

**Best Pharmaceuticals for Children Act (BPCA)  
Hematology Working Group Conference Call and Webcast  
July 1, 2011  
1:00 p.m.–1:50 p.m. ET**

**Participants**

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**Purpose**

The purpose of the call was to brainstorm ideas about therapeutic needs in pediatric hematology.

**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. More information is available at the following [FDA Web site](#).

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. During the 2010 outreach process, the NICHD received the following comments about the needs in pediatric hematology:

- The lack of dosing and safety data for therapeutics for pediatric thrombosis, including aspirin, low molecular weight (LMW) heparin, warfarin, and tissue plasminogen activator (tPA).

## **Open Forum**

The group discussed the following issues related to pediatric thrombosis:

- Thromboses are complicated by calcification and bone formation in blood vessels in postdialysis patients. The hematology and renal groups could work together on this cross-cutting issue.
- Heparin and other blood products (e.g., albumin, Plasmanate) are contaminated with aluminum and could be a problem for patients who receive them long-term. The FDA rule about aluminum contamination in parenteral nutrition solutions does not apply to biologics.
- Safely monitoring heparin is a major problem—particularly in younger children and children with multiple central lines.
- The priority list does not include a generation of drugs that includes direct Factor Xa inhibitors, direct thrombin inhibitors, and platelet therapeutics. There are almost no data on the use of these products in children. These products lack reversibility but have some advantages.

- Children with congenital heart defects are at the greatest risk for heparin-induced thrombocytopenia (HIT). Alternatives to heparin are needed when HIT is suspected. Alternatives are also needed for children with compromised renal function or hepatic failure.
- There have been some publications about age-based dosing of LMW heparin, but further study in a larger population is needed.
- Dosing recommendations for tPA vary widely.
- Researchers are looking for safe ways to reduce post-thrombotic syndrome.
- More information is needed about dosing based on age and developmental stage for older drugs such as heparin and warfarin.
- More information is needed about options to reverse anticoagulation in children who experience bleeding while on anticoagulants.
- The group should consider pharmacogenetic studies of warfarin and other agents in children.
- Aspirin may cause gastrointestinal complications. The group should decide whether to study low dose aspirin or buffered aspirin.
- In treating stroke in children, a major problem is whether to use aggressive anticoagulation. The adult literature cannot be translated to children because the mechanisms of disease are so different. Risk of bleeding is a concern in children.
- The International Pediatric Stroke Study is conducting observational studies but does not have much data about dosing and safety in children with strokes.
- It is not known whether children should receive tPA in the critical hours after a stroke. A large number of pediatric stroke patients have sickle cell disease, and there is no information on treatments other than transfusion.
- For children with congenital heart defects, there is debate about whether to treat a veno-occlusive thrombus in the catheterization laboratory or with low-dose tPA.
- There are more data for aspirin than for other antiplatelet agents. The group should not limit consideration to aspirin.
- Tranexamic acid is a new drug used to control bleeding. The drug is used in adult women, but there are no data in children. Because of concerns about renal failure with Amicar, clinicians are using tranexamic acid instead.

The group discussed the following additional issues:

- The group should consider whether arterial and venous clots are different diseases and should have separate recommendations.
- Arterial clots are not as common as venous clots, except in sickle cell disease. Data could first be collected on agents in the context of venous thrombosis. It would be reasonable to look at antiplatelet agents and tPA in the context of arterial disease.
- An article from the BPCA hydroxyurea study was recently published in *The Lancet*. A long-term follow-up study is ongoing. Manuscripts from hydroxyurea studies in older children will be published in the near future, and additional studies are starting. It is hoped that the research will lead to a label change.
- Erythropoietin was nominated for use in renal patients, and the renal working group will consider it. Erythropoietin was also nominated for use in neonates for hypoxic-ischemic encephalopathy, but there is no indication for that use.
- Children who receive long-term parenteral nutrition can only get iron intramuscularly or intravenously, which increases the number of times the central line is opened and increases

the risk of sepsis. An iron compound that could be mixed with parenteral solution would be safer.

**Next Steps:**

- Dr. Taylor-Zapata will send the article from the BPCA hydroxyurea study to the group.
- The next conference call will be scheduled in 4 to 6 weeks.