

**Best Pharmaceuticals for Children Act  
Annual Prioritization Meeting  
November 9–10, 2010  
Hilton Washington DC/Rockville Hotel and Executive Meeting Center  
Rockville, MD**

This meeting was sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (HHS) in support of the Best Pharmaceuticals for Children Act (BPCA) Program. The purpose of the meeting was to prioritize topics of study for pediatric therapeutic areas based on recommendations from experts in pediatric medicine and research.

The anticipated meeting outcomes were as follows:

- Provide BPCA study updates
- Review the prioritization process
- Refine the list of drugs for further study under the BPCA Program
- Assist the NICHD in identifying a future research agenda for the BPCA Program.

## **Day 1**

### **Welcome**

*Perdita Taylor-Zapata, M.D., Medical Officer, OPPB, CRMC, NICHD, NIH*

Dr. Taylor-Zapata welcomed the participants and thanked them and all BPCA stakeholders. She noted that the BPCA annual meetings are held to fulfill the legislative mandate to solicit input from pediatric experts to determine the needs in pediatric therapeutics. The field of pediatric therapeutics involves dosing and formulations for a broad age range of children. She briefly reviewed the federal legislation to improve the effectiveness and safety of medicines used in children, including BPCA. The 2002 BPCA legislation directed (1) the U.S. Food and Drug Administration (FDA) to encourage the pharmaceutical industry to perform pediatric studies to improve labeling for on-patent drug products used in children in exchange for an additional 6 months of patent exclusivity and (2) the NIH to sponsor needed studies of important off-patent drug products in cases where the pharmaceutical company (likely a generic manufacturer) would decline to perform the studies. The Food and Drug Administration Amendments Act (FDAAA) of 2007 reauthorized the 2002 BPCA and mandated that the NIH:

- Develop and publish a priority list of needs in pediatric therapeutics every 3 years, including drugs or indications that require further study
- Consider available information when deciding what studies to conduct
- Award funds to entities that have the expertise to conduct pediatric clinical trials or other research through multiple funding mechanisms
- Issue Proposed Pediatric Study Requests (PPSRs)
- Conduct a feasibility study on the compilation of information on drugs (formulary) for pediatric use.

Currently, 20 NIH Institutes and Centers contribute to BPCA's annual funding of \$25 million for clinical trials and required training.

The goal of BPCA's initial implementation was to fund studies of off-patent drugs that needed labeling changes. In the implementation, many issues were uncovered. For example, there may be no pharmacokinetics (PK) data for a drug that has been in use for decades. Some drugs and indications lacked necessary outcome measures. In response to such issues, the BPCA Program has recognized the need to evolve. During this day-and-a-half meeting, the participants discussed the evolution and future directions of the BPCA Program

## **BPCA Overviews**

### **Overview of Ongoing BPCA-Sponsored Projects**

*Anne Zajicek, M.D., Pharm.D., Acting Branch Chief, OPPB, CRMC, NICHD, NIH*

Dr. Zajicek presented an overview of the status of BPCA clinical trials and provided an update on labeling changes. She described BPCA training initiatives and the clinical trials infrastructure, and introduced the Pediatric Trials Network (PTN).

Under the 2002 legislation, the focus of the BPCA Program was to develop a master list of all off-patent drugs that lacked adequate pediatric labeling. The Program developed, prioritized, and published an annual list of these drugs. Under the 2007 legislation, the focus of the BPCA program shifted to therapeutic areas, with the goal of developing, prioritizing, and publishing an annual list of therapeutic gaps and specific pediatric needs. The BPCA process involves five steps: prioritizing therapeutic areas, issuing Written Requests (WRs) and PPSRs, conducting clinical trials, submitting data to the FDA, and changing labels of pediatric drugs. Publications are an additional Program outcome.

Dr. Zajicek reviewed the following BPCA clinical trials:

- Lorazepam for sedation
  - Purpose: safety, efficacy, and PK/pharmacodynamics (PD) study in children on mechanical ventilation in the intensive care unit
  - Design: comparison of lorazepam intermittent bolus versus lorazepam continuous infusion versus midazolam continuous infusion
  - Status: study completed; Clinical Study Report to be submitted to the FDA in the next month
- Lorazepam for status epilepticus
  - Purpose: safety, efficacy, and PK study of lorazepam in children with status epilepticus
  - Design: comparison of lorazepam and diazepam in children with status epilepticus in the emergency room; granted Exception from Informed Consent; conducted in the United States and Canada
  - Status: PK study Clinical Study Report submitted to the FDA; ongoing recruitment for the clinical trial

- Nitroprusside
  - Purpose: Study of blood pressure lowering effect of nitroprusside in children requiring blood pressure reduction
  - Status: blinded dose–response study completed; recruitment almost completed for longer term nitroprusside tachyphylaxis study
- Baclofen
  - Purpose: safety and PK/PD study of oral baclofen to reduce spasticity in children with cerebral palsy
  - Status: chart review completed; PK/PD study recruitment completed
- Lithium
  - Purpose: safety, efficacy, and PK study of lithium in children with bipolar illness
  - Status: PK study Clinical Study Report submitted to the FDA; recruitment ongoing for efficacy/safety study
- Meropenem
  - Purpose: safety, efficacy, and PK study of meropenem in neonates with suspected or confirmed abdominal infections
  - Status: recruitment completed; data analysis ongoing; Clinical Study Report to be submitted to the FDA in next month
- Hydroxyurea
  - Purpose: a National Heart, Lung, and Blood Institute (NHLBI) study (Baby HUG) of efficacy, safety, and PK of hydroxyurea in young children (ages 9–15 months) with sickle cell disease
  - Status: study unblinded in January 2010
- Dopamine
  - Purpose: to determine feasibility of a larger scale efficacy/safety trial of dopamine to treat hypotension in neonates; BPCA cofunding with Neonatal Research Network
  - Status: recruitment ongoing
- Oncology studies
  - Vincristine (VCR): studies to evaluate neurotoxicity and PK in children (National Cancer Institute–Children’s Oncology Group [NCI–COG])
  - Actinomycin-D (AMD): studies to evaluate incidence of hepatotoxicity/veno-occlusive disease and PK in children (NCI–COG)
    - Study 1: data extraction of National Wilms Tumor Study database for toxicity (completed)
    - Study 2: catheter-clearing experiments (completed)
    - Study 3: PK modeling of published VCR/AMD data to design prospective PK study (completed)
    - Study 4: Prospective PK study (recruitment ongoing)
  - Methotrexate: clinical studies to evaluate neurocognitive outcomes of pediatric patients with high-risk acute lymphoblastic leukemia (NCI–COG); relationship of neurocognitive testing to diffusion tensor imaging/magnetic resonance imaging (MRI); longitudinal and cross-sectional study
  - Daunomycin: disposition and response in relation to body mass index (BMI); recruitment completed; ongoing data analysis

- Isotretinoin: began with discussions with the Pediatric Subcommittee of the Oncologic Drug Advisory Committee concerning labeling for neuroblastoma (new indication) and new formulation; PPSR submitted; WR issued by the FDA, declined by industry, and received by the NIH; primary data received from the COG; Clinical Trials Agreement for formulation in review.

Clinical Study Reports will be submitted to the FDA from late 2010 to mid 2011 for the following studies:

- Meropenem
- Lorazepam for sedation
- Baclofen PK/PD
- Nitroprusside dose-response study
- Hydroxyurea
- Daunomycin.

The BPCA Program has achieved labeling changes for piperacillin/tazobactam (listed in 2004), pralidoxime (listed in 2006), and propylthiouracil. On September 9, 2010, the FDA approved the pediatric use of pralidoxime to treat poisoning by organophosphate pesticides and chemicals (for example, nerve agents). On June 4, 2010, the FDA issued a “Dear Doctor” letter notifying healthcare professionals of the risk of serious liver injury, including liver failure and death, with the use of propylthiouracil in adult and pediatric patients being treated for Graves’ disease. On June 21, 2010, the FDA issued a black box warning for propylthiouracil.

The scientific results of BPCA clinical trials include 18 publications, 4 papers submitted for publication, and 26 abstracts. Dr. Zajicek reviewed selected publications for the following studies:

- Lorazepam for status epilepticus
- Lithium
- Hydroxyurea
- VCR/AMD.

The BPCA Program is working with the Prematurity and Respiratory Outcomes Network’s neonatology data collection and the Collaborative Pediatric Critical Care Network’s asthma data collection to inform clinical trial design. The BPCA Program is also working with the Clinical and Translational Science Awards (CTSAs) concerning the needs for standardized outcome measures to inform clinical trials design. The areas of interest are neonatology, cardiovascular medicine, neurology, and asthma.

The BPCA Program is developing infrastructure for clinical pharmacology training and clinical trials, including study design, patient recruitment, data analysis, and formulations. Recognizing the need for infrastructure for all aspects of pediatric clinical trials performance, the BPCA Program awarded a task order to Duke University in September 2010 to establish the PTN. The PTN’s core areas include management, clinical trials performance, formulations development for clinical trials, clinical pharmacology study design and analysis, and device development (validation). Potential therapeutic areas for the PTN include cardiovascular diseases, infectious

diseases, respiratory diseases, gastroenterology, pediatric oncology, and neonatology. Another infrastructure initiative is the NIH–FDA formulation platform to develop an open-source, technically feasible platform based on chemical structure, to produce orally dissolvable solid dosage forms that are stable at high temperatures/humidity, taste-masked, with good oral absorption, in suitable dosage increments, and with minimal excipients.

BPCA Program plans for at least the next year include the following:

- New clinical trials under the PTN
- Use of the formulations platform to provide open-source information to manufacturers
- Meeting with CTSA sites on outcome measures grants
- Synthesis and analysis of current BPCA clinical trials data.

### **The FDA’s Approach to Development of Pediatric Therapeutics**

*Mary Dianne Murphy, M.D., F.A.A.P., Director, Office of Pediatric Therapeutics (OPT), Office of Special Medical Programs, Office of the Commissioner, FDA*

Dr. Murphy reviewed the U.S. regulatory processes for adult drug product development and pediatric drug development. The regulatory standard for approving and labeling a new drug product is adequate and well-controlled clinical trials. Adult drug product development is driven by the pharmaceutical industry. Since 1997, pediatric drug development has been driven by the federal government through an incentive process. Through the BPCA Program, the FDA and the NIH are collaborating to update pediatric labeling for off-patent drugs. FDAAA provided more flexibility to shift focus from off-patent drugs to identifying therapeutic areas.

Dr. Murphy reviewed the international impact of pediatric drug development. European Union law requires any adult drug application for exclusivity through a “centralized” process to have an approved Pediatric Investigational Plan (PIP). An application for an adult drug cannot be filed without a PIP. The PIP must be approved by the Pediatric Committee or the exclusivity incentive will not be given. The goal of this approach is appropriate pediatric labeling.

In collaboration, the FDA, the American Academy of Pediatrics, and the European Union have sought pediatric clinical trials of the same caliber as those required for adults for products being used in children. These product development trials should result in new pediatric labeling information. Including PK or PK/PD information without an assessment of efficacy and safety is not usually an acceptable regulatory approach. Exposing children to trials that are not going to provide the potential for direct benefit may not be ethical.

With regard to science and product development, much has been accomplished but much remains to be done. Impediments include not having fundamental knowledge of how children react differently and development of pediatric validated endpoints. There are many other programs to develop fundamental science questions but only one program to develop the knowledge for products being used in children every day. The goal of BPCA and Pediatric Research Equity Act (PREA) remains labeling knowledge, which is the metric for this public health program.

In deciding whether a drug product should be studied in a pediatric population (that is, issuing a WR or requiring pediatric studies), the FDA considers several factors:

- Public health benefit
- Appropriate risk/benefit, including ethical considerations
- Types of information needed, including replication of efficacy
- Age groups needed to obtain the information
- The types of studies needed to obtain the information—the studies have to be able to address efficacy, dosing, and safety issues.

Extrapolation allows the use of prior information to maximize the efficiency of pediatric trials from both scientific and ethical perspectives. Extrapolation begins by answering the following questions:

- What adult data exist?
  - Is the product already approved for use in adults for any indication?
  - Is the product approved for use in adults for the same indication of interest in children or a “similar” indication?
  - Were adolescents included in any of the above studies?
  - Are the PK/PD pathways similar between adults and children?
- What pediatric data exist?
  - How many pediatric subgroups have been studied?
  - Are there known developmental differences in the expression of the disease over ages?
  - Are there known developmental differences in PK?

Key extrapolation issues involve the existing certainty of (1) the similarity of the disease between adults and children and (2) the similarity of expected response to therapy between adults and children. There is an ethical mandate to minimize “unnecessary” exposure of the pediatric population to study risks. To maximize information, fundamental questions should be answered:

- Is this product safe and effective in children?
- Do validated pediatric endpoints exist?
- Does information exist on PK changes that occur over developmental stages?

When the course of the disease and the response to therapy are “sufficiently similar” in adults and in children, the efficacy in all pediatric populations does not have to be re-proved, provided the efficacy from adults or older pediatric population is from adequate and well-controlled trials.

When extrapolation has been successful, new pediatric labeling occurred about 80 percent of the time. When insufficient knowledge required two adequate and well-controlled trials in order to extrapolate, new pediatric labeling occurred only about 25 percent of the time.

The FDA has reviewed submitted studies between 1988 and 2008 in response to WRs. Six review divisions involving 72 percent of the WRs participated, and 102 products were evaluated. Approaches to extrapolation changed over time for 28 percent of the indications.

Between the end of 1997 and October 2010, as a result of BPCA and PREA studies, new pediatric labeling information was added for 396 products. Efficacy was not established in 72

products, new or enhanced safety information was added for 74 products, specific dosing changes/adjustments were made for 33 products, and age was expanded for 301 products.

The FDA and European legislation are driving pediatric product development on a global scale. The FDA and the European Medicines Agency have been convening monthly pediatric teleconferences to discuss PIPs and other issues. Between August 2007 and October 2010, 935 PIPs were approved. European legislation has mandated a pediatric clinical trials network and is likely going to drive future pediatric product development. Not all FDA studies are being conducted in the United States. Currently, more than 700 pediatric studies have been submitted for more than 300 products. Trials for pediatric product development have different and additional responsibilities.

With regard to the future, science will continue to better define how children are different, when those differences are maximal in their expression, and when the physiology and responses can be considered “sufficiently similar.” Even with this knowledge, it will not inform scientists about pediatric safety profiles. Long-term safety studies and neonatal studies continue to be extremely difficult issues. Considerable taxpayer money is being invested in the BPCA Program, and completing the Program’s work is a collective responsibility.

## **BPCA Updates**

### **Pediatric PK: Lithium, Baclofen, and Hydroxyurea**

*William Jusko, Ph.D., Professor and Chairman of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo*

Dr. Jusko reviewed the nearly completed analysis of single-dose PK of lithium, provided an interim report on data collected for PK/PD of baclofen, and presented some data on the hydroxyurea PK study.

**Lithium.** The purpose of the BPCA-funded Collaborative Lithium Trials (CoLT) is to (1) design long-term PK, safety, and efficacy studies of lithium in children and (2) develop optimized multiple dosage regimens from simulation models and empirical methods. The first phase of CoLT was a single-dose PK study. Lithium has been a standard treatment of bipolar disorder I (BP-I) in adults for almost 60 years. Lithium is not labeled for use in children and adolescents, and there is a paucity of information about PK, safety, and efficacy of lithium in children. Numerous adult studies of single-dose PK of lithium have been published. Only one study of single-dose lithium PK in children has been published (Vitiello et al., 1988). This study had nine subjects with a median age of 10.7 years (range 9.9–12.3 years) and a median body weight of 33 kg (range 27–56 kg). When not corrected for body size, the PK parameters for children are about the same as those in adults, with about the same clearance, volume, and half-life.

The study design for the CoLT single-dose PK analysis of lithium was as follows:

- Medically healthy outpatient youths (age 7–17 years)
- Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for BP-I in current manic or mixed state without active psychotic symptoms

- Score on Young Mania Rating Scale  $\geq 20$
- Random assignment to 600 mg or 900 mg single dose
- 8-hour fast before the dose
- Sampling: predose, 0.5, 1, 1.5, 2, 4, 8, 12, 24 hours and 48 or 72 hours.

Data were collected from 20 children (mean age of 9.9 years) and 19 adolescents (mean age of 14.0 years). There were approximately equal numbers of males and females. The predominate race was White. About half of the subjects received the 600 mg dose, and half received the 900 mg dose. The study used a population PK approach, with covariates of body size, age, sex, sexual maturation, and renal function. The major factor accounting for variability and differences in the PK profiles was body size, as determined by fat-free mass (FFM).

The conclusions for the CoLT single-dose PK analysis of lithium are as follows:

- Linear elimination was found for lithium over the studied dose range.
- FFM was identified as the most appropriate pediatric body size covariate.
- Difference in body size explains different PK parameters in children and adults.
- Pediatric patients in this study had lower weight-adjusted clearance or higher bioavailability than children from the Vitiello et al. study.
- The proposed starting dosage regimens for long-term study were shown to be safe by modeling.

**Baclofen.** The objectives of the baclofen efficacy and safety trials are as follows:

- Determine PK parameters of oral baclofen in children with spasticity associated with cerebral palsy
- Describe the relationship between plasma concentrations of oral baclofen and clinical measures of spasticity
- Determine optimal dosing range and interval for administration of oral baclofen for use in a randomized clinical trial of safety and efficacy.

Recruitment goal for the study is 70 subjects, with an age range of 2–16 years. Interim PK results (as of July 2010) are based on 22 subjects (11 males, 11 females; body weight 13.6–66.2 kg; age range 4.3–17.8 years). Dosing was as follows: 1 subject, 5 mg; 7 subjects, 10 mg; 2 subjects, 15 mg; and 12 subjects, 20 mg. Baclofen enantiomers were compared. Interim PK results are summarized as follows:

- R- and S-baclofen enantiomers exhibit identical absorption and disposition.
- Children with cerebral palsy exhibit moderate variability in PK.
- Protein binding was nil.
- PK is linear with dose.

Future work includes completion of the study with 70 subjects, population PK assessment to evaluate role of secondary factors in PK (for example, age and sex), and PK/PD assessments.

**Hydroxyurea.** PK studies have been completed for 265 subjects. Studies were conducted on two occasions. For the 142 subjects studied on Occasion I, the mean age was 14.3 months (range 9.3–19.6 months) and the mean weight was 10.1 kg (range 7.3–13.7 kg). For the 123 subjects studied



on Occasion II, the mean age was 38.2 months (range 33.6–42.8 months) and the mean body weight was 14.3 kg (range 11.0–18.5 kg). The hydroxyurea PK was more variable on Occasion II.

**Summary.** A wealth of excellent PK data has been obtained in pediatric studies with lithium, baclofen, and hydroxyurea. State-of-the-art population PK assessments have been or will be enacted for these drugs. PK/PD correlations will be sought.

### **BPCA PK/PD Experiences: Sodium Nitroprusside (SNP) and Oncology Studies with VCR and AMD**

*Jeffrey S. Barrett, Ph.D., F.C.P., Research Associate Professor, Division of Clinical Pharmacology and Therapeutics, Department of Pediatrics, University of Pennsylvania Medical School, Children's Hospital of Philadelphia*

**SNP.** The SNP study was initiated from a request from the BPCA Program to describe the dose–response relationship for SNP and to determine whether there is tolerance to the hypotensive effect. In response to the request, two studies were proposed: a dose-ranging study and long-term infusion study. The goal of the study was to develop a model of the SNP dose–response relationship. The dose-ranging study has been completed. The long-term infusion study is ongoing. Studying SNP has been challenging due to its undefined PK/PD relationship and its unsuitability for *in vivo* assays.

SNP metabolism involves four compounds: hydrogen cyanide, cyanide, thiocyanate, and thiosulfate. Study challenges included the lack of methodologic approaches and the instability of the compounds. A schema was proposed for the PK characterization of SNP, cyanide, and thiocyanate. The design schema had four phases: prestudy, blinded infusion with a broad dose range (0.3–3.0 mg/kg/minute), open treatment (essentially an effect control trial), and follow-up. A mean arterial pressure (MAP) target was assigned when the subject moved into the open treatment phase, and the SNP dose was titrated to achieve the target MAP.

The open treatment phase (OTP) generated a 2.3 megabyte (MB) dataset; the full OTP and blood pressure dataset is about 13 MB. The full dataset contains about 54,000 records.

A kinetic-pharmacodynamic (K-PD) conceptual model was used to characterize the elements of control and develop the model for the SNP dose–response relationship. The model is very predictive given the variability in the data; the variability was reasonable. The model can be used in a prospective manner. The clinical plausibility of the model is currently being investigated.

The milestones of the SNP study are as follows:

- First K-PD model to describe hemodynamic response in children (label)
- Thorough examination of physiologic plausibility of dosing, hemodynamic response, and covariate interaction
- Derivation of dosing considerations for infusion under the conditions of controlled hypotension (blinding considerations).

Additional learning from the SNP study included:

- New pharmacometric approaches to define management of patient hemodynamic response
- Methods for describing and identifying dosing patterns
- Understanding caregiver learning with respect to dose titration
- Training/educating young investigators.

**VCR/AMD.** The VCR/AMD study was initiated to answer the following questions for the BPCA Program:

- What is the incidence of toxicity in children?
- What are the toxicities and is there a relationship to dose, diagnosis, age, and/or body weight?
- Is there a relationship between systemic exposure and efficacy/toxicity?

Four projects were designed to answer these questions:

- Project 1, retrospective study: data mining of pooled historical data from Wilms tumor and rhabdomyosarcoma studies from 1986 to 2002 to define dose–toxicity relationships
- Project 2, catheter study: develop a methodology for dosing and PK sampling procedure using a single central venous catheter
- Project 3, modeling and simulation study: develop PK/PD models based on exposure–response relationships that incorporate physiologic-based and mechanistic expression
- Project 4, prospective study: PK/PD/outcome trial in children with cancer.

The milestones for the VCR/AMD study are as follows:

- A rigorous evaluation of historical dose–toxicity relationship across age/size indices
- Catheter clearing procedure for AMD and VCR so that dosing/sampling can occur from a single central venous catheter
- First simulation-based COG PK trial enrolling patients younger than 1 year of age in a nonstaggered design.

Additional learning from the VCR/AMD study included:

- Generalizable procedures for the *in vitro* evaluation of catheter clearance
- Clinical methodology for the *in vivo* evaluation of the catheter clearing procedure
- Model-based correction of catheter contamination and methodology for reporting accurate PK results.

### **Pediatric Hydroxyurea Phase III Clinical Trial**

*Jonathan Goldsmith, M.D., Project Officer, Division of Blood Diseases and Resources, NHLBI, NIH*

The Baby HUG study began in 2000 as a randomized double-blind placebo-controlled trial conducted in young children to test the hypothesis that hydroxyurea can prevent the onset of chronic end-organ damage in children recruited before 2 years of age. Pulmonary, renal, splenic, and brain function, as well developmental milestones, were studied as surrogate end markers of end-organ damage in Baby HUG Phase I. In 2008, Follow-up Study I began.

Phase III was a double-blind placebo-controlled trial to determine whether hydroxyurea treatment is safe, protects spleen and kidney function, and improves clinical and laboratory findings. The trial was conducted at 14 clinical sites. The first subject was randomized in October 2003, and the last was randomized September 2007. The study enrolled 193 subjects with a mean age of 13.6 months (range 9–17 months). The subjects received liquid hydroxyurea 20 mg/kg/day or placebo for 2 years. Of these subjects, 96 percent had sickle cell disease (HbSS).

Liquid hydroxyurea and placebo formulations were developed for the study. Formal stability and sterility programs were developed and conducted for each production lot.

Results of the interventional study showed that the coprimary spleen and renal endpoints were not achieved. However, secondary endpoints demonstrated highly significant benefits of hydroxyurea intervention. For the secondary endpoints, there were markedly reduced vaso-occlusive events—including pain, dactylitis, and acute chest syndrome—and improved hematologic counts—including hemoglobin, mean corpuscular volume, hemoglobin F (HbF), and reticulocytes. Safety endpoints included modest transient cytopenias.

Follow-up Study II for Phase III is projected to begin January 2012. This study is 5-year continued structured follow-up of consenting study subjects through the first decade of life. Study objectives are to:

- Characterize long-term toxicities and unexpected risks (if any) associated with hydroxyurea treatment at an early age
- Determine whether there are clinical benefits from the hydroxyurea treatment
- Document any alterations in the natural history of sickle cell disease associated with early hydroxyurea therapy.

Follow-up Study II will include enhanced neuropsychological, brain, cardiac, and pulmonary evaluations and continuing renal and spleen/liver monitoring. All children enrolled will be followed to a common termination date of December 31, 2016. Results will improve understanding of the natural history of sickle cell disease in young children and in a cohort receiving hydroxyurea. If hydroxyurea limits organ damage, the standard of care for children with sickle cell disease will be permanently altered.

**Questions and Discussion.** The following questions were asked and discussed:

- Have spleen and kidney scans been validated in children as outcomes? Have spleen and kidney scans been validated in the presence of hydroxyurea? Does hydroxyurea, which has some interesting binding and intracellular effects, have effects on the primary endpoints?

- There is little evidence on the validity of the scans. They may not be valid. Because of the importance of renal and splenic function, the scans were selected at the beginning of the study as a method to measure end-organ damage. If the clinical outcomes are valid and the scans are not, the clinical and economic impact should not be discounted. What are the neuropsychological and brain evaluations for Follow-up Study II?
  - These evaluations have not been specified in the Statement of Work for the contract. However, the study would be interested in MRI/magnetic resonance angiography of the brain, transcranial Doppler flow studies, and a battery of neuropsychological tests.
- How was compliance measured during the sustained treatment?
  - Compliance was assessed by returning the bottles of hydroxyurea liquid formulation, and a pharmacist determined the residual volumes. A substudy of compliance with penicillin based on urinalysis showed that the compliance rate was about 60 percent. The hydroxyurea compliance rate was about 80 percent.

### **Multiple Dose PK Study of Meropenem in Young Infants (<91 Days) with Suspected or Complicated Intra-Abdominal Infection**

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*Philip Brian Smith, M.D., M.H.S., M.P.H., Associate Professor, Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Duke University Medical Center, DCRI*

*Matthew M. Laughon, M.D., M.P.H., Assistant Professor, Division of Neonatal-Perinatal Medicine, Department of Pediatrics, University of North Carolina at Chapel Hill*

**Background.** Meropenem is a broad spectrum antibiotic. It is used to treat multidrug-resistant pathogens. The drug is useful as presumptive therapy in intra-abdominal infections. It is FDA-labeled for pediatric patients older than 3 months of age for meningitis and complicated intra-abdominal infections. There is substantial off-label use of meropenem in neonates. Seizure rates for meropenem are similar to active control arms in meningitis studies.

**Study Design.** The meropenem study was a multicenter, open-label study. It included four gestational age (GA)/postnatal age (PNA) groups and two blood sampling strategies. Assessments were population PK with sparse sampling, safety (adverse events [AEs], serious adverse events [SAEs], and clinical lab values), and efficacy/clinical response (alive, negative cultures, and presumptive clinical cure score). PK samples were collected once before and three times after first dose, and once before and twice after the steady-state dose. Safety/steady-state samples were collected once before and twice after steady-state dose. Dosing was as follows:

- Infants <32 weeks GA
  - <2 weeks PNA—20 mg/kg every 12 hours
  - ≥2 weeks PNA—20 mg/kg every 8 hours
- Infants ≥32 weeks GA
  - <2 weeks PNA—20 mg/kg every 8 hours
  - ≥2 weeks PNA—30 mg/kg every 8 hours.

**Study Results.** Summary PK, safety, and efficacy results are as follows:

- PK
  - 96 percent achieved the PD target for meropenem concentrations > 4 µg/mL for 50 percent of the dose interval.
  - 92 percent achieved the PD target for meropenem concentrations > 2 µg/mL for 75 percent of the dose interval.
  - Dosing strategy met the overall goals for exposure.
- Safety
  - 99/200 (50 percent) infants had an AE.
    - Highest: 26/39 (66.7 percent) among infants <32 weeks GA and <14 days PNA
  - 21/200 (11 percent) infants had an AE possibly related to meropenem.
    - Highest: 7/39 (17.9 percent) among infants <32 weeks GA and <14 days PNA
  - 30/316 (9 percent) of AEs were possibly related to meropenem.
  - No AEs were probably or definitely related to meropenem.
- Efficacy
  - 200 infants were enrolled in the trial.
    - 192 were evaluable for efficacy; 3 were missing components for efficacy score; there were 5 early terminations.
  - Mortality prior to efficacy assessment was 8/192 (4 percent).
    - Highest mortality (3/39 or 8 percent) was among infants <32 weeks GA and <14 days PNA.
  - Efficacy was achieved in 162/192 (84 percent) of the infants.
  - Lowest efficacy (29/39 or 74 percent) was among infants <32 weeks GA and <14 days PNA.

**Dissemination Plan.** A study follow-up will assess whether meropenem dosing changes clinical practice due the study results. The assessment began with an examination of the Pediatrix Clinical Data Warehouse to determine past practice patterns. Pediatrix is a private consortium of neonatal units that takes care of about 25 percent of the infants admitted to neonatal intensive care units (NICUs) in the United States. The records of about 630,000 infants who were discharged from 1997 to 2009 were examined. About 3,000 of the infants were treated with meropenem, with an increase in use over time. In 2009, about 600 of 7,800 infants were treated with meropenem. A majority of the infants received a total of 40 mg/kg/day. Other doses were 60, 80, and 100 mg/kg/day. Most of the infants were dosed twice a day. In addition to the Pediatrix data, the study follow-up will gather data from a meropenem use provider survey to determine current practice. The survey data will include patient prescribing pattern, dose, patient descriptions, and dosing information sources. After the meropenem study results are published, providers will be surveyed 1 year later to assess changes in dosing practice. Dissemination of study results will target national organizations, dosing guidelines, quality improvement networks, conferences, industry, and social media.

**Questions, Comments, and Discussion.** Comments, questions, and discussion topics were as follows:

- Most neonatal units have specific dosing guidelines based on Neofax. If the data are compelling enough, Neofax would be a good place to start with disseminating the new meropenem dosing.
  - There is a verbal agreement with Neofax to update the meropenem dosing guidelines based on study results.
- There is a concern that meropenem may be overused as a result of changes in dosing guidelines. The guidelines should caution that meropenem may not be appropriate for every baby with intra-abdominal infection, given the emerging resistance patterns..
  - The study was concerned about the actual use of broadly acting agents in the emerging resistance patterns. The purpose of the study was to provide good data on one broadly acting drug in the neonatal unit as a last resort.
  - The trial design was modified to be broader than the original WR. The modified trial design improved the enrollment rate.
  - Administration strategies for intravenous infusion and clinical indications are being modeled.
- What is the generalizability of the Pediatrix data warehouse?
  - The data warehouse contains electronic records used primarily for billing. Pediatrix provides 20–25 percent of all the hospitalized critical care for newborns in North America. The study has an agreement with Pediatrix to provide immediate feedback on dosing. The study is working with Pediatrix to ascertain the accuracy of the data.
- Question about the meropenem formulation?
  - The meropenem formulation was a commercial product.

### **General Questions, Comments, and Discussion of the Morning Presentations**

General questions, comments, and discussion topics were as follows:

- Given inpatient variability of certain drugs, what is the need for concentration control trials to guide individual dose?
  - Inpatient variability is to be expected. With normal subjects and no marked pharmacogenetic factor in the disposition of the drug, typical variability is about 30 percent. When any type of additional variable is introduced, the variability is bound to increase. It may be important to introduce therapeutic monitoring for controlling therapy with certain drugs. With regard to the need for concentration control trials versus effect control trials, there is role for both approaches for particular drugs. Determining the appropriateness would depend on the specific agent and circumstances.
- For a pediatric drug without a well-defined outcome measure, where drug concentration is the only thing that can be controlled, should concentration control trials be required?
  - Without having some assessment of concentration during a study, it is challenging to determine why there is a lack of effect. Knowing concentration provides a baseline for the study.
- With regard to baclofen, what is the effect of dietary intake of certain foods (for example those containing lipids or heavy fats), fasting, or time of administration after a meal?

- The baclofen study had explicit conditions for drug administration and patient assessments, and the study was tightly controlled. The patients fasted before baclofen administration. There is the potential for other factors to affect drug absorption and bioavailability.
- Given the variability among children (for example, body weight), PK studies with fixed-dose designs may not be an appropriate approach for establishing exposure–response relationships. Using a range of drug doses/exposures may be a more appropriate approach.
- Are there contingency plans for the sunseting of BPCA and PREA?
  - At this time, there are no contingency plans. The OPPB and the FDA are currently focusing on the continuing implementation of the BPCA Program and raising awareness of the Program’s success so far. The sunseting of BCPA and PREA has the potential to negatively impact pediatric drug studies and relabeling efforts.
- What are the consequences of the topics that are chosen for study in the BPCA Program?
  - The BPCA Program made decisions about frequency versus severity of pediatric disorders and conditions. Severity was chosen because of existing infrastructure to study those conditions. What is missing are data on primary care practice, primarily because of the lack of infrastructure to collect these data. There has been some focus on nonsevere pediatric conditions such as the use of selective serotonin reuptake inhibitors, attention deficit/hyperactivity disorder, and infectious diseases. There have been studies on these conditions.
- Neonatal studies remain a critical issue/concern.

## **Prioritization Overview**

### **The Evolution of the BPCA Prioritization Process**

*Perdita Taylor-Zapata, M.D., Medical Officer, OPPB, CRMC, NICHD, NIH*

The BPCA process involves five steps: prioritization, WR/PPSR, clinical trial, data submission to the FDA, and label change. Dr. Taylor-Zapata reviewed the history of the prioritization process.

- The BPCA requires that the NIH identify the drugs of highest priority for study in pediatric populations. Initially, in June 2002, a drug prioritization process was established that attempted to rank each off-patent drug on the “candidate list” by considering use and potential public health benefit and by combining this information with expert opinion and public discussion.
- The initial experience with the early prioritization process showed that much more information was needed about the frequency of medications used in children, about the current practice of medications used in children, both on- and off-patent drugs, and the actual conditions for which the medications were being used in the United States.
- The “master list” of pediatric drugs for study originated from original Food and Drug Administration Modernization Act list published in May 1998. The list included all 428 approved drugs—defined as a drug that is approved for use in adults for indications that occur in the pediatric population. The list included on-patent as well as off-patent drugs. In July 2002, the FDA updated the list of off-patent drugs used in pediatric patients and named 246 off-patent drugs used in pediatric patients. The first BPCA list was published in the

*Federal Register* in January 2003; 12 drugs were listed. In August 2003, 8 additional drugs were listed, and in February 2004, 5 more were listed. The master list was updated in April 2004 and included 179 drugs used in pediatric patients. A new process for listing preliminary drugs for consideration was implemented in August 2004. In a January 2005 *Federal Register* notice, drugs were listed for multiple avenues of study:

- 9 drugs were listed for further clinical study (2 on-patent drugs).
  - 1 drug was listed for relabeling based on the literature.
  - 4 drugs were listed for systemic literature review (1 on-patent drug).
- After review of the BPCA listing process, and after the results of outreach to experts in 2005, the NIH in consultation with the FDA modified the prioritization process to a condition-based or therapeutic class-based approach for 2006–2007. Also during this time, the BPCA Program determined that the master list of off-patent drugs was difficult to develop because of fluctuating patent status of many drugs, and the master list was abandoned. An April 2006 *Federal Register* notice listed for the first time specific drugs and therapeutic areas of interest. A second list was published in March 2007. In 2007, the BPCA was reauthorized, and it was determined that the needs in pediatric therapeutics would be listed every 3 years. The reauthorization also provided the NIH with a more proactive role in developing PPSRs. As of the September 2009 priority list, 79 drugs and 34 therapeutic areas have been identified as BPCA priorities.
  - The BPCA prioritization process was developed in response to the legislative mandate and recently refined to identify gaps in pediatric therapeutics—primarily off-patent drugs—that need further study through clinical trials or other avenues of research.
  - Several lessons have been learned over the past several years. In developing a priority list, the BPCA Program needs more up-front input to gather information on preliminary drugs (for example, information on frequency of use and frequency of condition) as well as expert input. A better approach is needed for mass outreach input. The BPCA Program needs to enhance NIH interagency collaborations. For the drug list determination, the prioritization process needs to be clarified.
  - For this year, the NIH has worked with a contractor, The Lewin Group, to help the OPPB refine and revise the BPCA prioritization process.

## **BPCA Prioritization Process**

*Clifford Goodman, Ph.D., Vice President, The Lewin Group*

Dr. Goodman described the new prioritization process, including approach and methods, and provided results of new prioritization process for the BPCA priority list of therapeutic needs. For the BPCA Program, the NICHD defined three stages to revise the prioritization process:

- Define prioritization objectives and goals
- Define guiding principles through research of other prioritization processes
- Revise the process based on guiding principles and feedback from stakeholders.

**Define Prioritization Objectives and Goals.** The steps in defining objectives and goals were to develop (1) a systematic, objective process of prioritizing research and (2) extensive participatory outreach activities to incorporate public input from a broad group of stakeholders, including practicing pediatricians, professional societies, and advocates.



**Define Guiding Principles.** Four guiding principles were identified through research on existing health-related prioritization processes:

- A well-defined process, using a systematic approach with clear objectives and outcomes
- Well-defined objective criteria that are mutually exclusive and a manageable number
- Legitimacy and fairness, including transparency, stakeholder input, a dynamic process, and leadership
- Expert involvement to inform and contribute to the process and add credibility.

**Revise the Process.** Revising the prioritization process involved in four stages:

- **Public outreach:** More than 60 organizations were contacted prior to the nomination period to determine the best method by which to reach memberships.
- **Gather nominations:** 107 nominations were received. Some were either incomplete or were duplicate submissions. These nominations were removed or condensed into unique nominations, leaving 67 qualifying nominations.
- **Prioritize nominations:** There were three stages to evaluation of nominations, each with its own criteria.
  - Threshold criteria that are relevant to BPCA mission and goals, with no disqualifying ethical concerns and no significant sources of existing funding
  - Prioritization criteria, using an evidence score, an impact score, and a population score
  - Final considerations, including workgroup and FDA nominations, a balanced portfolio, and feasibility
- **Public comment.**

Of the 67 qualifying nominations, 8 were removed from consideration due to threshold criteria application, leaving 59 remaining nominations. The majority of the final nominations considered were for drugs (30). Other types of nominations were drug class (11), devices (10), and biologics (8). Six therapeutic areas were included in the final nominations: neonatology (16), cardiology (15), neurology (7), gastroenterology (7), respiratory (4), and dermatology (3).

Through a Request for Information and outreach materials, evaluators were recruited and selected to further extend the public role. More than 40 volunteers expressed interest, and 22 evaluators were selected, including a mix of advocates, physicians, and researchers. Each evaluator reviewed approximately 10 nominations. Each nomination was reviewed by a minimum of three evaluators. Each nomination was scored on each of the three prioritization criteria (evidence, impact, and population). The evaluators were provided considerations for scoring but were not told the values of the weights to be applied. Scores were averaged across evaluators by criterion. The 59 nominations were scored, weighted, and ranked to add to the 2009 priorities, creating the preliminary 2011 priority list. Once all scores were received, weights approved by an expert panel were applied, resulting in a weighted final score for each nomination.

Once scores were reviewed by the OPPB for consistency across reviewers, nominations were ranked by score and divided into three tiers. Within each tier, nominations are grouped by therapeutic area; scores are not considered from this point forward.

- Tier 1—top 25 percent (16): Nominations in this tier will receive highest attention from the NICHD.
- Tier 2—middle 50 percent (28): Nominations in this tier may be considered by the NICHD depending on changing concerns or feasibility considerations.
- Tier 3—lowest 25 percent (15): Nominations in this tier will not be emphasized in the 2011 priority list but may be considered at a later date.

Five additional nominations from the 2010 BPCA workgroups and 6 nominations from the FDA were added to Tier II, making 70 nominations entering the final considerations stage. The balanced portfolio element of the process allowed the NICHD to consider three elements to determine whether a nomination is moved from one tier to another. Based on these elements, 6 nominations changed tiers. The new process allows for additional public comment regarding the nominations through the BPCA Annual Prioritization Meeting. Once public input is incorporated, feasibility will be considered as a final “go/no go” decision. The FDA will provide input on these considerations and advise whether similar efforts are under way or forthcoming. The list with nominations determined to not be feasible will be kept as a record of important research topics but will not be funded or considered for funding in the near future.

### **General Comments and Discussion of the Afternoon Presentations**

General comments and discussion topics were as follows:

- Representatives from Parents United for Pharmaceutical Safety and Accountability nominated Singulair for the 2011 priority list. Several representatives described their personal experiences with the neuropsychiatric, behavioral, and sleep disorder side effects of Singular in their children. The representatives expressed the need for better safety evaluations and labeling for Singular.
- Ethical and scientific concerns with excluding drugs with black box warnings were discussed, including
  - Use of drugs despite black box warnings
  - Off-label use of drugs
  - Review of black box warnings to determine consideration for the drug priority list
- Several meeting participants noted the FDA’s consumer-based reporting program (MedWatch) for reporting adverse events for patent-protected drugs such as Singular.

### **BPCA Therapeutic Area Working Groups**

*Perdita Taylor-Zapata, M.D., Medical Officer, OPPB, CRMC, NICHD, NIH*

Under its new prioritization process, the BPCA Program is expanding its outreach to include a broader range of stakeholders with earlier involvement and input into the process. Expanded outreach includes the use of outside evaluators in the evaluations of drugs nominated for the priority list and also includes the development of therapeutic working groups. In 2009, the BPCA Program began an annual process of developing working groups in specific therapeutic areas in order to: (1) gathered further information from a core group of experts in the diagnosis, treatment, and prevention of diseases; (2) identified gaps in knowledge (research agenda) in the treatments of the disease areas; and (3) encouraged improvement in safety and efficacy data of

existing treatment modalities. The 2009 BPCA therapeutic area working groups were Adolescent Therapeutics, Safety of Cold and Cough, and Safety of Atypical Antipsychotics. The 2010 BPCA therapeutic area working groups were formed based on recommendations at the 2009 Annual Priority Meeting. They are Endocrinology, Gastroenterology, and Neurology.

## **2010 Therapeutic Area Working Groups Breakout Sessions**

Each of the 2010 therapeutic area working groups held a breakout session to discuss and identify additions to the draft list of nominations to the 2010–2011 BPCA priority list of needs in pediatric therapeutics. The working leaders and breakout session facilitators were as follows:

- Endocrine Therapeutics Working Group
  - Group Leader: Paul Kaplowitz, M.D., Ph.D., Division Head, Division of Endocrinology and Diabetes, Children’s National Medical Center
  - Facilitator: Anne Zajicek, M.D., Pharm.D., Acting Branch Chief, OPPB, CRMC, NICHD, NIH
- Gastrointestinal Disease Therapeutics Working Group
  - Group Leader: Ii-Lun Chen, M.D., Medical Officer, Division of Gastroenterology Products, Center for Drug Evaluation and Research (CDER), FDA
  - Facilitator: George Giacoia, M.D., Medical Officer, CRMC, NICHD, NIH
- Neurology Disease Therapeutics Working Group
  - Group Leader: Steven Weinstein, M.D., Director of Pediatric Epilepsy, Weill Cornell Medical College
  - Facilitators: Zhaoxia Ren, M.D., Ph.D., Medical Officer, OPPB, CRMC, NICHD, NIH, and David Siegel, M.D., Medical Officer, OPPB, CRMC, NICHD, NIH

## **Day 2**

### **Introduction to Day 2 Activities**

*Perdita Taylor-Zapata, M.D., Medical Officer, OPPB, CRMC, NICHD, NIH*

Dr. Taylor-Zapata explained that the second day of the meeting would focus on future directions of the BPCA Program.

## **Final Recommendations from the 2010 BPCA Therapeutic Area Working Groups**

### **Endocrine Therapeutics Working Group**

*Paul Kaplowitz, M.D., Ph.D., Division Head, Division of Endocrinology and Diabetes, Children’s National Medical Center*

The working group identified four priorities for therapeutic agents:

- Metformin for polycystic ovary syndrome (PCOS)
- Bisphosphonates for osteoporosis associated with chronic illness
- Cyproheptadine as an appetite stimulant in children with no gastrointestinal or endocrine disease and poor oral intake
- Aromatase inhibitors for peripubertal children with short stature.

**Metformin for PCOS.** The working group reported the following:

- Patient population: Patient population is teenage girls with menstrual irregularities with evidence of androgen excess. Most but not all are of these patients are obese. The number of teenage girls with PCOS has increased as the obesity epidemic has intensified.
- Potential impact of treatment: Adult data have shown that metformin restores menses in many but not most patients, the effect on androgen excess is modest, and efficacy in restoration of fertility is not impressive. Metformin is associated with weight loss (sometimes significant) in a proportion of patients.
- Clinical need: The main other drug class—oral contraceptives—used for restoring menses in PCOS has significant side effects and is associated with weight gain. Metformin is free of serious side effects aside from gastrointestinal intolerance in about 5 percent of patients. Metformin has a long history (in the United Kingdom since 1958; in the United States since 1995) of safety when used for prolonged periods in type 2 diabetes. Metformin is an inexpensive off-patent drug.
- Study design: The outcome measures would include frequency of menses over a defined period (for example, 6 months), weight loss or decrease in BMI, measures of insulin sensitivity and improved glucose homeostasis (as many PCOS patients have insulin resistance and/or prediabetes), and measure of hirsutism using the Ferriman-Galwey score.
- Feasibility concerns: Metformin is currently not approved for adults with PCOS, although off-label use is widespread. Approved use of metformin in children older than 10 years of age with type 2 diabetes lessens this concern. It should not be difficult to find study subjects. An appropriate comparison group would have to be identified. A comparison group could receive placebo or oral contraceptives. Incentives for the manufacturers of this generic drug to commit resources to do this study well with sufficient numbers to identify subgroups that are excellent or poor responders are a concern.
- Recommendation: Metformin for PCOS should be a high priority for pediatric studies of a common condition that is likely to become increasingly common and for which there is no satisfactory FDA-approved therapies.

**Bisphosphonates for Pediatric Osteoporosis.** The working group reported the following:

- Background: Despite widespread use for low bone density and increased fracture risk in older adults, there are few pediatric data on these agents. An exception is the use in children with osteogenesis imperfecta in which some studies have shown reduction in fracture rate. Questions remain as to whether the reduction in bone fracture is a drug effect or due to a prescription for reduced physical activity in study subjects. Studies in burn patients are preliminary but promising. Despite the lack of data, there is much off-label use of this drug category in children with low bone density, particularly in steroid-induced osteoporosis.
- Proposed study: The best groups to study would be patients with chronic inflammatory conditions requiring a long-term moderate-to-high dose of glucocorticoids. The study would involve specialists in gastroenterology (for example, those who treat inflammatory bowel disease patients) and rheumatology (for example, those who treat juvenile rheumatoid arthritis patients). The simplest outcome measure would be increases in bone mineral density. The most important outcome measure would be reduction of fracture rate. The study would require a large number of subjects studied over many years.

- Concerns and barriers: There are ethical concerns about such a study because preliminary studies in this population have not yielded impressive results and bisphosphonates have rare but significant side effects (for example, osteonecrosis of the jaw). Such a study would require many collaborators and significant resources to enroll enough patients and follow them long enough to give definitive results.

**Cyproheptadine for Poor Weight Gain.** The working group reported the following:

- Background: Endocrine and gastrointestinal specialists are seeing large numbers of young children (typically 2–8 years of age) whose linear growth is marginal and who are very underweight (BMI < 10th percentile). These children have no signs or symptoms of gastrointestinal or endocrine disease. Parents are frustrated by their child’s failure to take in adequately calories and protein, and many resort to constant nagging to finish a meal. Extensive gastrointestinal workups are often done to rule out pathology. The results are almost always negative.
- Adult studies: Cyproheptadine was developed as an antihistamine but also has serotonin antagonist effects. Several studies in adults dating back to the 1960s showed significant effect on appetite and weight gain. Cyproheptadine is well tolerated and safer than other appetite-enhancing drugs such as megestrol. The major side effect is drowsiness, which is usually transient. There have been few pediatric studies, although two studies of cyproheptadine as an appetite stimulus in cystic fibrosis used both children and adults subjects.
- Study design: The study would recruit subjects from pediatric gastrointestinal and endocrine practices. Subjects would have marginal linear growth (height  $\leq$ 10th percentile) and be underweight by BMI criteria (<10th percentile). The study would exclude patients with known or suspected gastrointestinal or endocrine disorders or with actual weight loss. Two subgroups could be studied: idiopathic and drug-induced (for example, children taking stimulant medications). Dose titration could be used to reduce drowsiness, if needed. Study duration would be 6–12 months. Outcomes would be changes in BMI standard deviation and height standard deviation, as well as reduction in parental worry and frustration.
- Feasibility: A concern for such a study is whether there is a need for pediatric data for a drug that is already being used off-label in both adults and children. No major barriers were identified. Such a study would require minimal resources because the main outcomes are based on simple measurements. Useful patient response information could be obtained in 6–12 months.

**Aromatase Inhibitors for Short Stature.** The working group reported the following:

- Background: Currently, there is no effective treatment for children with short stature with poor predicted adult height identified in the peripubertal period. For these children, there is little or no benefit of growth hormone once the growth spurt starts. It is known that estrogens are the key hormone for advancing bone maturation and causing epiphyseal fusion. Studies in the past decade (many from Finland) have shown that aromatase inhibitors approved for breast cancer can lower the conversion of testosterone to estradiol in teenage boys and slow bone age advance.
- Concerns: There is widespread off-label use of aromatase inhibitors among certain pediatric endocrinologists. Despite improved predicted height, there is a lack of definitive data on

improvement of adult height in children with idiopathic short stature (ISS). Slowing of growth during puberty may offset the benefit of slower bone age advancement. Animal data have shown possible long-term effects on testicular development. Testosterone levels rise rapidly in the first few months of aromatase inhibitor treatment.

- **Conclusions:** It is not clear that aromatase inhibitor therapy in short boys is “ready for prime time.” In 2005, the FDA refused to permit Novartis to conduct a study of letrozole in healthy short boys. Concerns about wide off-label use may offset concerns about efficacy and potential reproductive toxicity.

**Other Concerns of the Endocrine Working Group.** The working group reported the following:

- **Promotion of off-label use of insulin-like growth factor 1 (IGF-1):** Drug companies are promoting the off-label use of IGF-1 in boys with ISS who do not meet the FDA requirement of both height and IGF-1 levels at least 3 standard deviations below the mean. Published studies show high incidence of side effects (compared with growth hormone treatment), including hypoglycemia, increased intracranial pressure, and possibly earlier onset of puberty. Clinicians have reported off-label marketing of IGF-1 to the FDA, which is investigating. Strategies to discourage off-label use of IGF-1 by clinicians should be explored.
- **Lack of pediatric-friendly dosage forms of commonly used hormones:** Levothyroxine is available in limited dosage strengths suitable for small children. Tablets are 25, 50, and 75 mcg, but there are no 37 or 62 mcg tablets. There is no stable liquid formulation for children in United States. However, a levothyroxine oral solution (Leventa) is being marketed for dogs. Hydrocortisone is also available in limited dosage strengths suitable for children. The lowest dose is 5 mg, but small children may need as little as 1.25 mg per dose. The liquid formulation of hydrocortisone was taken off the market years ago due to problems keeping the drug in suspension.

**Problems and Possible Solutions.** The cost of getting approval for new dosages and formulations of generic drugs is perceived by manufacturers as high relative to potential profit. Better public–private partnerships are needed to incentivize drug companies. The BPCA Program should try to convince at least one drug company to market their hormone product line as “child friendly.” The issue of pediatric dose formulations transcends endocrine therapeutics and needs to be addressed at a broader level.

### **Gastrointestinal Disease Therapeutics Working Group**

*Li-Lun Chen, M.D., Medical Officer, Division of Gastroenterology Products, CDER, FDA*

The working group nominated eight drugs for the 2010 priority list of therapeutic needs:

- **Polyethylene glycol (PEG) 3350:** This drug should be studied in all pediatric age groups, starting with infants at 6 months of age. The indications are occasional and chronic constipation, as well as fecal impaction. The study design would use active controls—comparing currently used anticonstipation medications or milk of magnesia with PEG 3350. The trial would be dose ranging and 6–12 months in length. The goal is to establish dosing recommendations and safety. Lack of information on the absorption of lower molecular

weight PEGs is a concern. Lower molecular weight PEGs may have neuropsychiatric side effects. Because PEG is an off-patent drug, it should be inexpensive to study. Because behavioral modification is a component of constipation, it needs to be standardized throughout the trial.

- **Ursodiol:** This drug is used to treat cholestasis. The study population would be patients with cystic fibrosis, primary sclerosing cholangitis, and parenteral nutrition–induced liver disease—particularly the NICU population. The study design would be a placebo-controlled trial to assess dose response. Measures of efficacy would include GGT liver enzymes, bilirubin levels, and bile salt levels. The working group recommended a data safety monitoring board for the trial.
- **Megestrol:** This drug is a progesterone derivative. The indication is to increase appetite in poor weight gain patients. The recommended age group for study is toddlers and older. The study design would be a placebo-controlled trial lasting at least several weeks to evaluate increase in caloric intake and weight gain. Further information is needed on the appropriate duration of treatment, long-term safety, and endocrine effects.
- **Cyproheptadine:** This drug is used to treat cyclic vomiting and chronic periumbilical abdominal pain. Cyproheptadine may enhance appetite. The study population would be children older than 5 years of age. The study design would assess efficacy of cyproheptadine, amitriptyline, and placebo. Efficacy of amitriptyline and cyproheptadine in different age groups could possibly be compared. Outcome measures would be reductions in vomiting and pain. Additional information is needed to inform dosing recommendations and safety of long-term use.
- **Prokinetic and promotility drugs:** This class of drugs includes metoclopramide, which has significant side effects and concerns about long-term use. There is an overall need to develop prokinetic and promotility drugs and a need to reevaluate currently available drugs in this area. Gastroschisis patients could benefit from these drugs. Promotility agents are thought to decrease the time to tolerance of feeding. Other promotility drugs are baclofen, erythromycin, and cisapride. The working group recommended collaboration with the Neurology Working Group to research the use of baclofen. Impedance studies can be used to evaluate gastrointestinal reflux and motility. Erythromycin needs to be evaluated for safety and changes in microflora. Subpopulations at risk for major cisapride side effects need to be better understood.
- **Parenteral nutrition products:** These products include intralipids, Omegaven, and SMOF. There has been little advance in the knowledge of nutritional support of pediatric patients. There needs to be better understanding of the effects of changing dose of intralipids and whether it has an effect on liver disease outcomes. There also needs to be better understanding of whether different intralipid products have effects on liver disease outcomes. Because of the variations in practice, prospective longitudinal studies are needed to standardize practice. There are many subpopulations, which are broad with different physiologies and volumes. Studies could help tie the type of intralipid to biologic phenotypes. There is a need for biomarkers to understand responses to therapy. There needs to be a better understanding of the effects of parenteral nutrition products on neurocognitive function. There is a lack of understanding of micronutrient composition. However, there is empiric information on the composition of the trace elements. There should be studies to

optimize doses for various age groups. There needs to be a better understanding of the contribution of parenteral nutrition products on myelination.

- **Probiotics:** These food supplements are used to prevent necrotizing enterocolitis and bacterial overgrowth and restore the normal gut microbiome. Study subjects would be the NICU population younger than 32 weeks of age and stem cell transplantation patients. Feasibility issues include lack of FDA regulation and product manufacturing standards. These are not pharmaceutical-grade products. There are variations in content of specific bacteria being marketed. Mass spectrometry could be used to identify bacteria and understand effect of probiotics on the gut microbiome.
- **Proton pump inhibitors (PPIs):** Because of long-term use and safety concerns, PPIs as a class should be considered for prospective longitudinal studies. Patients with neurological issues should be targeted in these studies.

**Summary.** Two key issues for pediatric drug trials are to define dose–response relationships and to collect more dose-ranging information. More translational science should be used as a foundation for pediatric drug trials. PK/PD measures, as well as surrogates, should be developed and used to translate effect into efficacy so that more targeted trials can be done in pediatric patients.

### **Neurology Disease Therapeutics Working Group**

*Steven Weinstein, M.D., Director of Pediatric Epilepsy, Weill Cornell Medical College*

Dr. Weinstein provided background information on pediatric neurology disease. Measurements for neurology disease and development disorders are generally lacking. Distinguishing learning difficulties that are a reflection of the child and his environment versus those due to an underlying difference in brain function can be challenging. In a typical pediatric neurology practice, about one-third of the patients seek treatment for headache, one-third for developmental disorders, and one-third for epilepsy. Children’s hospitals are focusing more on acute management of neurologic complications of other disorders. Defining neurologic disorders is challenging without standardized scales. Whether early interventions can change the natural history of a neurological disorder is not known.

The working group reviewed nine drugs on the 2010 priority list of therapeutic needs:

- Levetiracetam for epilepsy and headache
- Topiramate for migraine
- Amitriptyline for migraine
- Propranolol for migraine prophylaxis
- Midazolam (intramuscular [IM]) for seizures especially due to mass casualty nerve agent–induced seizures
- Tissue plasminogen activator (tPA) for stroke in children
- Near-infrared spectroscopy for monitoring head trauma and blood flow
- Interferon beta 1B for multiple sclerosis (MS)
- Selective serotonin reuptake inhibitors for core (or associated) symptoms of autism spectrum disorder (ASD).



The working group discussed autism and traumatic brain injury (TBI) because of media-driven attention, the high volume of these disorders, and the need to develop therapeutics for them. The working group did not recommend that these disorders be considered for the priority list of therapeutic needs for the following reasons. An NIH consortium to study autism already exists. There are few patients with severe TBI, and a network already exists to study severe TBI. Although there are an overwhelming number of patients with concussion, treatment approaches are not standardized, treatments have not been shown to be effective, and medical hypothesis are needed to study concussion. The working group reported the following:

- **IM midazolam:** This drug is relevant for treating bioterrorism events, and there are many other causes to use it. The Rapid Anticonvulsant Medications Prior to Arrival Trial is already studying IM midazolam for paramedic treatment of prolonged seizures.
- **tPA:** The number of patients for tPA is very small, the window for administration is limited, and the risk factors for complications are unknown. The Pediatric Stroke Networks (Toronto) is planning a study of tPA.
- **Interferon beta 1B for MS:** The number of MS patients that would benefit from interferon beta 1B treatment is unknown. In Canada, the prevalence is estimated to be less than 0.9/100,000. Objective outcomes include clinical flairs, disability scales, and MRI. No one in the working group championed interferon beta 1B treatment for MS.
- **Headache (migraine):** Defining the study population for prophylactic treatment of migraine is challenging. It may be possible to characterize and stratify patients based on MRI, magnetic imaging spectroscopy, and functional MRI. Biomarkers such as *MTHFR* and *ACE D/I* polymorphisms are being studied. Study design for prophylactic migraine treatment would include baseline incidence and comparison of intervention and placebo using functional imaging and/or biomarker. It would be a short-term study. Potential interventions are amitriptyline, topiramate, propranolol, levetiracetam, cyproheptadine, and valproate.
- **Anesthetic-associated neurodegeneration:** The working group proposed an epidemiological study of neurodegeneration in the immature brain, altered development outcomes, and learning disabilities following the administration of anesthetic agents early in life. Because the effects of early life anesthetics cannot readily be studied in human infants, animal models would initially be required. Sensitive and specific biomarkers for risk of apoptosis would need to be identified. Once biomarkers are established, infant studies focusing on dose, combination therapy, and exposure duration could be conducted.
- **Non-ASD aggression:** The working group discussed oppositional defiant disorder and conduct disorders. Studying these disorders are challenging because of child biological factors; school factors; parent psychological factors; and familial contributions such as divorce, marital distress, and violence; parent–child interactions; and psychophysiological and genetic influences. Another challenge is that many of these children have already received medications (for example, risperidone).

**Comments and Discussion.** Comments and discussion topics were as follows:

- It can be challenging to differentiate the effect of placebo versus effect of medications such as amitriptyline for migraine prophylaxis. Response rates to placebo can be as high as 50 percent.

- Several studies with nonhuman primates have shown anesthetic-associated neurodegeneration and cognitive deficits. For example, primates exposed to a single dose of ketamine in the first week of life show cognitive deficits at 3 years of age.
- Two multiarm studies of antiepileptic medications have shown impressive results from a public health perspective. The differences in impact of the newer drugs versus older drugs are smaller or nonexistent.
- The length of treatment in clinical trials (for example, 6 months) is different in terms of what is being measured than the length of treatment in usual, real practice.
- Existing data sources of medication use in the community could identify children by the length of time currently on medication. This approach could help define who are the best candidates for neurological studies and could help identify the most useful inclusion criteria.
- There are challenges for studying the long-term consequences of treatment.
- The FDA is interested in studying, for example, aggression in children, as long as the disease or the set of symptoms is not “pseudospecific.” The FDA is open to a variety of endpoints and a variety of study designs. Multiarm studies of drugs such as antiepileptics have been conducted and have proven to be very challenging. The FDA is open to discussing multiarm studies.
- Objective outcome measures of neurocognitive functioning can provide better data than subjective reporting of drug efficacy. One problem with using objective outcome measures is the lack of baseline testing.
- There is the need to define endpoints and show efficacy for FDA drug approval for specific diagnoses. Aggression is not an FDA-approved indication for medication development in child and adolescent psychiatry.
- FDA drug approvals are evidence based. Demonstrating drug efficacy in a population with a particular diagnosis would provide necessary evidence. Characterizing aggression symptoms across disease entities and identifying measurable endpoints could lead to FDA approval, regardless of underlying etiologies.

### **Pediatric Clinical Pharmacology: The Lifeline for Rescuing the Therapeutic Orphan**

*Gregory L. Kearns, Pharm.D., Ph.D., Marion Merrell Dow/Missouri Chair of Pediatric Medical Research, Professor of Pediatrics and Pharmacology, Director, Pediatric Pharmacology Research Unit, Children’s Mercy Hospitals and Clinics*

Highlights of Dr. Kearns’ presentation are as follows:

- Pediatric clinical pharmacology facts: Children are not small adults; they have different PK and PD compared with adults. About 70 percent of all marketed drugs are not suitably labeled for pediatric use. In some instances, pediatric patients are included in studies as an “afterthought.” The biggest issue remains determining the safe and effective dose for pediatrics.
- The therapeutic orphan: In 1963, scientists recognized that infants and children were becoming “therapeutic or pharmaceutical orphans.” Many of the drugs released since 1962 carried an “orphaning” clause (for example “Not to be used in children” and “not recommended for use in infants and children”) because few studies had been conducted in these age groups.

- Statement of need: Over the past decade, the view of the needs for pediatric drugs has evolved. In 2010, the American Academy of Pediatrics stated that it is unethical to deny children appropriate access to existing and new therapeutic agents. It is the combined responsibility of the pediatric community, pharmaceutical industry, and regulatory agencies to design, approve, and conduct high-quality studies in children.
- Legislation to rescue the therapeutic orphan: From 1979 to 2007, legislation has introduced regulations and statutes for pediatric therapeutics: The Pediatric Rule, the Food and Drug Administration Modernization Act, BPCA, PREA, and FDAAA. Regulations have produced a data-rich environment and improved drug use in pediatrics. Through March 2010, 383 WRs have been issued. Over the past 3 years, 224 studies of safety, efficacy, PK, and PK/PD have resulted in 355 pediatric labeling changes. More than 100,000 patients have been studied since 1997.
- PK: Many studies over the past decade have shown that developmental differences in PK should be used to determine dose of pediatric drugs. The developmental differences include age, gene expression, and body weight.
- Pharmacogenetics (PG): Practical and useful application of clinical PG has resulted in product labeling (for example, warfarin). There are a number of reasons to study pediatric PG. Drugs developed for adult disease are not necessarily equally appropriate for pediatric disease. Children and adults may not have the same mechanisms for nominally the same disease. Variability in drug disposition and response in children has an added measure of complexity—ontogeny. Adverse responses to medications and environmental contaminants early in life can have life-long consequences. Children with asthma, autism, attention deficit/hyperactivity disorder (ADHD), and epilepsy become adults with asthma, autism, ADHD, and epilepsy. The essentials of clinical PG are establishing a quantitative link between phenotype and genotype; translating phenotype into accurate, quantitative reflection of protein (for example, enzyme and transporter) activity; and translating the genetic information provided by the “marker” into a quantifiable and reliable altered dosing scheme.
- PD: There are many examples of age-dependent differences in PD, including (1) a higher incidence of valproate-associated hepatotoxicity in young infants, (2) a greater frequency of paradoxical central nervous system reactions to diphenhydramine in infants, (3) greater weight gain associated with atypical antipsychotic agents in adolescents, and (4) altered warfarin dose effect in children with congenital heart disease and prepubertal children. There are a number of challenges to conducting robust PD studies in pediatric patients, including (1) lack of validated, dynamic endpoints, (2) non-child friendly “gold standard” endpoints used in adults, (3) predominance of acute diseases in pediatrics, and (4) potential ontogenical influence on drug-receptor interaction
- Developmental PD: The next, necessary frontier for pediatric clinical pharmacology is developmental PD. It not reasonable to assume that children, when compared with adults, have a similar disease progression and similar PD.
- Biomarkers: Biomarkers need to be integrated into the pediatric drug development process.
- Summary: In rescuing the therapeutic orphan, stakeholders have done the following:
  - Improved pediatric drug use, including labeling, safety, and age-appropriate dosing
  - Expanded resources for conducting research
  - Developed new approaches for study design
  - Expanded existing knowledge in the field

- Provided proof-of-concept for PK/PD/PG integration in pediatric studies
- Expanded the horizons of research in developmental pharmacology
- Leveraged resources in the pharmaceutical industry
- Created proof-of-concept, which is now emulated globally.

## **Future Directions for BPCA: 2011 and Beyond**

### **Formulations Initiatives**

#### **Pediatric Formulations: Research Considerations**

*George Giacoia, M.D, Medical Officer, CRMC, NICHD, NIH*

Dr. Giacoia provided an overview of the lack of appropriate pediatric formulations, reviewed some of the NIH's research interests in taste of pediatric formulations, listed gaps in knowledge of taste and excipients, described a joint European (EU) Pediatric Formulations Initiative (PFI)–US PFI project to develop a database of excipients for pediatric use, and listed some of the issues in research in pediatric formulations. Highlights of his presentation are as follows:

- **Pediatric formulations:** The lack of appropriate pediatric formulations involve economic issues and technical and scientific issues. Economic issues include the size of the pediatric market, the cost of developing formulations for different age groups, and the cost of keeping a formulation in the channels of trade. Technical and scientific issues include solubility, identification of the correct solid form (for example, polymorph, salt, and amorphus), stability, taste, variable dosing, and child-friendly dosage forms. NIH basic research and industry applied research are the traditional approaches to formulations development. However, the paradigm is changing. Advances in biological sciences blur distinctions between basic and applied research. Industry has an increased role in basic research, with a greater role of biotech companies. The NIH has more involvement in public–private partnerships.
- **Research interests:** The NIH has increased funding for pediatric formulations research. For example, the National Institute of Deafness and Communication Disorder has funded 245 grants under its taste and smell program. Research interests of the OPPB and the US PFI include the following:
  - Taste masking and testing
  - Safety and toxicity of excipients (EU PFI–US PFI joint project)
  - Application of toxicogenomics to preclinical and clinical studies of drug and excipient toxicity and safety evaluation
  - Development of research strategy to study drug bioavailability in children
  - Studies of drug adherence in children.
- **Gaps in knowledge:** The needs to improve knowledge of taste in pediatric formulations are as follows.
  - Age appropriate methodologies for testing children
  - Systematic approach to the bad taste of liquid formulations through multifaceted programs
  - Improved understanding of molecular structure–taste relationships of drugs

- Methodologies for screening formulations early on when it is impossible for humans to taste.
- Excipients: The gaps in knowledge of excipients in pediatric formulations are as follows:
  - Clinical consequences of excipient exposure are largely unknown.
  - Accepted daily and cumulative intake of excipients has not been established in pediatrics.
  - Accepted daily intake recommendations in the pediatric literature are mostly based on adult studies.
  - Regulatory agencies do not provide guidance for industry on nonclinical studies for safety evaluation of excipients in children.
  - The susceptibility to excipient adverse reactions has not been studied in relation to the state of development of organ systems for metabolism, elimination, and receptor functional readiness.
  - Available information is distributed over many sources.
  - Potential pharmaceutical–excipient interactions in different types of pediatric formulations are unknown.
- Excipients database: In a joint project, the EU PFI and US PFI are developing a database of excipients for pediatric use. The purpose of the excipients database is to:
  - Conduct a high-level scientific literature review of the pharmacology, toxicology, and safety data of a selected group of excipients used in pediatric formulations
  - Identify knowledge gaps and needed studies or provide the basis for the development of hypothesis-driven safety or toxicity studies
  - Determine the relationship between exposure and evidence of clinically significant toxicity in the pediatric population as a whole or in pediatric subpopulations.
- Research issues: Issues regarding research in pediatric formulations are as follows:
  - Fragmentation of research efforts
  - Sharing of information currently unavailable
  - Role of precompetitive research and intellectual property
  - Conflicting research interests
  - Harmonization of approaches of stakeholders
  - Coordination of efforts/transaction relationships.

### **Formulations Initiative: The FDA–NIH Collaboration**

*Mansoor A. Khan, Ph.D., Director, Division of Product Quality Research, CDER, FDA*

Dr. Khan reviewed the FDA–NIH collaboration in formulations development. Highlights of his presentation are as follows:

- Pediatric formulation needs: Needs for pediatric formulations include:
  - Easy-to-swallow or dissolvable dosage form
  - Palatability
  - Minimal/safe excipients
  - Ability to titrate dose
  - Adequate bioavailability
  - Stability in high heat and humidity
  - Avoidance of extemporaneous compounding
  - Commercial availability.

- The FDA–NIH collaboration: The collaboration is focusing on:
  - A list of legacy products with pediatric needs
  - Products with lack of pharmaceutical industry interest for development
  - Acute global needs
  - Consideration of taste, solubility, stability, and other technical challenges
  - Active pharmaceutical ingredients amenable to certain well-established platforms
  - Grouping products and appropriate platforms by appropriately considering chemistry, PC, and PK properties and using computational models
  - Developing case studies
  - Discussing, presenting, and publishing for worldwide dissemination.
- Conclusions: There is an acute need for the development of pediatric products. By a collaborative multidisciplinary approach, products can be developed for all ages within the pediatric population. The FDA–NIH collaboration is under way to fill some scientific and technological gaps.

### **Pediatric Antiretroviral Drug Formulations: Consultation of Expertise**

*Bill G. Kapogiannis, M.D., Medical Officer, Pediatric, Adolescent, and Maternal AIDS Branch, CRMC, NICHD, NIH*

In this discussion session, Dr. Kapogiannis sought consultation regarding a potential initiative to stimulate interest in developing extended-release formulations of antiretroviral agents for use in pediatrics and for adolescents in particular.

**Background Information.** It is estimated that, globally, more than 33 million people are living with HIV. About 2 million of these people are younger than 15 years of age. About 50 percent of new infections occur in people 15–24 years of age. Adherence to antiretroviral treatment in youth is estimated to be 50–60 percent. In the United States, it is estimated that 100,000–150,000 youth are infected with HIV. HIV deaths in youth are generally related to nonadherence to antiretroviral treatment. Extended-release formulations of antiretroviral drugs may potentially improve adherence. Dr. Kapogiannis conducted a literature search and found no citations for human clinical trials of extended-release antiretroviral formulations. Although many antiretroviral drugs have been developed, no extended-release formulations have been developed. Dr. Kapogiannis asked for input on feasibility issues in developing a federal initiative to stimulate interest in antiretroviral extended-release formulations.

**Discussion.** Discussion topics included the following:

- Oral formulations, including tablets, that can be administered to adolescents and young children
- Types of compounds that could be used in a patch or injectable drug
- Dosage issues
- Creating a small working group to discuss the initiative
- Formulations for immunosuppressive drugs in transplant recipients and monitoring adherence
- University of Cincinnati adherence center, which has received NIH grants
- Developing preexposure prophylaxis compounds

- Effects of reformulations and drug-delivery systems on dose–response relationships
- Effects of frequency of treatment and ease of administration on adherence.

### **Discussion of the Next Steps and Closing Remarks**

*Anne Zajicek, M.D., Pharm.D., Acting Branch Chief, OPPB, CRMC, NICHD, NIH*  
*Perdita Taylor-Zapata, M.D., Medical Officer, OPPB, CRMC, NICHD, NIH*

This meeting summarized BPCA Program activities since the 2002 legislation was passed. Since 2002, the NIH has been interested in the scientific projects that have been implemented, including collaborations with the CTSA's, clinical trials, and outcome measures. The BPCA Program has had flexibility in conducting drug studies because it is not the New Drug Application holder and the flexibility to conduct comparative trials. BPCA studies have generated large amounts of data, which will be made available to the public. BPCA Program activities, including the prioritization process, have been transparent, which allows public discussion of the results. A de-identified database will be created and will be in the public domain. Because it is federally funded, the BPCA Program has published—and will continue publishing—the results of its studies. Clinical Study Reports will continue to be submitted to the FDA. Lessons learned include the following:

- It is expensive and challenging to conduct clinical trials.
- Developing infrastructure with core programs such as the PTN is the best way to facilitate BPCA trials.
- A working relationship with the FDA has been essential to the success of the BPCA Program.

Short-term plans include expanding participation in the PTN, developing the FDA–NIH formulations platform to provide open-source information to manufacturers, meeting with CTSA sites to discuss outcome measure grants, and creating a database of BPCA clinical trials data. Other areas of interest are determining normal values of biomarkers in children and involving children with intellectual and developmental disabilities.

In conclusion, the BPCA listing process will continue; the studies that come out of the prioritization process will, for the most part, be managed by the PTN; and the PTN and Steering Committee will further refine the priorities of drugs and therapeutic areas to identify high-priority areas. The PTN wants to be as inclusive as possible, is seeking broad expertise, and would like to establish additional sites. Investigators interested in participating in the PTN should contact Dr. Benjamin.

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