteria are met (e.g., its use would provide a meaningful therapeutic benefit to the pediatric population). However, the Pediatric Research Equity Act does not apply to sildenafil use for pulmonary hypertension, because drugs with an orphan designation are exempt from this requirement.

An orphan status designation carries its own benefits, but pediatric studies cannot be required once such a designation is given. The BPCA (20), first enacted in legislation in 1997, extends marketing exclusivity for the moiety (sildenafil in the example in the previous text), not just the product studied (Revatio trademark) for 6 months for doing agreed-upon studies in children. The studies requested can be for the same or different indications than an adult indication. Under the BPCA, the FDA can request that sponsors conduct studies for pulmonary hypertension by issuing a Written Request. This program is entirely voluntary, and a sponsor may or may not agree to conduct the requested studies.

The 1994 Pediatric Labeling Regulation (21) also introduced the concept of extrapolation of efficacy from adequate and well-controlled adult trials if: 1) the course of the disease; and 2) the expected response to therapy are sufficiently similar between children and adults (22). Utilizing these legislative and regulatory tools, the FDA has been able to request and require studies that have resulted in over 600 product labels with new pediatric information (23), but labeling of medications for children with life-threatening disease remains challenging. This includes 1 antiarrhythmic and 14 antihypertensive medications.

In 2007, the European Union (EU) enacted similar laws. There are 3 important differences between the EU and U.S. laws in this area. Specifically, EU laws: 1) provide for additional marketing exclusivity for performing required pediatric studies; 2) do not specify an independent voluntary process for requesting studies, which permits requesting studies for pediatric-only conditions absent a corresponding adult indication; and 3) stipulate no exclusion of orphan products under the requirements. Thus, pulmonary hypertension would not be excluded from the EU requirement for pediatric studies.

There is a concerted effort to utilize the same clinical trials for the same indication and products on a global basis (24). Monthly international Pediatric Cluster meetings occur between the FDA, European Medicines Agency, Japan Pharmaceuticals and Medical Devices Agency, Health Canada, and Australian Therapeutic Goods Administration. Since 2007, the FDA and European Medicines Agency have met via teleconference at least monthly, adding the Japan Pharmaceuticals and Medical Devices Agency, Health Canada, and Australian Therapeutic Goods Administration over the following years, and sometimes (with working subgroups) 2 or 3 times per month. The Pediatric Cluster has addressed over 1,000 issues for 400 products since 2007. Fifteen common commentaries were sent to sponsors from 2012 to 2015 including 1 related to cardiac therapy (25). Consensus is reached about 75% of the time, with differences in legislation, standards of care, regulatory processes, and culture preventing 100% agreement.

## BARRIERS TO PEDIATRIC DRUG TRIALS

---

Some characteristics of the pediatric population pose challenges to the development of pediatric drug trials. Infants and children go through stages of rapid growth and development, which can alter the pharmacokinetics and pharmacodynamics of some therapeutics. Additionally, the long life expectancy of children (relative to adult subjects) can make appropriate study endpoints difficult to define. For example, appropriate different endpoints may be needed at different ages given the performance capabilities of the pediatric population(s) being studied. Importantly, the small patient population limits the market, and therefore potential revenue, for the pharmaceutical industry, which otherwise might pursue pediatric drug development more rigorously. Finally, the ethics of clinical research in children remain a significant issue. More recently, however, an understanding of the importance of research to advance childhood therapies has led to a new perspective that children need appropriate protection of rights and safety *during* research rather than protection from research (26).

Despite the processes described in the previous section, important barriers to pediatric drug trials and development still remain. One challenge relates to the relative rarity of congenital and acquired pediatric cardiovascular disease. The STARTS-1 and -2 trials serve as examples of the difficulty in conducting clinical trials for pediatric diseases; several studies have suggested that pediatric pulmonary arterial hypertension occurs in fewer than 5 children per million (27). The small population of children affected by cardiovascular disease makes it difficult to design well-powered randomized clinical trials to test the effectiveness and safety of new therapeutics. As adult trials typically precede pediatric trials, there may be significant barriers to enrollment of children in trials. Clinicians and families often assume that the beneficial effect of a novel agent in adults will logically translate to a benefit in children. Once a medication is approved in adults, parents are often unwilling to agree with randomization of the study drug. This, in turn, may make it difficult to enroll pediatric study subjects. However, age-related differences in both the underlying diseases and pharmacodynamics make it imperative to study such novel agents in all age groups. Indeed, less than 50% of the pediatric trials issued as a pediatric study request by the FDA and completed were shown to be efficacious (25).

A 2014 review of the effect of pediatric exclusivity, which provides 6 months of additional market protection to drug sponsors in exchange for studying their products in children, found that efficacy was less likely to be established in oncology, cardiovascular, and endocrine drugs than in gastrointestinal and pain/anesthesia

drugs (28). The lack of similarities between pediatric and adult populations and inadequate accepted alternative endpoints may prevent extrapolation of efficacy or development of exposure response studies to determine if pediatric and adult populations responded to a drug similarly. Studies to evaluate pharmacokinetics/pharmacodynamics and safety may be sufficient if efficacy can be extrapolated.

## FDA PERSPECTIVE ON PEDIATRIC BARRIERS

---

Prior to 2007, the BPCA appeared to be the main stimulus for studies resulting in pediatric labeling. In recent years, more studies have been submitted under the Pediatric Research Equity Act pediatric requirement. This shift may reflect the many challenges in negotiating studies to be conducted to obtain additional marketing exclusivity under BPCA, especially if the pediatric indication(s) are different from those underlying the adult approval.

An appropriate endpoint for a clinical trial should measure improvements in how a patient feels, functions, or survives. Alternatively, a validated surrogate reflecting such effects may be used. A surrogate endpoint is defined by the FDA as a clinical endpoint other than survival or irreversible morbidity “that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit...” (29). However, there are few validated surrogates that predict long-term outcomes or benefit in children. In pulmonary hypertension, the FDA helped establish that a change in pulmonary vascular resistance index was a valid surrogate for a change in exercise capacity. However, measurement of pulmonary vascular resistance index using invasive hemodynamic monitoring in children specifically for research purposes fails to provide the required safeguards for children enrolled in clinical investigations, as it does not offer any sufficient compensating clinical benefit. The risk of cardiac catheterization is higher than in adults, making measurement of hemodynamics a problematic endpoint.

Sponsors often seek to reduce the uncertainties in their development programs by following what has worked previously. Where studies are being conducted for the purpose of obtaining an indication, the FDA will only give advice about what is acceptable. For studies intended to satisfy BPCA requirements, the FDA sets the standard (by issuing a Written Request) in negotiation with the sponsor. Because the sponsor will obtain 6 additional months of exclusive marketing for fulfillment of the Written Request regardless of whether the trial is successful in proving efficacy and safety, the FDA has the primary responsibility for ensuring that the development program has the best chance of success.

This usually means, where appropriate, adhering closely in pediatric studies to corresponding endpoints used in adults or, when confident of the relationship between the adult and pediatric endpoints, selecting an appropriate pediatric endpoint.

In addition to ensuring adherence to requirements for establishing the safety and efficacy of pediatric therapeutics, the FDA's Office of Pediatric Therapeutics, the Center for Drug Evaluation and Research's Division of Pediatric and Maternal Health, the Rare Disease Program, and the Division of Cardiovascular and Renal Products are all committed to working with sponsors to develop new therapies for pulmonary hypertension in children.

## FUTURE DIRECTIONS

Investigators designing trials to study therapeutics in children may need to consider alternatives to the classic randomized controlled trial design. For example, adaptive trial designs could be used in which interim analyses affect subsequent randomization schemes. Prospective adaptive designs could also be planned to use interim data analyses to modify study eligibility criteria, treatment regimens (e.g., dose or schedule), or study endpoints (e.g., which prespecified endpoint to use, use of composite endpoint, timing of assessment) (30). Adaptive study designs, if used, must be specified prospectively, with blinded interim analyses, and with the recognition that such designs can increase the chance of false positive study results (i.e., type 1 errors). Novel techniques, such as activity measurement, may allow for approval if the medication can show that a child functions better.

The use of surrogate study endpoints can be particularly important in pediatric studies, in which long-term outcomes (potentially decades) relevant to children are difficult to assess. Such surrogate endpoints can be clinical, physiological, or biochemical. If an endpoint is an accepted surrogate, there is no obligation to confirm clinical benefits. The use of such an endpoint is a

reasonable substitution for decades-long research. The FDA notes that when a drug's approval is based on a study design using "reasonably likely" surrogate endpoints, there may be a requirement for post-marketing studies to verify the drug's effectiveness and safety. However, this only applies to the setting of a "reasonably likely" surrogate being used as the basis for accelerated approval.

Additionally, personalized medicine promises to improve clinical research as well as clinical care. In the future, novel methodologies to improve the design of therapeutics research in small populations might include study "enrichment" techniques, whereby genetic or physiological biomarkers are used to enhance study power by enrolling subsets of patients with either: 1) predicted increased treatment effects; or 2) predicted increased risk of adverse effects (31). Computer modeling and simulation, possibly integrated with pharmacogenetics data, might be used in the future to decrease the number of human subjects needed to conduct meaningful therapeutic trials. Careful attention to pediatric clinical pharmacology early in study design can also help to optimize initial dose selection and data sampling. Registry studies may also have value in the pediatric population.

The ultimate goal of pediatric drug studies is to approve drugs that are safe and effective in children, ultimately improving care for the pediatric population to which they apply. Significant progress has been made in improving the environment for developing and conducting randomized clinical trials. The STARTS-1 and -2 trials for pulmonary hypertension in children highlight several of the challenges that we face in establishing safety, efficacy, and labeling for pediatric cardiovascular drugs, but have provided valuable lessons applicable to future pediatric study design. Thoughtful, alternative study designs should be considered to optimize pharmacological treatment of cardiovascular diseases in children. Professional societies and regulators should be partnering in these efforts.

## REFERENCES

1. Li JS, Cohen-Wolkowicz M, Pasquali SK. Pediatric cardiovascular drug trials, lessons learned. *J Cardiovasc Pharmacol*. 2011;58:4-8.
2. Sachs AN, Avant D, Lee CS, Rodriguez W, Murphy MD. Pediatric information in drug product labeling. *JAMA*. 2012;307:1914-5.
3. Sampson MR, Benjamin DK, Cohen-Wolkowicz M. Evidence-based guidelines for pediatric clinical trials: focus on StaR Child Health. *Expert Rev Clin Pharmacol*. 2012;5:525-31.
4. Lindell-Osuagwu L, Korhonen MJ, Saano S, Helin-Tanninen M, Naaranlahti T, Kokki H. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. *J Clin Pharm Ther*. 2009;34:277-87.
5. Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opin Drug Saf*. 2006;5:703-18.
6. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. *Arch Pediatr Adolesc Med*. 2007;161:282-90.
7. Connor EM, Smoyer WE, Davis JM, et al. Meeting the demand for pediatric clinical trials. *Sci Transl Med*. 2014;6:227f511.
8. Pasquali SK, Hall M, Slonim AD, et al. Off-label use of cardiovascular medications in children hospitalized with congenital and acquired heart disease. *Circ Cardiovasc Qual Outcomes*. 2008;1:74-83.
9. Maltz LA, Klugman D, Spaeder MC, Wessel DL. Off-label drug use in a single-center pediatric cardiac intensive care unit. *World J Pediatr Congenit Heart Surg*. 2013;4:262-6.
10. Wessel DL, Berger F, Li JS, et al. Clopidogrel in infants with systemic-to-pulmonary-artery shunts. *N Engl J Med*. 2013;368:2377-84.
11. Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial of pulsed corticosteroid therapy for

primary treatment of Kawasaki disease. *N Engl J Med*. 2007;356:663-75.

12. Lacro RV, Dietz HC, Sleeper LA, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. *N Engl J Med*. 2014;371:2061-71.

13. Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA*. 2007;298:1171-9.

14. Hsu DT, Zak V, Mahony L, et al. Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation*. 2010;122:333-40.

15. Adatia I, Haworth SG, Wegner M, et al. Clinical trials in neonates and children: Report of the pulmonary hypertension academic research consortium pediatric advisory committee. *Pulm Circ*. 2013;3:252-66.

16. Mahony L, Sleeper LA, Anderson PA, et al. The Pediatric Heart Network: a primer for the conduct of multicenter studies in children with congenital and acquired heart disease. *Pediatr Cardiol*. 2006;27:191-8.

17. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. *Circulation*. 2012;125:324-34.

18. Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. *Circulation*. 2014;129:1914-23.

19. One Hundred Tenth Congress of the United States of America. Food and Drug Administration Amendments Act of 2007. Title IV: The Pediatric Research Equity Act.

Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf>. Accessed April 12, 2017.

20. One Hundred Tenth Congress of the United States of America. Food and Drug Administration Amendments Act of 2007. Title V: Best Pharmaceuticals for Children Act. Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf>. Accessed April 12, 2017.

21. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Specific requirements on content and format of labeling for human prescription drugs; revision of 'Pediatric Use' subsection in the labeling. Federal Register. 1994; 59:64240.

22. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics*. 2011;128:e1242-9.

23. U.S. Food and Drug Administration. New pediatric labeling information database. Available at: <http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>. Accessed April 12, 2017.

24. Dunne J, Murphy MD, Rodriguez WJ. The globalization of pediatric clinical trials. *Pediatrics*. 2012;130:e1583-91.

25. U.S. Food and Drug Administration. International Collaboration/Pediatric Cluster. Available at: <http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106621.htm>. Accessed April 12, 2017.

26. Rose K. Challenges in pediatric drug development: a pharmaceutical industry perspective. *Paediatr Drugs*. 2009;11:57-9.

27. van Loon RL, Roofthoof MT, Hillege HL, et al. Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. *Circulation*. 2011;124:1755-64.

28. Wharton GT, Murphy MD, Avant D, et al. Impact of pediatric exclusivity on drug labeling and demonstrations of efficacy. *Pediatrics*. 2014;134:e512-8.

29. U.S. Food and Drug Administration. New drug, antibiotic and biological drug product regulations: accelerated approval. Proposed rule. 2014. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>. Accessed April 12, 2017.

30. U.S. Food and Drug Administration. Guidance for industry: adaptive design clinical trials for drugs and biologics. 2010. Available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm201790.pdf>. Accessed April 12, 2017.

31. Blaus A, Madabushi R, Pacanowski M, et al. Personalized cardiovascular medicine today: a Food and Drug Administration/Center for Drug Evaluation and Research perspective. *Circulation*. 2015;132:1425-32.

---

**KEY WORDS** Health Policy Statement, drug development, pediatric clinical trials, sildenafil, U.S. Food and Drug Administration

**APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—  
 2017 ACC/AAP/AHA HEALTH POLICY STATEMENT ON OPPORTUNITIES AND CHALLENGES IN  
 PEDIATRIC DRUG DEVELOPMENT: LEARNING FROM SILDENAFIL**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Craig A. Sable (Chair)	Children's National Medical Center—Training Director	None	None	None	None	None	None
D. Dunbar Ivy	The Children's Hospital Colorado—Professor of Pediatrics; Section Head, Cardiology	<ul style="list-style-type: none"> <li>■ Actelion</li> <li>■ Eli Lilly</li> <li>■ Gilead</li> <li>■ Pfizer</li> <li>■ United Therapeutics</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>■ Eli Lilly*</li> <li>■ United Therapeutics</li> </ul>	None
Robert H. Beekman III	Children's Hospital Medical Center of Cincinnati—Professor of Pediatric Cardiology	None	None	None	None	None	None
Helene D. Clayton-Jeter	Director, U.S. Food and Drug Administration Cardiovascular and Endocrine Liaison Program	None	None	None	None	None	None
Kathy J. Jenkins	Children's Hospital Boston—Senior Associate in Cardiology; Senior Vice President, Chief Safety and Quality Officer	None	None	None	<ul style="list-style-type: none"> <li>■ NuMed†</li> </ul>	None	None
William T. Mahle	Children's Healthcare of Atlanta—Chief, Cardiac Services; Medical Director, Clinical Research; Medical Director, Heart Transplant	None	None	None	None	None	None
William R. Morrow	Children's National Medical Center—Executive Vice President, Chief Clinical Officer	None	None	None	None	None	None
Mary Dianne Murphy	U.S. Food and Drug Administration—Director, Office of Pediatric Therapeutics‡	None	None	None	None	None	None
Robert M. Nelson	U.S. Food and Drug Administration—Deputy Director, Office of Pediatric Therapeutics	None	None	None	None	None	None
Geoffrey L. Rosenthal	University of Maryland Hospital for Children—Director, Division of Cardiology	None	None	None	None	None	None
Norman Stockbridge	U.S. Food and Drug Administration Division of Cardiovascular and Renal Products—Director	None	None	None	None	None	None
David L. Wessel	Children's National Health System—Executive Vice President and Chief Medical Officer, Hospital and Specialty Services; Ikaria Distinguished Professor of Critical Care Medicine	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥\$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC, a person has a *relevant* relationship if: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household* has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the *document*.

\*No financial benefit.

†Significant relationship.

‡Retired from the U.S. Food and Drug Administration during the development of this Health Policy Statement.

**APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2017 ACC/AAP/AHA HEALTH POLICY STATEMENT ON OPPORTUNITIES AND CHALLENGES IN PEDIATRIC DRUG DEVELOPMENT: LEARNING FROM SILDENAFIL**

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Louis I. Bezold	Official Reviewer—AHA	University of Kentucky Division of Pediatric Cardiology—Division Chief of Pediatric Cardiology	None	None	None	None	■ Intersocietal Accreditation Commission	None
Richard J. Kovacs	Official Reviewer—ACC Science and Quality Committee	Indiana University School of Medicine—Q.E. and Sally Russell Professor of Cardiology; Krannert Institute of Cardiology—Clinical Director	■ Biomedical Systems* ■ Theravance	None	None	■ Armaron Pharmaceuticals† ■ Astra Zeneca (DSMB) ■ Biotie (DSMB) ■ Eli Lilly* ■ Siemens† ■ Teva Pharmaceuticals (DSMB)	■ Cook Incorporated—Med Institute*	None
Shaji C. Menon	Official Reviewer—AAP	University of Utah—Associate Professor of Pediatrics; Adjunct Associate Professor of Radiology	None	None	None	None	None	None
David Procaccini	Official Reviewer—AHA	The Johns Hopkins Hospital—Clinical Pharmacy Specialist, Pediatric Intensive Care & Cardiology; Pediatric Anticoagulation Management Services, Co-Chair	None	None	None	None	None	None
Geetha Raghuvver	Official Reviewer—ACC BOG	Children's Mercy Hospital—Cardiologist; Professor of Pediatrics	None	None	None	None	None	None
Robin Steinhorn	Official Reviewer—AAP	Children's National Medical Center—Senior Vice President, Hospital Based Specialties; George Washington University—Professor of Pediatrics	None	None	None	■ United Therapeutics†	None	None
Brian D. Hanna	Organizational—Pediatric Pulmonary Hypertension Network	Children's Hospital of Philadelphia—Director, Section of Pulmonary Hypertension, Division of Cardiology; The Perelman School of Medicine, University of Pennsylvania—Clinical Professor of Pediatrics	None	None	None	■ Acteleon ■ United Therapeutics	■ Eli Lilly	None
Erika Berman Rosenszweig	Organizational—Pulmonary Hypertension Association	Columbia University Medical Center—New York Presbyterian—Associate Professor of Pediatrics in Medicine; Associate Chief of Pediatric Cardiology	■ Actelion ■ Ikaria	None	None	None	None	None
David W. Brown	Content Reviewer—ACC ACPC Council	Boston Children's Hospital—Attending Physician in Cardiology; Director, Pediatric Cardiology Fellowship Program; Harvard Medical School—Associate Professor of Pediatrics	None	None	None	None	None	None

Continued on the next page

**APPENDIX 2. CONTINUED**

<b>Reviewer</b>	<b>Representation</b>	<b>Employment</b>	<b>Consultant</b>	<b>Speakers Bureau</b>	<b>Ownership/ Partnership/ Principal</b>	<b>Personal Research</b>	<b>Institutional, Organizational, or Other Financial Benefit</b>	<b>Expert Witness</b>
Devyani Chowdhury	Content Reviewer—ACC ACPC Council	Cardiology Care for Children—Director	None	None	None	None	None	None
Timothy F. Feltes	Content Reviewer—ACC ACPC Council	Nationwide Children’s Hospital—Chief, Pediatric Cardiology and Co Director of the Heart Center	None	None	None	None	None	None
Gerard R. Martin	Content Reviewer—ACC Health Affairs Committee	Global Services—Medical Director; Children’s National Health System Medical Director, Global Services—C.R. Beyda Professor of Cardiology	None	None	None	None	■ American Board of Internal Medicine†	None
Kenneth M. Shaffer	Content Reviewer—ACC ACPC Council	Children’s Cardiology Associates—General Cardiologist; Mednax—Cardiology Director of Quality and Safety	None	None	None	None	None	None
Thad F. Waites	Content Reviewer—ACC Health Affairs Committee	Forrest General Hospital—Medical Director, Cath Lab	None	None	None	None	None	None

This table represents the comprehensive relationships of reviewers with industry and other entities that were disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥\$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person’s gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

\*Significant relationship.

†No financial benefit.

AAP indicates American Academy of Pediatrics; ACC, American College of Cardiology; ACPC, Adult Congenital and Pediatric Cardiology; AHA, American Heart Association; and DSMB, Data Safety Monitoring Board.