***Eunice Kennedy Shriver* National Institute of Child Health and Human Development**
National Institutes of Health
Best Pharmaceuticals for Children Act
2014 Annual Stakeholders Meeting
December 10, 2014
Natcher Conference Center
Bethesda, MD

This meeting was sponsored by the Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB), *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 meeting was open to the public and included invitees from various organizations including but not limited to academic institutions, NIH Institutes and Centers, the U.S. Food and Drug Administration (FDA), industry, and members of pediatric advocacy groups.

The purpose of the meeting was to provide updates on the BPCA program.

Welcome

Perdita Taylor-Zapata, M.D., Medical Officer, OPPTB, NICHD, NIH

Dr. Taylor-Zapata welcomed the participants and thanked them and all BPCA stakeholders. She reviewed the scope of pediatric therapeutics and provided a brief overview of the BPCA program and stakeholders. She gave an overview of the day's agenda and moved to presentations.

NIH Perspective on the BPCA: Clinical Trials, Training, Formulations

Anne Zajicek, Pharm.D., M.D., Branch Chief, OPPTB, NICHD, NIH

Dr. Zajicek provided an overview of the history of the BPCA program's approach to fulfilling its mission of relabeling pediatric drugs. In 2002, a master list of all off-patent drugs that lacked adequate pediatric labeling was developed, with the goal of developing, prioritizing, and publishing an annual list of drugs. In 2007 and 2012, the approach shifted to focus on therapeutic areas, with the goal of developing, prioritizing, and publishing an annual list of therapeutic areas and specific needs. Dr. Zajicek described the BPCA process for labeling changes and submitting data from the NIH to the FDA. She explained that the purpose of the BPCA legislation is to apply therapeutic findings for relabeling. She noted that, over the past several years, the program has had to address some global issues: extrapolation, outcome measures, clinical trial design, and formulations.

Dr. Zajicek reviewed the following BPCA program clinical trials.

Lorazepam for Status Epilepticus. This trial involved two studies comparing lorazepam and diazepam to treat status epilepticus. Study 1 looked at pharmacokinetics (PK) and preconsenting children for emergency room (ER) visits. Study 2 looked at efficacy and safety. Another aspect of this trial was using exception from informed consent in the ER. Dr. Zajicek briefly discussed

the definition of exception from informed consent in the FDA's guidance for institutional review boards (IRBs), clinical investigators, and sponsors. The trial went through every step of the guidance. The results of the trial showed that lorazepam and diazepam were equally safe and efficacious. The BPCA program is in the process of submitting the data to the FDA for potential label changes. To date, this trial has produced four publications.

Sodium Nitroprusside for Controlled Hypotension. This trial also involved two studies. Study 1 was a double-blind randomized control trial (RCT) of 0.3–3 mcg/kg/min nitroprusside in children receiving controlled hypotension in the operating room. The second study was a double-blind RCT of nitroprusside in children requiring hypotension in the intensive care unit to determine tachyphylaxis. Efficacy in the pediatric population was established based on adult trials and supported by the dose-ranging trial (Study 1) and an open-label trial of at least 12 hour infusion at a rate that achieved adequate mean arterial pressure control (Study 2) with pediatric patients on sodium nitroprusside. No novel safety issues were seen in these studies in pediatric patients. The results of this trial led to multiple labeling changes for the pediatric use of nitroprusside. To date, this trial has produced three publications.

Lithium for Acute Mania in Children with Bipolar Disease. This trial also involved two studies. Study 1 was a PK and dosing study, and study 2 was a double-blind RCT for efficacy and safety. The trial has resulted in publications describing the study methods, dosing strategies, and lithium PK. Slow recruitment was an issue for the trial. Study 2 results are pending submission to the FDA.

Oral Baclofen for Spasticity. There were two components to this trial: a chart review to determine feasibility and a PK/pharmacodynamics (PD) study. One paper on population PK has been published for this trial. Other publications are pending.

Meropenem for Acute Intra-abdominal infections in Infants Younger than 90 Days of Age. This was a PK, safety, and efficacy study in 200 infants. The results showed that meropenem is safe and effective for treating acute intra-abdominal infections in neonates. The FDA is reviewing the study's data for potential labeling changes. The basis for the study was to address questions about the adverse event profiles associated with meropenem versus imipenem/cilastatin therapy in a retrospective cohort study of 5,566 infants. So far, the BPCA meropenem trial has resulted in five papers.

Azithromycin (AZI): Treatment of *Ureaplasma urealyticum* Pneumonia and Effect on Bronchopulmonary Dysplasia (BPD). One study has been completed on PK and dosing. The results showed that 20 mg/kg/day for 3 days was the effective dose. A second ongoing study is investigating AZI to prevent BPD in *Ureaplasma*-infected preterm neonates. The outcome measure is eradication of respiratory tract *Ureaplasma* infection that might lead to physiologic BPD in preterm neonates. The study will compare pulmonary outcomes at 36 weeks postmenstrual age and 6 months adjusted age in infants treated with AZI versus placebo. This trial has resulted in four publications to date.

Vincristine, Actinomycin-D. This trial investigated the relationship of dose, PK, age, and other parameters to veno-occlusive disease in young children with cancer who have been treated with these drugs. The trial was conducted by the Children's Oncology Group (COG). Studies included line-clearing method; PK; chart review to gather PD data on neurotoxicity, hepatotoxicity,

dosing, and demographics; and PK/PD modeling. The PK/PD modeling study is ongoing. To date, the trial has produced a series of publications.

Dopamine. The study of the use of dopamine to control neonatal hypotension has been challenging due to the lack of equipoise among neonatologists and consistent outcome measures. Dr. Zajicek reviewed a 2012 Neonatal Research Network pilot study of dopamine to treat neonatal hypotension. This pilot study generated numerous questions about validating endpoints for neonates with hypotension. She noted the following needs for neonatal studies:

- Improved feasibility: innovative clinical trial designs, observational data gathering, consent issues
- Rationale for extrapolation from preclinical models, children/adults
- Validation of clinical trial endpoints, including biomarkers (biochemical, imaging).

Hydroxyurea. The Baby HUG trial, which was co-funded by the National Heart, Lung, and Blood Institute (NHLBI), was conducted to determine the safety and effectiveness hydroxyurea to treat children with sickle cell disease. This was an RCT (placebo versus hydroxyurea) of about 200 children. Outcome measures included acute chest syndrome, pain, dactylitis, and transfusion. The trial has resulted in 59 publications and important recommendations for treating children with sickle cell disease. The study results have been submitted to the FDA.

Dr. Zajicek reviewed the following BPCA projects.

Electronic Health Records (EHRs) Project. This collaborative project, which was co-funded by the Health Resources and Services Administration (HRSA), was conducted to determine whether EHRs can be used to collect data on use of or adverse events related to asthma and second generation antipsychotic medications in nonacademic medical settings. The project was implemented through the American Academy of Pediatrics (AAP) Pediatric Research in the Office Setting (ePROS) Comparative Effectiveness Research through Collaborative Electronic Reporting (CER2) network. In addition, HRSA has created the Confederated Pediatric Electronic Health Record Research Network (CPEHRRN) to conduct cutting-edge pharmacoepidemiological studies of EHRs from about 800,000 U.S. children.

Clinical Trial Design. The BPCA program has supported the publication of several papers on clinical trial design for pediatric therapeutics.

Dr. Zajicek explained that the BPCA program is funded through collaborations with NIH ICs in proportion to the IC's involvement in the BPCA program. These ICs and their areas of collaboration are as follows:

- NHLBI
  - Pediatric Respiratory Outcomes Program (PROP)
  - Baby HUG Trial
- National Institute of Allergy and Infectious Diseases and NHLBI
  - Co-funding of pediatric asthma outcomes workshop
- National Institute of Neurological Disorders and Stroke
  - Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) Trial
  - NeuroNext migraine prophylaxis trial

  - Collaborations with NIH ICs
- National Cancer Institute (with COG)
  - Vincristine
  - Actinomycin-D
  - Methotrexate
  - Daunomycin
- National Institute of Diabetes and Digestive and Kidney Diseases
  - TrialNet
  - DirectNet
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
  - Grant co-funding to prioritize dermatologic conditions and treatments
- National Library of Medicine
  - Efforts on developing the STEP (Safety and Toxicity of Excipients in Pediatrics) database with the European Union.

Dr. Zajicek listed 18 BPCA outcome measure projects that have been recommended for funding:

- Development of a PK algorithm to improve neonatal outcomes (Duke University)
- Advanced MRI to assess neonatal care and outcome (University of Texas Health Sciences Center)
- Targets and barriers for hydroxyurea use in sickle hemoglobinopathies (Columbia University)
- Improving management of the neonatal abstinence syndrome (University of Utah)
- Cardiac outcome measures for pediatric muscular dystrophy (University of Pittsburgh)
- Outcome measures for chronic lung disease of prematurity (University of North Carolina, Chapel Hill)
- Small volume fentanyl PK/PD and pharmacogenetics in neonates (University of Colorado)
- Outcome measures for trials in children with autism (University of California, Davis)
- Wireless home-based tools for studying sleep in autism (Vanderbilt University)
- Pediatric cardiac intensive care data standards repository (University of Michigan)
- Methadone versus morphine PK/PD in infants after cardiac surgery (Stanford University)
- Predictors of vincristine-induced peripheral neuropathy (University of Indiana)
- Nasal potential difference studies utilizing CFTR modulators (University of Alabama Birmingham)
- Efficacy outcomes measures in antihypertensive trials in children (Case Western Reserve University)
- Effect of body mass index on exposure-response relationships to lisinopril in Children (Case Western Reserve University)
- Advancing Patient Reported Outcomes (PROs) in children with cystic fibrosis (University of Washington)
- Pediatric hypertension outcome measures (AECOM)
- Improving BPD predictors and outcomes for clinical trials (Tufts University).

Two areas of infrastructure needs are training and clinical trials network. To address clinical pharmacology training, the BPCA program has collaborated with the National Institute of General Medical Sciences T32 training program and the NICHD T32 training program. To address infrastructure needs for basic/translational/clinical drug development, the U54 Research in Pediatric Developmental Centers Program was funded at four sites. The Pediatric Trials

Network (PTN) created a flexible infrastructure to perform pediatric clinical trials. The PTN's core elements are:

- Management (site performance)
- Study design/clinical pharmacology
- Recruitment
- Formulations development
- Sample assay
- Device development/validation.

Dr. Zajicek described the activities at the Duke University PTN site, which includes

- Developing "therapeutics"
- Using other means to gather and incorporate data to minimize recruitment
- Increasing the number of academic sites and investigators
- Incorporating training into clinical trials
- Incorporating device validation into clinical trials
- Using small-volume analytics for PK specimens.

In 2002, the BPCA program recognized continual problems with the lack of pediatric formulations, including excipients, intravenous (IV) volumes, and oral dosage forms. To help address pediatric formulations issues, the NIH–FDA Formulations Platform Inter-Agency Agreement was implemented. The purpose of this agreement is to develop an approach for producing oral dosage forms of various Biopharmaceutics Classification System class drugs that are stable in heat and humidity, tasteless or taste-masked, preferably solid orally dissolvable dosage forms, and in clinically useful dosage increments.

In summarizing, Dr. Zajicek said there has been steady progress in improving pediatric therapeutics, particularly in the areas of publications, labeling, and regulatory training. However, areas of need remain; they include extrapolation, outcome measures, clinical trial designs, and formulations.

Over 110 Years: What Have We Learned About Using Therapies to Treat Children?

M. Dianne Murphy, M.D., Director, Office of Pediatric Therapeutics, Office of the Commissioner, FDA

Dr. Murphy presented the FDA's perspective on accomplishments and future directions for pediatric therapeutics, specifically decreasing the use of off-label drug products by providing information from studies in pediatric patients. She began by reviewing the historical milestones and legislation regarding pediatric drugs.

- 1902—The Biologics Control Act is enacted following the death of 22 children from tainted antitoxins.
- 1938—Federal Food, Drug, and Cosmetic Act (FD&C Act) mandates that drugs must be safe; enacted after 100 deaths, many in children, after use of Elixir Sulfanilamide.
- 1962—Following the thalidomide tragedy in Europe, the Kefauver–Harris amendments require effectiveness.
- 1962—The FD&C Act is amended; drugs not tested in children should not be used in children.

- 1974—AAP Committee on Drugs issues guidelines for evaluating drugs for pediatric use.
- 1977—AAP issues guidelines for ethical conduct in pediatric studies.
- 1979—The FDA requires sponsors to conduct pediatric clinical trials before including pediatric information in the labeling.
- 1990—The Institute of Medicine holds a workshop regarding the lack of labeling for pediatric drugs.
- 1992—The FDA proposes the Pediatric Labeling Rule and proposes extrapolation of efficacy from other data.
- 1994—Final Rule on Pediatric Labeling formalizes extrapolation of efficacy and requires manufacturers to update labeling if pediatric data exist; however, it allows a disclaimer to the labeling for drugs not evaluated in children.
- 1994—The Pediatric Plan encourages voluntary development of pediatric data.
- 1997—The Food and Drug Administration Modernization Act (FDAMA) creates pediatric exclusivity provision (voluntary) and provides 6-month exclusivity incentive.
- 1998—The Pediatric Rule (mandatory) states that products are required to include pediatric assessments if the drug is likely to be used in a ''substantial number of pediatric patients'' (50,000) or if it may provide a ''meaningful therapeutic benefit.''
- 2002—The Pediatric Rule is declared invalid by D.C. Federal Court because the rule exceeded the FDA's authority.
- 2002—FDAMA is reauthorized as BPCA. It maintains 6-month exclusivity added to patent life of the active moiety, creates the Office of Pediatric Therapeutics, and mandates pediatric focused safety reviews.
- 2003—The Pediatric Research Equity Act (PREA) re-establishes many components of the FDA's 1998 Pediatric Rule; orphan products are exempted.
- 2007—The Food and Drug Administration Amendments Act reauthorizes BPCA and PREA for 5 years; the Pediatric Review Committee is formed; studies submitted will result in labeling; negative and positive results of pediatric studies will be placed in labeling.
- 2012—The Food and Drug Administration Safety and Innovation Act makes BPCA and PREA permanent.

This legislation has allowed the FDA to incentivize and require pediatric drug product development and to build liaisons with the NICHD, the NIH, and academia. FDA–NIH collaborations have developed a knowledge base about the process to encourage academicians to submit data to the FDA for review and potential relabeling for pediatric therapeutics.

Dr. Murphy discussed the stages of the evolution of pediatric drug development, which include the involvement of the FDA, investigators, physicians, and parents.

- Stage 1—Off-label use is just the state of being for pediatric therapy, and the experts know how to use these products.
- Stage 2—Trials are important, but children are a vulnerable population and should not be in research.
- Stage 3—Having products studied in pediatrics is important, but the activity of pediatric clinical trials in this area is not important to investigators or their careers as they already know how to conduct and report pediatric trials.
- Stage 4—Trial requests and data requirements are different if the data from a trial are to be submitted to the FDA for marketing approval for pediatrics, but this is not the investigators' problem.

- Stage 5—There are a number of models of interactions with the FDA when therapies are needed, such as individual Investigational New Drug (IND) applications, sponsor-related studies, and NICHD-related studies.
- Stage 6—Pediatricians and families need to be part of larger standing research networks if pediatric studies are going to be completed in an efficient and effective manner.
- Stage 7—Europe has mandated pediatric networks and funding for them and actually has a larger pediatric population than the United States.
- Stage 8—Stakeholders need to unite in their efforts to provide a U.S. pediatric product development research network that can deliver data for potential relabeling to the FDA and international regulators.

Dr. Murphy listed the following needs, accomplishments, and issues for pediatric product development in the 21st century:

- Pediatric product development is necessary to meet the standards of the 21st century to continue to improve pediatric health.
- Regulatory and congressional efforts over the last 15 years have changed what is going to be accepted for pediatric therapies.
- The role of the pediatrician as either practitioner or academician is increasingly important in accomplishing this pediatric public health issue.
- Product development trials must be implemented in a manner that permits the data to be submitted to the FDA in a searchable manner.
- Product development trial investigators should have discussions with FDA scientists before trial implementation, during implementation if there are any issues, and before data submission.
- The FDA and the NICHD are working together to have patient-level data (anonymized) available to researchers.
- Data from pediatric product development trials should inform future trials, particularly in the area of failed trials.
- Committing to a pediatric product development trial means all investigators are held responsible for meeting goals, otherwise they will endanger the network or be dropped.
- Public health (governments), academia, and business have to work together to make this happen.
- Approaches that have worked include contracts versus grants, data reproducibility, data that survive inspections, and validating endpoints or incorporating validating efforts into trials.
- More trained pediatric investigators and more recognition by academia for this type of public health work are needed.
- Continued development of FDA–NICHD interactions at the Division levels within the FDA is needed.
- An effective, efficient pediatric product development network needs to be developed.

Dr. Murphy described the progress so far. From 1997 to 2014, 546 products have been studied in pediatrics and have new pediatric information in the label. Last year, the first product study results were submitted and labeled as a result of the "docket" process involving the FDA, the NIH, and investigators. About a dozen more products are soon to be submitted to the FDA from the NICHD. Two hundred and ninety eight products studied under the pediatric legislation have had reviews by the Pediatric Advisory Committee for postmarketing safety. Monthly conferences with four other regulatory authorities have resulted in discussion of more than 200 products and resolution of many trial design, safety, and ethical issues.

Dr. Murphy said there are two general principles for pediatric drug development: (1) pediatric patients should have access to products that have been appropriately evaluated, and (2) product development programs should include pediatric studies when pediatric use is anticipated. She noted that academicians and practitioners have always been part of product development trials. As this activity has increased, more academicians and practitioners need to be involved, and they need to understand the differences in the standards required by the FDA versus data submitted for publication. Pediatric networks need to be highly efficient, knowledgeable, and able to deliver what they promise while maintaining high ethical and scientific standards.

Dr. Murphy reviewed the positives concerning clinical investigators and pediatric product development. Clinical investigators have expertise about the disease and therapies. They have access to the patient population, interactions with their families, and access to pediatric-specific resources. In addition, clinical investigators have institutional familiarity and the desire to improve patient treatment options.

Regarding issues with FDA requirements, clinical investigators need to understand that the trial design should have been discussed with the FDA, and they should know how to interact with the FDA. Clinical investigators should have expertise in study implementation issues including IRB's, data systems and laboratory requirements. Clinical investigators should also have the ability to provide source data, respond to inspections, and have reproducible results.

Problems with clinical investigators have included the lack of documentation for parental permission or pediatric assent, the lack of IRB process documentation, and the lack of reproducibility of laboratory tests. Problems also include the inability to validate documentation, poor quality of data, and the inability to enroll or follow patients.

Dr. Murphy presented two graphs. One showed an overview of failed BPCA pediatric efficacy trial outcomes from 1998 to 2012 by therapeutic group; the other showed a cluster distribution of failed pediatric trials by disease/disorder. The factors contributing to failed pediatric trials include trial design issues, study endpoint issues, inappropriate patient selection, insufficient sample size, poor dose selection, and difference in PK.

The creation of national or global pediatric networks offers a solution to failed trial outcomes. Advantages of networks include

- Investigator vetting
- Process streamlining with careful documentation
- Central IRBs
- Central contracting
- Performance metrics
- Quality reviews as part of processes
- Identification of efficiencies and effectiveness processes
- Expertise in interactions with regulators.

Networks are necessary because children should not be in a trial that is not optimally designed to answer the question. Data loss verges on unethical conduct. The cost of standing up and taking down individual networks for each product is prohibitive. The most frequent failure is that of recruitment—promising more than can be delivered.

There are a number of concerns for 21st century pediatric product development. Products for many pediatric-specific and rare diseases are not studied. Many of the studies that have been performed have been in older age groups and for products with potential use in both adults and pediatrics. Products for young children, neonates, and rare pediatric diseases are still a challenge to study. Validated endpoints in younger children or rare pediatric diseases are lacking. Some fundamental tools are still missing (for example, validated neurocognitive assessment tools). The "tyranny of small numbers" makes studies logistically difficult. Pediatric-specific expertise within industry, the FDA, the NIH, and nonpediatric academic centers still needs to grow.

With regard to 21st century projections, products used in children should be studied in children within the ethical parameters established for pediatrics. Children are protected *through* research, not from it; knowledge is powerful medicine. The last fourth of the 20th century saw legal mechanisms put in place on an international scale to address the need for pediatric product information. The FDA and other stakeholders have learned much from the more than 500 products studied in pediatrics but are now entering an even more difficult level of product development. Effective and efficient pediatric networks are needed to move forward in improving pediatric therapies.

In conclusion, Dr. Murphy said the pediatric medical community should insist on incorporation of evidence-based treatment sufficient to support pediatric product labeling. Journal publication and expert opinion are not sufficient. Pediatric product labeling is not the sole responsibility of the FDA or drug product developers. The entire pediatric community should be committed to address the pediatric product labeling issue. This community includes academic researchers and community practitioners, patients and patient organizations, professional societies, and allied health care providers. Most importantly, stakeholders need to develop networks to conduct appropriate pediatric clinical trials.

Pediatric Trials Network

Danny Benjamin, M.D., Ph.D., Faculty Associate Director, Duke Clinical Research Institute, Duke University Medical Center

Dr. Benjamin reported on the progress of the PTN. He began by describing the PTN's structure and administrative core and showing a map of PTN sites. The PTN has implemented 33 projects: 17 are prospective–retrospective clinical trials and 16 are laboratory, meta-analytic, or infrastructure development trials. The PTN has 160 sites. A total of 2,773 subjects have been enrolled at 92 sites. Many sites have implemented more than one study. Forty-nine molecules are currently under study.

The following innovations have been, or are currently being, spearheaded by the PTN:

- Data access
- Federated IRB
- Master contracts
- Master protocols
- Multi-arm PK/PD and safety studies
- Obesity dosing
- Pediatric opportunistic PK studies (POPS).

Dr. Benjamin reviewed 10 trials completed by the PTN; several represent partnership efforts with other networks. The trials studied nine molecules and one device.

Acyclovir. This was an open-label PK and safety study in neonates. The safety evaluation used chart reviews and analysis of electronic medical record (EMR) data in infants. There were 32 PK analyses, 60 chart reviews, and analysis of 400 EMRs. Three sites conducted the PK analyses, and four conducted retrospective chart reviews. Findings: Dosing based on postmenstrual age. Clinical study report (CSR) data were submitted. Label change is pending on additional retrospective data analyses.

Ampicillin. This was a PK study and retrospective safety analysis of EMR data in infants. There were 75 infants in the PK analyses. The safety analysis included 68 infants from a retrospective cohort and 200,000 infants from an electronic medical record. Findings: Ampicillin is well tolerated; dosing based on postnatal age and gestational age. CSR data were submitted in December 2014. Label change is pending.

Clindamycin Obesity. This was an open-label PK and safety study of 22 obese children 2–17 years of age at 4 sites. Findings: Interim analysis—dose based on weight alone; no adjustment based on obesity. CSR data will tentatively be submitted in April 2015.

Fluconazole. This was a randomized, double-blind, PK and safety study of prophylaxis treatment in infants weighing less than 750 g. Risk of spontaneous intestinal perforations was analyzed. Of the 361 subjects, 188 received fluconazole and 173 received placebo. The study was conducted at 32 sites. Findings: Fluconazole was well tolerated but did not prevent primary outcomes of death or candidiasis; there was no increased risk of spontaneous intestinal perforation. CSR data will tentatively be submitted in January 2015.

Hydroxyurea. This was an open-label PK study of liquid hydroxyurea formulation in 39 children 2–17 years of age with sickle cell anemia at 8 sites. Findings: Dose adjustments are not required based on formulation or age. CSR data were submitted. Label change is pending review of Baby HUG results.

Lisinopril. This was an open-label PK and safety study of 26 children 2–17 years of age with kidney transplant at 7 sites. Findings: Lisinopril was well tolerated; exposure was similar to children with normal kidneys. CSR data were submitted in December 2014. Label change has been requested.

Metronidazole. This was an open-label PK and safety study of 24 premature infants at 3 sites. Findings: Metronidazole was well tolerated; dose by postmenstrual age; loading dose. CSR data were submitted. Label change pending results of the current study under way titled the Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections trial (SCAMP).

Midazolam. This was a secondary analysis of available PK data in children and analysis of patient-level data from RAMPART study to support indication for status epilepticus in children and nerve agent treatment in children. Analyses are ongoing. Pre-IND meeting was requested in December 2014.

Piperacillin-Tazobactam. This was an open-label PK and safety study in 32 infants younger than 61 days of age at 4 sites. Findings: Piperacillin-tazobactam was well tolerated; dosing based on postmenstrual age. CSR data were submitted to the FDA. Label change is pending results of SCAMP.

TAPE. This was an observational study of 2-D and 3-D Mercy TAPE weight estimation devices in 625 evaluable children 2–16 years of age at 3 sites. Findings: These devices outperform the Broselow tape device for pediatric weight estimation and can be used in a wider range of children. CSR data were submitted. Device approval is pending.

Dr. Benjamin reviewed six ongoing PTN studies.

Methadone. This is an open-label PK and safety study of enteral methadone in children 3 months to 18 years of age. The study's purpose is to evaluate methadone PK and investigate its safety profile and the influence of genetic polymorphisms, metabolites, and PD. Target enrollment is 24–36 subjects. The study is being conducted at five sites. Enrollment is ongoing (N = 22).

Pantoprazole. This is an open-label PK and safety study in obese children 6–17 years of age. The study's purpose is to evaluate absorption, elimination, and clearance of pantoprazole in children; compare these parameters with those in nonobese children; and investigate safety profile and genetic factors on PK. Target enrollment is 40 subjects. The study is being conducted at three sites. Enrollment is ongoing (N = 16).

POPS. This is an open-label opportunistic PK study of understudied drugs in children given as part of standard of care. Target enrollment is 2,000 subjects. The study will be conducted at up to 40 sites in the United States, Singapore, Israel, the United Kingdom, and Canada. To date, 37 drugs of interest (DOI) have been identified. PK analyses are ongoing as DOI cohorts close. The data will be used for support of CSR submissions (clindamycin and ampicillin) and the development of new studies. Enrollment is ongoing (N = 1,525).

SCAMP. This is a randomized safety study to evaluate ampicillin, metronidazole, clindamycin, and piperacillin-tazobactam in infants with complicated intra-abdominal infections at 51 sites. Target enrollment is 374 subjects. Enrollment is ongoing (N = 20).

Sildenafil. This is an open-label PK and safety study in infants 28 weeks of gestation or less. Cohort 1 will receive standard of care (oral or IV). Cohort 2 will receive a single IV dose. Target enrollment is 41 subjects. The study is being conducted at seven sites. Enrollment is ongoing (N = 25).

Staph Trio. This is an open-label PK and safety study of rifampin, ticarcillin-clavulanate, and clindamycin in infants. Target enrollment is 48 subjects. The study is being conducted at 11 sites. Enrollment is ongoing (N = 39).

The following trials are starting this fiscal year.

Baby TAPE. This is an open-label study to develop a weight estimation device in newborns and infants. Target enrollment is 2,000 subjects at up to 7 sites. Enrollment is to begin May 2015.

Furosemide. This is a randomized, placebo-controlled, masked, PK, safety and efficacy study in premature infants at risk for BPD. Target enrollment is 120 subjects at 25 sites. Enrollment is to begin June 2015.

Dr. Benjamin reviewed pediatric–biodefense dual projects that have clinical utility- and disaster-related components, PTN pediatric obesity projects, and BPCA priorities that have been conducted by the PTN in the following areas:

- Respiratory diseases
- Intensive care
- Biodefense research
- Pediatric cancer
- Psychiatric disorders
- Neurological diseases
- Neonatal research
- Adolescent research
- Hematologic diseases
- Dermatologic diseases
- Gastrointestinal diseases
- Special considerations.

Dr. Benjamin reviewed the PTN presentations and publications to date. He discussed training; FDA meetings by drug/device; the Mercy TAPE study; and the acyclovir, ampicillin, and lisinopril population PK studies.

Questions and Discussion

Facilitator: Dr. Taylor-Zapata

Questions and discussion topics included:

- Recruitment/enrollment impediments and barriers because of black box warnings
- Mechanisms for guidance on pediatric trial designs in dermatology
- Enrollment of subpopulations.

Dr. Taylor-Zapata ended the meeting by thanking all of the local and virtual attendees for being a part of this meeting and their continued interest in the BPCA program.