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 US Food and Drug Administration

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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. 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.

The STARTS-1 and -2 trials (Sildenafil in Treatment-Naive Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension) and subsequent 2012 US 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.


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prescribed at least 1 medication that is used “off-label.”
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. 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. 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.

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. 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. The lack of appropriate endpoints to evaluate the effect of disease from the neonate to the adolescent creates an additional challenge.

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. 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; to date, over 300 peer-reviewed publications have resulted from Pediatric Heart Network–sponsored studies, including drug trials in children with single-ventricle physiology, Kawasaki Disease, and Marfan syndrome.

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. 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), 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, 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 simi-
lar condition exists in children and other criteria are met (eg,
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 hyperten-
sion, 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 stud-
ied (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 Regulation21 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 simi-
lar 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
and regulatory tools, the FDA has been able to request and
require studies that have resulted in over 600 product labels
and labeling of medications.

In 2007, the European Union (EU) enacted similar laws.
There are 3 important differences between the EU and US
laws in this area. Specifically, EU laws: 1) provide for addi-
tional 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 indica-
tion; 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 clini-
cal 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 1000 issues for 400 products since 2007. Fifteen com-
mon 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, stand-
ards of care, regulatory processes, and culture preventing
100% agreement.

### Barriers to Pediatric Drug Trials

Some characteristics of the pediatric population pose chal-
lenges 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 pharmaceu-
tical 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 popu-
lation 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 sig-
nificant 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 sub-
jects. 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 chil-
dren, found that efficacy was less likely to be established in
oncology, cardiovascular, and endocrine drugs than in gastro-
intestinal and pain/anesthesia drugs.28 The lack of similari-
ties 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/pharma-
codynamics 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.” 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 (eg, dose or schedule), or study endpoints (eg, which prespecified endpoint to use, use of composite endpoint, timing of assessment). 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 (ie, 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, pathophysiologic, 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. 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**

Opportunities and Challenges in Pediatric Drug Development: Learning From Sildenafil

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

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Key Words: AHA Scientific Statements • drug development • pediatric clinical trials • sildenafil • US Food and Drug Administration
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<td>Devyani Chowdhury</td>
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<td>Cardiology Care for Children—Director</td>
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<td>Timothy F. Feltes</td>
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Appendix 2. Continued

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<td>Gerard R. Martin</td>
<td>Content Reviewer—ACC Health Affairs Committee</td>
<td>Global Services—Medical Director; Children’s National Health System Medical Director; Global Services—C.R. Beyda Professor of Cardiology</td>
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*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.
2017 ACC/AAP/AHA Health Policy Statement on Opportunities and Challenges in Pediatric Drug Development: Learning From Sildenafil

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<td>Actelion, Eli Lilly, Gilead, Pfizer, United Therapeutics</td>
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<td>Helene D. Clayton-Jeter</td>
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<td>Kathy J. Jenkins</td>
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<td>Institute for Relevant Clinical Data Analytics*, Lantheus*, Medtronic†, Novartis*, NuMed†</td>
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<td>William T. Mahle</td>
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<td>Mary Dianne Murphy</td>
<td>U.S. Food and Drug Administration—Director, Office of Pediatric Therapeutics‡</td>
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* No financial benefit.
† Significant relationship.
‡ Retired from the U.S. Food and Drug Administration during the development of this Health Policy Statement.