

**Best Pharmaceuticals for Children Act (BPCA)
Pulmonary Therapeutic Area Working Group Conference Call and Webcast
June 30, 2011
1:00 p.m.–2:00 p.m. ET**

Participants

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Purpose

The purpose of this conference call and webcast was to:

- Provide an overview of the BPCA program
- Brainstorm ideas on the needs in pediatric pulmonary therapeutics
- Develop a first draft of the working group's "wish list"
- Plan for the working group's next call.

The BPCA Program

Dr. Taylor-Zapata reviewed the background of the BPCA legislation and the work being carried out in the BPCA program, which is a collaboration between the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH). The goal of the BPCA program is to improve the effectiveness and safety of medicines used in children. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is the lead agency responsible for funding studies that will address and subsequently close knowledge gaps for therapeutics used in children. As of June 2011, under the BPCA and Pediatric Research Equity Act, about 346 studies have been completed, leading to about 410 labeling changes. Dr. Taylor-Zapata noted that the [FDA Web site](#) is a good resource.

The NIH pediatric drug development program has two main components: (1) developing and establishing a prioritization process that will identify gaps in pediatric therapeutics, including drugs and biologics, that need further study; and (2) conducting clinical trials of primarily off-patent drugs that have been prioritized for further study. The activities within the 2007 BPCA for drug development and testing fall into three general categories:

- Identifying and prioritizing therapeutic needs
- Developing Written Requests and Proposed Pediatric Study Requests
- Conducting studies.

BPCA outreach efforts include key experts in the field of pediatric pharmacology, mass outreach to major pediatric organizations, the development of therapeutic area working groups, and annual meetings to present working groups' recommendations and develop a priority list of needs in pediatric therapeutics. The BPCA program has continued to improve the prioritization process by making it more objective, increasing global outreach with a broader range of stakeholders and earlier expert input, and including outside evaluators.

Each year, the NICHD identifies three new areas for focus for that calendar year. Therapeutic area working groups are pulled together to discuss the therapeutic needs in that area of pediatric medicine. The NIH asks for recommendations of drugs (drug classes), biologics, and/or other areas of research that affect therapeutics that need further study in pediatrics.

For 2011, the therapeutic areas are pulmonary, hematology, and renal. Working groups for these three areas have been formed. The groups will meet via teleconference two or three times a year. Minutes of meetings will be posted on the BPCA Web site and distributed to working group members. The working groups' recommendations will be presented at the 2011 annual BPCA prioritization meeting and could lead to future studies, workshops, and publications. Working groups will be invited to participate in the annual meeting.

The BPCA mandate is to identify needs in pediatric therapeutics. The NICHD is fully aware that other Institutes have led research efforts and funded studies in each of the therapeutic areas. The NICHD is not trying to duplicate any other research efforts. The NICHD became interested in the following needs in the pulmonary therapeutic area due to recommendations from the 2010 BPCA outreach process:

- Treatment strategies in pulmonary hypertension of different etiologies
- Treatment alternatives for the prevention of secondary illnesses in cystic fibrosis (CF).

Examples of final recommendations from the Pulmonary Therapeutic Area Working Group include:

- Proposed therapeutic area(s)
- Proposed therapeutic drug class, agent, or device
- Background information on drug use, effectiveness, safety, etc.
- Identification of gaps, such as:
 - Clinical need
 - Lack of pediatric dosing, safety, efficacy
 - Research need
 - Ethical concerns
 - Feasibility concerns.

Open Forum

- There is a need for intravenous (IV) formulations of pulmonary hypertension drugs that are currently available only as oral formulations, such as sildenafil. For example, an IV sildenafil formulation would help children transition from IV milrinone to oral sildenafil. A call participant noted that there is an approved IV sildenafil formulation, but it has not been studied in children. A phase 2 clinical trial to study IV sildenafil in full-term infants with persistent pulmonary hypertension is under way. The trial is funded by the National Heart, Lung, and Blood Institute. There are still questions regarding sildenafil about the efficacy, duration of treatment, and pharmacokinetics (PK) in neonatal and pediatric populations.
- There is tendency to consider persistent pulmonary hypertension (PPH), particularly in neonates, as a single disease. PPH with different etiologies or different factors associated with it may require different therapeutic approaches. For example, sildenafil may be effective for one type of pulmonary hypertension but not for another.
- Stronger and more discriminative biomarkers for underlying pathologies of PPH would help determine more appropriate targeted therapies. Researchers do not know what underlying pathobiologic pathways are most important in one child with PPH versus another child. Clinicians may not specifically know which children need to be treated and for how long (i.e., when the natural history suggests the pulmonary hypertension may resolve without intervention). The impact of long-term, continuous treatment on the development of pulmonary vasculature is also not known.
- There are no good data on specific pediatric subgroups, such as the prevalence of pulmonary hypertension, the number of children who resolve their pulmonary hypertension with or without therapy, and the number of children who need long-term treatment. There are no

good data on the long-term effects of one-time drug exposure. Defining treatment success and scientifically proving treatment success have been challenging.

- Dr. Nielsen asked whether there are biomarkers that are more specific and sensitive than cardiac echo (e.g., serum markers). Global biomarkers of cardiac function or endothelin inhibition are probably more relevant to clinicians, whereas etiologic biomarkers such as gene polymorphism are more relevant to scientists. Dr. Nielsen clarified that specific biomarkers could help understand therapeutic responses and long-term outcomes, and therefore help target certain interventions to certain children. Defining successful therapeutic outcomes in pulmonary hypertension has been problematic. For example, the 6-minute walk test, which is validated in adults, has not been validated in children. In adults, the 6-minute walk test at diagnosis correlates with prognosis, but improvement with therapy does not correlate with prognosis. There is a need to track short-term outcomes that correlate with longer term outcomes (e.g., mortality).
- Dr. Davis asked whether the working group should avoid considering novel agents that are currently being used or being developed for specific indications, or whether the working group should focus on drugs being used in adult populations that could be scaled down for neonates or younger children. Dr. Taylor-Zapata explained that labeling changes for novel agents require two safety and efficacy studies. Because of the feasibility issues, certain drugs have not been considered for BPCA studies.
- Currently, more information on the safety of pediatric pulmonary hypertension therapeutics is needed.
- Information on epidemiology (e.g., clinical morbidity and cost) of the different classes of pediatric pulmonary hypertension is also needed.
- Dr. Retsch-Bogart asked for clarification on the meaning of secondary illnesses in CF, that is, whether they include lung infections as a consequence of the underlying CF pathophysiology or complications related to the treatment of lung disease or gastrointestinal disease. Dr. Taylor-Zapata replied that secondary illnesses could include both pathophysiology and complications.
- Treatment alternatives for the prevention of secondary illnesses in CF could include antioxidants and novel anti-inflammatory agents to modulate severity of illness in CF.
- A question was asked: Would the BPCA program consider studies of the management of drug allergies, which is an increasing problem in patients that are heavily treated? The answer was yes. Patients receiving anti-infective agents develop hypersensitivity reactions. Studies could help identify those patient groups by focusing on the pathophysiology of allergy and drug-specific reactions.
- The FDA is open to accepting appropriate feedback and providing comment on promising new pediatric pulmonary hypertension therapeutic agents. Dr. Taylor-Zapata agrees to help facilitate discussions with investigators and the FDA regarding novel therapeutics.
- Another area in which information is inadequate is aerosolized drug delivery to ventilated patients in the neonatal and pediatric intensive care units. There is variation in practice due to inadequate information. There is the need for devices to enhance aerosol delivery and reduce variability in delivery. There is a need for better testing and development of aerosol drug-delivery devices. In particular, devices are needed that can efficiently, safely, and uniformly deliver drugs to the lungs of intubated infants or infants on continuous positive airway pressure machines.

- Another area for study is drug deposition and individual markers for drugs for upper airway obstruction such as croup and asthma. IV formulations for some useful drugs are not available, and delivery systems for drugs that might be better administered by inhalation are not available.
- Information on drugs and medical countermeasures for chemical (e.g., nerve agents and cyanide), radiological, and nuclear exposures is lacking, as is information on specific medication dosing for treatment of biological exposures. Safety, efficacy, PK, and pharmacodynamics should be studied.
- Long- and short-term toxicity of drugs for pediatric asthma and allergic lung disease (e.g., albuterol and terbutaline) is another area for consideration.

Next Steps:

- Working group members should send their ideas and suggestions to Dr. Taylor-Zapata.
- Meeting minutes will be distributed to the working group in the coming weeks.
- A second working group call will be scheduled in about 6–8 weeks.