

**Best Pharmaceuticals for Children Act (BPCA)
Pulmonary Therapeutic Area Working Group Conference Call and Webcast
August 16, 2011
11:00 a.m.–12:00 p.m. ET**

Participants

Steven H. Abman, M.D.
John Alexander, M.D., M.P.H.
Jack Aranda, M.D., Ph.D.
Kimberly W. Benner, Pharm.D., B.C.P.S., F.A.S.H.P.
John T. Berger, III, M.D.
Louis Chicoine, M.D.
Beth Durmowicz, M.D.
Oluchi Elewachi, Pharm.D., M.P.H.
Thomas Green, M.D.
James M. Greenberg, M.D.
Gregory Hammer, M.D.
Sabrina Heidemann, M.D.
Nadia Hejazi, M.D.
Abraham Karkowsky, M.D., Ph.D.
Greg Kearns, Pharm.D., Ph.D.
Matthew M. Laughon, M.D., M.P.H.
Heber C. Nielsen, M.D.
Hanna Phan, Pharm.D., B.C.P.S.
DeWayne Pursley, M.D., M.P.H.
Mary Purucker, M.D., Ph.D.
Michael Reed, Pharm.D., F.C.C.P., F.C.P.
George Z. Retsch-Bogart, M.D.
Paul N. Severin, M.D.
Peter Starke, M.D.
Perdita Taylor-Zapata, M.D.
Teri Moser Woo, Ph.D., R.N., C.N.L., C.P.N.P.

Purpose

The purpose of this conference call and webcast was to:

- Review the Working Group's wish list from the first call
- Provide more specific details on recommendations.

Discussion

Dr. Taylor-Zapata reviewed the purpose of the Working Group and of the group's second call. The group will prioritize recommendations during a third call in 4 to 6 weeks. The recommendations will be presented at the BPCA Annual Meeting in December 2011.

She suggested that the group focus on the following issues:

- Describe the standard of care in the treatment of the therapeutic area.
- Describe the extent of the need to improve the quality of pharmacokinetics/ pharmacodynamics, efficacy, and safety studies for children being treated.

A table of discussion points was distributed before the call. Dr. Nielsen led the group's discussion of these points, noting that the group focused on three areas: (1) pulmonary hypertension; (2) cystic fibrosis; and (3) asthma, allergic lung disease, and croup. Dr. Nielsen asked Working Group members to identify their interest in one or more of these three areas and share their thoughts during the next conference call.

He suggested that the group discuss how these three areas relate to the following gaps, which were listed in the table of discussion points:

Pathophysiology, including biomarkers:

- The group previously discussed the need for more discriminate biomarkers for underlying pathologies of primary pulmonary hypertension to help determine targeted therapies.
- In response to a question, Dr. Nielsen said that the discussion point referred to biomarkers of disease process, but biomarkers of efficacy would also be relevant.
- A U.S. Food and Drug Administration advisory committee agreed that the pulmonary vascular resistance index (PVRI) was an acceptable biomarker for sildenafil. The biomarker has been validated in adults and correlates with the walk distance test.
- Dr. Nielsen asked whether more studies were needed to validate PVRI in young children. It was noted that more data are needed about changes in the natural course of the disease rather than changes in a surrogate marker like PVRI.
- Dr. Hammer noted that some plasma biomarkers have been correlated with pulmonary hypertension therapy in adults, but these biomarkers have not been validated in children. A 2010 article in the journal *Biomarkers* looked at biomarkers such as plasma concentration of matrix metalloproteinase-2 and other molecules. The researchers found a correlation between some biomarkers and response to therapy related to tissue remodeling.
- PVRI was correlated with three classes of drugs. It is unlikely that biomarkers that have not been validated can be used to change labeling.
- A recent publication suggests that endothelin-1 correlates with severity of pulmonary hypertension in congenital and diaphragmatic hernia.
- Dr. Nielsen identified two issues: (1) testing available drugs for approval in children and (2) finding biomarkers that can determine what drugs are appropriate treatments for diseases in children. The group needs to address both issues.
- Dr. Nielsen asked the group to suggest drugs that are well studied in adults but not in children.
- Dr. Greenberg said that neonatologists encounter pulmonary hypertension associated with meconium aspiration, congenital malformations, and bronchopulmonary dysplasia (BPD). Infants are frequently exposed to drugs, such as flolan, milrinone, and sildenafil, that have not been studied in neonates. The Prematurity and Respiratory Outcomes Program (PROP), supported by the National Heart, Lung, and Blood Institute, is studying drug exposure in

BPD to identify biomarkers that predict outcomes. The PROP has avoided pulmonary hypertension in association with BPD.

- Dr. Nielsen agreed that there is a lack of understanding about how these drugs work in neonates. The PROP may collect data that could be mined. Existing studies are collecting data on neonates, and the data could be used to examine efficacy and biomarkers.
- Dr. Berger noted that data are lacking for pulmonary hypertension in children who have a congenital heart disease repair, bone marrow or stem cell transplants, and chromosomal abnormalities or dysmorphic syndromes.

Epidemiology/prevalence:

- The group previously identified two issues: (1) the number of children who need long-term therapy and (2) the number of children whose pulmonary hypertension resolves with or without therapy.
- Dr. Berger noted that many issues surrounding pulmonary hypertension in premature infants are unknown. A data registry or a long-term, multicenter study would be important.
- Dr. Nielsen asked whether these issues should also be studied in older children. Dr. Berger said that long-term, multicenter data are lacking for all of the pediatric populations with pulmonary hypertension. Data have been collected in England, but the data are cross-sectional, not longitudinal.
- Dr. Nielsen suggested that studies of drugs to treat pulmonary hypertension in children could be built onto a long-term study.
- Dr. Pursley said that most unlabeled nitric oxide use is unrelated to pulmonary hypertension. Dr. Nielsen noted that a National Institutes of Health consensus meeting on the use of nitric oxide to prevent BPD found that there are no data on gender, race, and other characteristics that could be used to determine risk factors. Because BPD leads to pulmonary hypertension, the use of nitric oxide to prevent BPD is relevant to the group.

Outcomes—biomarkers of treatment effect:

- Dr. Retsch-Bogart suggested examining genetic factors related to drug allergies in cystic fibrosis. Beta-lactams, especially fluoroquinolones, are the main source of reactions. Dr. Retsch-Bogart identified cystic fibrosis as his area of interest and said he would discuss this issue with an allergist at his institution.

Drug safety studies:

- Dr. Nielsen noted that the group previously discussed drug safety studies related to pulmonary hypertension. More information is needed about drugs used in the neonatal intensive care unit (NICU).
- Dr. Severin said that medical countermeasures against exposures to chemical or biological agents should be studied in children. Strategic national stockpiles only have adult autoinjectors. Autoinjectors should be designed for children, and information about dosing, needle size, and safety is needed.

Formulations/drug delivery:

- Dr. Nielsen asked whether intravenous (IV) formulations were needed for drugs other than sildenafil.

- IV endothelin receptor antagonists are not yet approved for use in adults, but these drugs should be explored for use in the ICU or NICU setting.
- Aerosolized pulmonary vasodilators used to treat pulmonary hypertension have not been adequately studied in children. Dr. Benner said she would work on this area.
- More information is needed about aerosolized anti-inflammatory drugs used to treat interstitial lung disease.
- Dr. Retsch-Bogart said that high-efficiency nebulizers are being developed for new antibiotic formulations. Studies of dose and deposition in younger children are lacking.
- Dr. Nielsen added that some younger children do not willingly inhale medication. It is important to differentiate between younger and older children.

Novel agents:

- Dr. Nielsen noted that developing novel agents is much more expensive than targeting existing drugs for pediatric uses. In the category of novel agents, the group could consider new treatments that are being developed in adults and need testing in children.
- It was noted that nitric oxide never would have been approved in children based on adult data. Pulmonary hypertension may differ in children and adults, and some treatments should be tried in children very early on. Drugs that impair alveolarization could cause adverse effects in infants.
- Dr. Nielsen discussed novel agents that are being used to alter vascular development in the eye. An important part of BPD is vascular remodeling. Some of these ocular therapies could be evaluated for treatment of pulmonary hypertension.

Treatment alternatives:

- Dr. Retsch-Bogart noted that more anti-inflammatory therapies for cystic fibrosis are needed. Treatments for chronic obstructive pulmonary disease, such as phosphodiesterase-antagonists, might be applied to cystic fibrosis. Drs. Retsch-Bogart and Abman will discuss this issue.

Drug toxicities:

- Dr. Greenberg said that there is a need to understand the long-term toxicity of sildenafil.
- Dr. Nielsen added that information about the long-term use of albuterol in premature infants is also needed.
- Data about long-term toxicity are lacking for many drugs used to treat pulmonary hypertension and asthma.
- Dr. Retsch-Bogart added that drug tolerance and response may change over time.

Cross-cutting issues:

- The lung-blood interface, sickle cell disease, and bone marrow transplants were mentioned as possible cross-cutting issues.
- Even though patients with sickle cell disease may have elevated tricuspid regurgitant jets, they may not have cardiovascular disease. Dr. Nielsen said that this issue was related to the need for biomarkers for pulmonary hypertension.

The group discussed the feasibility of studying these issues. Dr. Nielsen noted that the discussion points spreadsheet includes a column for information about how to study each topic. The group can provide input and discuss the feasibility of studies during the next conference call.

Action Items:

- Dr. Nielsen asked Working Group members to identify their interest in one or more of three areas: pulmonary hypertension; cystic fibrosis; or asthma, allergic lung disease, and croup. Members should share their thoughts about these areas during the next conference call.
- Dr. Taylor-Zapata will e-mail participants about their areas of interest and a time for the next conference call.
- The next conference call will take place in September or early October.