Best Pharmaceuticals for Children Act
Annual Prioritization Meeting
December 8–9, 2011
Legacy Hotel and 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 review lessons learned from the implementation of the BPCA Program and to discuss topics of study for pediatric therapeutic areas based on recommendations from experts in pediatric medicine and research. The role of the meeting participants was to assist the NICHD in identifying the 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 goal of the BPCA legislation is to improve labeling of pediatric drugs. 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. Currently, 21 NIH Institutes and Centers contribute to BPCA's annual funding of $25 million for clinical research, clinical drug trials, and training. The goal of BPCA's initial implementation was to fund studies of off-patent drugs that needed labeling changes. During implementation, many issues were uncovered, including the need to evolve from drug prioritization lists to drug development.

Lessons Learned from the NIH Implementation of the BPCA Program

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

Some of the lessons learned to date include the need for partnerships, the need for an objective prioritization process, feasibility determination (frequency of use/condition defined for children), and the need for infrastructure so that infrastructure is not the driver of feasibility.

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. Considerations for prioritization included the availability

of safety and efficacy data and whether reformulations are needed. 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. Considerations for prioritization included potential health benefits of research and adequacy of necessary infrastructure.

The complexities of the prioritization process involve the overlapping issues and interaction among prioritization, feasibility, and infrastructure. Prioritization should be objective and not be constrained by infrastructure problems. It should maximize public involvement; provide input in therapeutic areas and medications; and help determine therapeutic areas, specific diseases, and medications of greatest interest. For 2011, the areas of focus are hematology, pulmonary, and renal therapeutics and formulations.

The complexities of pediatric clinical trials include the small number of available patients; the need for data collections that might augment clinical trials; phenotyping; validated outcome measures; the need for a convenient, pediatric and family-friendly environment; consent/assent; and blood sampling.

Feasibility issues include problems with databases, frequency of condition, frequency of medication use, problems with adult ICD-9 (billing) codes, lack of connection between condition and prescription fills, and relationship to infrastructure.

The BPCA Program has partnered with existing infrastructure for clinical trials and data collection for clinical trials construction:

- The National Cancer Institute/Children's Oncology Group—vincristine, actinomycin-D, daunomycin, methotrexate, and isotretinoin
- The National Heart, Lung and Blood Institute (NHLBI)—hydroxyurea (Baby HUG)
- The Health Resources and Services Administration (HRSA): Pediatric Emergency Care and Applied Research Network (PECARN)—lorazepam for status epilepticus
- The NHLBI: Pediatric Respiratory Outcomes Program—respiratory medications
- The NICHD: the Neonatal Research Network (hypotension trial feasibility) and the Critical Care Research Network (medications used to treat status asthmaticus in intensive care units [ICUs]).

The BPCA Program is developing infrastructure for pharmacology expertise training. Together with the National Institute of General Medical Sciences, the BPCA Program has cofunded T32 pediatric clinical pharmacology training programs at eight sites. The NICHD has funded T32 programs at four sites. In response to the need for a model for basic/translational/clinical drug development, the BPCA developed the U54 Research in Pediatric Developmental Pharmacology Centers Program, which is funded at four sites.

Since 2003, the BPCA Program has completed eight clinical trials. There are seven ongoing clinical trials being implemented through the Pediatric Trials Network (PTN). Other BPCA Program activities include studies of devices, outcome measures, and special populations (children with intellectual and developmental disabilities and neonates). In addition, the BPCA

Program is developing infrastructure through projects such as the PTN, the Pediatric Formulations Initiative (PFI), and the NIH-FDA formulations platform.

In conclusion, the NIH and the FDA have developed a strong partnership in the BPCA Program. There has been slow but steady progress in completion of clinical trials and data submission for labeling changes. However, there is a continuing need for access to observational data for safety and efficacy in children.

The FDA's Perspective and Lessons Learned—BPCA

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

The pediatric community is now better at defining how children are different in their response to therapies. Although therapeutic options for children are improving, about 20 percent of clinical trials for efficacy failed. In 15–20 percent of the trials, enhanced or new pediatric safety signals were found. Determining the correct dose is still a challenge. However, from 1997 to 2011, pediatric studies have resulted in 426 pediatric labeling changes in the United States.

Pediatric clinical trials have a number of unresolved issues:

- Clinical trials that fail to obtain the indication or prove effectiveness can be informative.
- Safety remains a challenge.
- There have been few long-term pediatric studies.
- Pediatric studies need to spend time defining the correct dose.

Because there is little economic interest in obtaining labeling for children, the only reason studies are being conducted is because of two tools: (1) the incentive of 6 months of exclusivity and (2) the requirement that is triggered only if there is a similar adult indication for which a sponsor is seeking an approval. If investigators get the dose wrong or if the effect size is much less than expected and the trial does not demonstrate efficacy—unlike the situation in adult trials where the sponsor will do whatever it takes to modify approach and doses to get the indication—there are no more studies.

Formulations are expensive to develop and difficult for certain types of products. In order to best address the issue of formulations, the NICHD and the FDA have developed a Web-based formulations platform to post publicly available data. The platform consists of three stages, the first of which was just completed and posted.

The United States is still the largest player in conducting pediatric trials, with more than 80 percent of pediatric trials having at least one U.S. site. However, Europe has now received more than 1,000 Pediatric Investigational Plans. A shift in how trials are being conducted and where they are conducted is expected. Pediatric trials require more centers to enroll patients because of the small population size. Networks are mandated in Europe, and they are well on their way to developing pediatric networks. Investigators need to be part of a network where the level of quality control can meet FDA standards.

The role of networks is to develop expertise in design and implementation of pediatric product development trials. Networks can provide pediatric-resourced infrastructure. Network collaboration will develop the science of pediatric endpoints while designing and conducting the product development trials. Networks will help investigators become experts in what the FDA requires for pediatric studies. Networks will allow investigators to share and mine the data to enrich future trials. Both the investigators and the divisions at the FDA are learning about the new processes involved in submission of data generated by the NICHD pediatric contracts and grants.

The "docket" process is a new process for submitting data from the NICHD off-patent drug pediatric trials. Trial data information now has to be assigned an Investigational New Drug (IND) or New Drug Application (NDA) number and linked to a sponsor's labeling. Data need to be submitted in formats that allow multiple reviewers with different expertise to manipulate the data. Data sent into the IND are not transparent. If the goal is to make all of the pediatric studies available to as many people as possible, then it has to come to the FDA in a public way. A new process has been instituted for pediatrics where the investigators and the NICHD meet with the division before sending the data to the public docket. On the docket, expectations are explained and discussed, and data needs and availability are reviewed. The FDA reviewers have to learn that the NIH is not a sponsor and that the data were collected in response to an FDA-issued Written Request (WR), which the NICHD turned into a contract. The divisions then have to negotiate with the label holder after they decide what can go into the label based on what the data will support. The divisions want to be in the strongest possible position, which requires good data.

The first five NICHD contract studies, in response to FDA WRs, are now coming to the FDA. Networks that can deliver pediatric product development clinical trials for the full spectrum of studies are being developed. Half of the products listed in the *Physician's Desk Reference* (minus certain excluded over-the-counter products) that are being used in pediatrics have now been studied in children. Pediatric safety issues and the need for long-term studies are receiving more attention. Neonates and mechanism-of-action targets are the new frontiers for pediatric product development.

Questions and Discussion

The following issues and topics were discussed:

- Collaboration with the United States Pharmacopeia (USP) for pediatric formulations
- Issues of extemporaneous formulations (for example, lack of quality control)
- WR requirements for age-appropriate formulations, including stability and bioavailability
- Drug manufacturer "ownership" of off-patent medications
- Publication of the FDA's medical, pharmacologic, and statistical reviews of trials
- Utility of data posted on the FDA docket
- Availability of study data posted on the docket from the NICHD
- Peer-reviewed reports on the prevalence of drug usage and indication
- Trial design to gather data on oncology products

- Collecting data on pediatric adverse events (AEs) from electronic databases such as the Mini-Sentinel pilot program and the Adverse Event Reporting System
- Quality of assumptions used in the design of clinical trials
- Gaps between actual and expected enrollment in pediatric trials
- Approaches for improving pediatric enrollment
- Harmonization with NIH resources such as the Clinical and Translational Science Awards (CTSA) program and pediatric centers/networks
- Costs per trial
- The role of the American Academy of Pediatrics (AAP) to inform about why certain regulations are required.

Baclofen Study

David Siegel, M.D., Medical Officer, OPPB, NICHD, NIH

Baclofen is a skeletal muscle relaxant that is FDA approved for the treatment of spasticity in adults with multiple sclerosis and spinal cord injury. Although oral baclofen has been used for several decades for the treatment of spasticity in adults and in children, there are very few data regarding the pharmacokinetic (PK) or pharmacodynamic (PD) properties of baclofen in children. There is frequent off-label use of baclofen in children with cerebral palsy (CP). Oral baclofen was listed in the January 2003 *Federal Register* list of drugs requiring further study under the BPCA Program. The FDA issued a WR for studies. Because industry declined, the NICHD sponsored four studies:

- Chart review study
- PK/PD study
- Safety and efficacy trial (a randomized control trial [RCT])
- Observational/safety study (follow-up neurodevelopmental outcomes after 1 year of continuous treatment with baclofen).

Chart Review Objectives. The primary study objectives were to describe the following:

- Characteristics of the pediatric population using oral baclofen to manage the spasticity of CP including age at onset of taking the drug, severity of spasticity, and level of functional mobility.
- Safety of oral baclofen in 200 pediatric subjects (under the assumption that at least 50 percent will use oral baclofen for a full year)
- Treatment course and reason for treatment changes (from oral baclofen to other therapies, additional therapies, etc.), withdrawal, and AEs associated with treatment and withdrawal.

PK/PD Study Objectives. The primary study objectives were to:

- Determine PK parameters of oral baclofen in children with spasticity associated with CP
- 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 an RCT of safety and efficacy.

Despite delays in the initiation of the study and problems with developing a liquid formulation, preliminary results showed that investigators were able to successfully describe the PK of baclofen and obtain PD measures for spasticity that seem to show an effect of baclofen.

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

Dr. Siegel

There is substantial off-label use of meropenem in infants <3 months of age as presumptive therapy in intra-abdominal infections. Meropenem is FDA-labeled for pediatric patients >3 months of age for meningitis and complicated intra-abdominal infections. In previous studies, its toxicity has been found to be similar to imipenem except that it may be less likely to cause seizures.

A clinical trial of 200 infants in four gestational age/postnatal age cohorts was conducted for PK, safety, and efficacy–clinical response. Two blood-sampling strategies were used. Infants were dosed for 3–21 days.

Efficacy Results. Of the 200 infants enrolled in the trial, 195 were included in the efficacy population and 192 of 195 were evaluable for efficacy. Prior to the efficacy assessment, 8 of the 192 infants died. Mortality was highest among infants <32 weeks gestational age (GA) and <2 weeks postnatal age (PNA) (3 of 39). None of the 50 infants with ≥32 weeks GA died prior to the efficacy visit. Efficacy success—defined as being alive with negative cultures from normally sterile body fluids and a presumptive clinical cure score ≥7 at the efficacy assessment—was achieved in 162 of 192 infants. Efficacy success was lowest among infants <32 weeks GA and <2 weeks PNA (29 of 39) and highest among infants ≥32 weeks GA (51 of 55).

Safety Results. This cohort represented a group of critically ill and premature infants with respiratory illness, gastrointestinal disorders, cardiovascular conditions, and blood/lymphatic system problems. Most of these infants were premature with a median GA at birth of 27.8 weeks. Overall, 99 of 200 infants suffered an AE during the study. An AE of special interest was defined as either a seizure or a level II laboratory AE. The proportion of infants with AEs was highest (26 of 39) among infants <32 weeks GA and <2 weeks PNA. Only 21 of 200 infants were determined to have an AE possibly related to meropenem, and this proportion was highest (7 of 39) among infants <32 weeks GA and <2 weeks PNA. Of the 316 AEs reported, only 30 were determined to be possibly related to meropenem. These 30 AEs included 7 seizures and 4 episodes of elevated bilirubin. No AEs were determined to be probably or definitely related to meropenem. Nine infants experienced a level II laboratory AE, and all were <32 weeks GA. These 9 events included 5 elevated conjugated bilirubin levels, 3 elevated serum creatinine levels, and 1 elevated aspartate aminotransferase concentration. Clinical seizures were reported in 10 infants. However, only 1 was confirmed by electroencephalogram (EEG). Seizures were most commonly reported among infants <32 weeks GA and <2 weeks PNA (4 of 39). A total of 36 serious adverse events (SAEs) were reported in 34 infants. SAEs were most commonly reported among infants <32 weeks GA and <2 weeks PNA (9 of 39). Only 2 of the SAEs were determined to be possibly related to study drug (isolated ileal perforation and an episode of

fungal sepsis). There were 11 deaths in the study population. None of the deaths were determined to be related to meropenem. All deaths occurred in infants <32 weeks GA.

Drug Studies in Newborns Revisited

George Giacoia, M.D., Medical Officer, OPPB, NICHD, NIH

Very few drugs have labeling information for newborns in relation to the remarkable number of off-patent and off-labeled drugs used. A very small number of trials have demonstrated efficacy in newborns. Because of this, there remains a need to re-evaluate current approaches for drug studies in this special population. Factors that need to be considered in these studies include:

- The number of drugs used in the neonatal intensive care units (NICUs) and practice standards
- Developmental characteristics (23–42 weeks GA) of the population
- Characterization of newborn conditions and diseases
- Limited knowledge of the clinical pharmacology of drugs across viable GA span
- Cluster of factors that limits or prevents the implementation of drug studies in sick newborns
- Search for evidence—regulatory versus scientific viewpoints
- Regulatory, academic, and economic limitations.

The developmental distance between 23 weeks GA and 42 weeks GA is large, and the full impact of developmental immaturity is unknown. However functional immaturity of physiologic processes and organ function has a profound effect on absorption, distribution, metabolism, and excretion (ADME). Among GA groups, there is great biologic variability and altered responses to drugs, as well as differential mortality. With regard to neonatal diseases and conditions, adaptation to extrauterine life overlaps with the expression of conditions or diseases. Diagnostic criteria for some conditions are not standardized, and definitions of some abnormal outcome variables are not established. There is also biologic variability among neonatal diseases and conditions. Issues for adverse drug effects include the multiplicity of concomitantly used drugs and conditions, potentially toxic excipients, the lack of data systems to identify adverse drug effects, and the lack of prespecifying the types of adverse drug effects.

Studies of drugs in newborns can inform the scientific underpinnings across developmental stages by (1) developing a knowledge base and framework by which FDA-based studies can be developed by pharmaceutical companies, studies of off-patent drugs under the BPCA Program, and scientific-based studies; and (2) adopting an incremental approach for dosing recommendations and demonstration of efficacy and safety. Components for pediatric drug studies should be as follows:

- Harmonized diagnosis
- Determination of dosing and exposure response
- Preliminary studies (may include *in vitro* animal studies)
- Development of an updatable prior knowledge database
- Simulation and modeling *in vitro* studies
- PK and/or PK-PD studies
- Exposure-response studies
- Identification and development of endpoints and biomarkers
- Validation and testing in ongoing studies

- Development of a newborn knowledge database, with analyses of failed trials
- Pilot study to determine feasibility of performing an efficacy trial
- Design and performance of definitive efficacy trials to serve as a model trial for future FDA-compliant studies
- Development of pediatric biomarkers, harmonization of outcome and composite endpoints, and harmonization of long-term outcomes across therapeutic areas.

The paradigm shift in studying drugs in newborns involves:
- Promoting rational therapeutics for the most vulnerable population
- Concentrating on achievable goals
- Testing new approaches including comparative and other effectiveness trials
- Collecting valuable information/evidence from opportunistic and observational trials
- Giving priority to determining appropriate dosing and identifying/discovering PD measurements that can serve as surrogates of efficacy
- Identifying a mechanism to involve industry and neonatal networks in addressing the needs.

Status Epilepticus (SE) Progress Report

Dr. Giacoia

The investigation of lorazepam treatment for SE involved two studies. Eleven U.S. and Canadian institutions participated in the studies.

Study 1—Lorazepam PK. The primary objective of this study was to evaluate the PK of a single intravenous (IV) dose of lorazepam in pediatric patients aged 3 months to less than 18 years treated for SE or with a history of SE in order to determine the appropriate dose of lorazepam for Study 2. The study was initiated on April 7, 2005, and completed on October 3, 2006. Sixty-nine patients were enrolled and evaluated.

Study 2—Use of Lorazepam for the Treatment of Pediatric SE: A Randomized Double-blinded Trial of Lorazepam and Diazepam. This was the first study performed in pediatrics using an exception from informed consent (EFIC). The study's primary objective was to test whether lorazepam is efficacious and safe in treating pediatric SE compared with diazepam. Secondary objectives were to (1) determine population PK of lorazepam using sparse sampling, (2) determine the feasibility of identifying patients for informed consent prior to arrival in SE for an RCT of lorazepam versus diazepam for pediatric SE, (3) describe the experience of community consultation and public disclosure, and (4) determine the feasibility of enrolling pediatric patients under an EFIC.

Pretrial challenges included defining SE and clarifying what type of seizure-like activity qualified. The value and role of EEGs and clinical cessation of seizures were discussed as endpoints. Another challenge was measurement of excipients. Challenges of using an EFIC included defining community, the length of community outreach, poor attendance at community meetings, and time for institutional review board (IRB) approval (median of 10 months). Challenges during the trial included hectic emergency care in a chaotic atmosphere, enrollment

disqualification due to home or prehospital treatment with benzodiazepines, late information leading to early termination, and implementation of the randomization scheme.

EFIC activities began in January 2007 and varied by site, depending on requirements by individual IRBs. Activities included surveys, focus groups, community meetings, newspaper ads, a national press release, TV spots, radio announcements, brochures, flyers, a national Web site, and a 24-hour hotline.

So far, 278 participants have been randomized into the study; 241 participants were dosed. The intent-to-treat population (includes all randomized and dosed participants) is 241; 262 participants are required to complete Study 2. Of the 278 participants, 228 required only an initial dose, 39 required a second dose 5 minutes after the initial dose, and 11 required a third dose 12 minutes after the initial dose. Of the 278 participants, 101 had a prior seizure and 73 had not. Data are missing for 104 of the participants. Of the 101 participants with a prior seizure, 25 had febrile seizures and 75 had afebrile seizures. Seizure type is missing for 1 participant.

Questions and Discussion

The following issues and topics were discussed:

- Participants' glucose and electrolyte values (normal) and cases of encephalitis (a few) and meningitis (none)
- Study infrastructure development
- Lessons learned in conducting studies
- Ability of clinical research organizations to collect quality data and adhere to protocols
- Difficulties in obtaining informed consent for premature infants
- The EFIC process as a deterrent to conducting studies
- Publishing lessons learned about process issues of conducting pediatric clinical trials.

The PTN

Danny Benjamin, M.D., Ph.D., M.P.H., Professor of Pediatrics, Duke University School of Medicine, Faculty Associate Director, Duke Clinical Research Institute

The primary objective of the NICHD-sponsored PTN is to create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health. The PTN is studying product formulation, drug dose, efficacy, safety, and device validation. Evidence of success will be completed trials that improve dosing, safety information, labeling, and ultimately child health. The PTN has five core components: clinical pharmacology, PK, safety and ethics, devices, and mentorship.

In 2011, protocols were completed for studies of hypertension, metronidazole, hydroxyurea, acyclovir, understudied drugs (the population PK [POPS] opportunistic study), lisinopril PK, and Taking the Guesswork out of Pediatric Weight Estimation (TAPE). Protocols have been drafted for studies of midazolam (analysis of previously collected data), ampicillin (PK and efficacy study in infants), and obesity (analysis to provide preliminary data and hand-held application for dosing in obese children).

Dr. Benjamin reviewed the objectives, study population, study duration, number of study sites, and enrollment status of the following protocols.

- Safety and PK of Multiple Dose Metronidazole in Premature Infants
- An Open Label Study to Describe the PK of Acyclovir in Premature Infants
- PK and Relative Bioavailability of a Liquid Formulation of Hydroxyurea in Pediatric Patients with Sickle Cell Anemia
- PK of Understudied Drugs Administered to Children per Standard of Care
- Safety and PK of Lisinopril in Pediatric Kidney Transplant Recipients
- TAPE: Validation of the Mercy TAPE.

Dr. Benjamin presented the following data from the metronidazole safety and PK study: demographic distribution, individual EBE PK parameter estimates by postnatal age group, concentration versus time, and clearance versus postmenstrual (postconception) age. The data have not been peer reviewed.

The PTN mechanism for conducting multiple trials allows master service agreements with study sites. Once the master service agreements are in place, subsequent trials become addendums to the contract. If a study site is successful and delivers on time and on budget with its first small trial, the PTN will award the site a contract for a second, larger trial. The PTN mitigates risk to the NIH and investigators and facilitates communication with the NIH. The PTN has reduced per-patient pricing by 30–50 percent and pricing for faculty (that is, thought leaders). Operations (staff) efficiency has been much improved. The PTN has shown that main contract timelines can be shortened through its more efficient processes.

In 2012, the PTN has tentative plans for studies of *Staphylococcus aureus* infection, hypertension in transplant patients, obesity and exposure safety, POPS II, methadone for pain management, acyclovir for neonatal herpes simplex virus, and adolescent statin use. The POPS study provides an opportunity for the new site to participate in the PTN. Subjects of the POPS study are children who interact with the health care system (for example, admitted to the pediatric intensive care unit (PICU) or seen in the emergency room). The study will focus on prioritized off-patent therapeutics that have insufficient dosing information in their clinical stratum.

Questions and Discussion

The following issues and topics were discussed:

- The PTN's training of sites, development of standard operating procedures, and involvement of international sites for the device trial
- Short- and long-term outcome studies
- Sample integrity and interim analyses of samples
- Preliminary and supportive data to inform subsequent trials; comparison to epidemiologic data
- Role of the POPS study mechanism to change labeling
- Value of the PTN in advancing pediatric therapeutics and conducting pediatric drug studies

- Design/determination of meaningful endpoints for pediatric drug studies.

Lithium: The Final Frontier

Dr. Taylor-Zapata, M.D.

Lithium is currently labeled for treatment of acute mania episodes and maintenance in bipolar disorder in adults and children older than 12 years. The BPCA Program listed lithium in 2004 (WR received). That same year, a Request for Proposals was developed for pediatric lithium studies of pharmacology, efficacy and safety, and long-term safety. In 2005, a study was proposed, reviewed, and awarded. The original proposal included five studies, which were later combined into two large studies. Study 1 investigated PK and safety of maximum tolerated dose (300, 600, and 900 milligrams). It enrolled 60 subjects over 18 months. Study 2 investigated efficacy and safety (acute efficacy and discontinuation studies; long-term safety). Lithium was randomized to placebo in this 8-week study, after which the subjects were enrolled in a long-term (24-week) safety study. Responders were subsequently enrolled in a discontinuation (withdrawal) study and followed for several months.

The lessons learned from Study 1 involved logistical issues (contract negotiations and protocol deliberations). Lessons learned from Study 2 involved feasibility issues (study design, placebo effect, and recruitment). The target enrollment for Study 2 was 225 subjects. The first subject was enrolled in June 2010. As of December 6, 2011, 46 subjects had enrolled. The expected recruitment timeline was too aggressive. Study 2 expected to enroll about 180 subjects by the end of December 2011. To date, efforts to increase enrollment include recruitment incentives, protocol "advertising," protocol changes (for example, decreasing the number of assessments), and the addition of new study sites. The protocol changes went into effect in June 2011.

In summary, studies that build their program from the ground up—not from the top down—by starting small and starting slowly will not be set up for failure. Studies that use this approach will be better positioned for larger subsequent studies.

Introduction of the 2011 BPCA Therapeutic Area Working Groups

Dr. Taylor-Zapata

The desired outcome of the BPCA Program is labeling changes. The desired outcome of the BPCA prioritization process is to create a prioritized list of pediatric needs that closely aligns with BPCA's mission and goals. Developing a reasonable and feasible list of needs in pediatric therapeutics with studies funded under the BPCA Program can close the gaps in knowledge in the label and scientific knowledge of a therapy.

One of the lessons learned in prioritizing is that more data on the drugs (for example, frequency of use, standard of care, study design, and targeted patient population) being recommended for study are needed early in the process. Expert input is required to gather these data. The initial approach to gathering this data was mass outreach. Because of the poor responses, the BPCA Program concluded that a better approach was needed. The new approach was to seek a broader range of input from more stakeholders with earlier input. In addition, input from outside

evaluators was needed. For the drug list determination, the BPCA Program wanted to make the process more clear and objective.

The prioritization process now incorporates therapeutic expertise by forming working groups in related therapeutic areas. Three working groups are formed each year. The working groups help the NICHD identify gaps in knowledge in the treatments of the disease areas (for example, available evidence and standards of care) and provide the NICHD with their judgment and opinions on the studies that need to be done in their area of expertise (for example, impact and feasibility).

The 2011 working groups are the Hematology Therapeutic Working Group, the Pulmonary Therapeutic Working Group, and the Renal Disease Therapeutic Working Group. The charge to the working groups was to (1) summarize current knowledge, standards of care, and existing data; (2) identify barriers and/or gaps in knowledge; and (3) suggest ways to address barriers and/or knowledge gaps. Each working group convened four teleconferences. They developed lists of key therapeutic gap areas, narrowed down areas of interest, and made final recommendations for study. The working groups' final recommendations are presented below. The goal of this process is to refine the list of drugs for further study under the BPCA Program and further prioritize the recommended studies.

Hematology Therapeutic Working Group

Courtney Thornburg, M.S., M.D. (Working Group Leader), Associate Professor of Pediatrics, Co-Director, Duke Comprehensive Hemostasis and Thrombosis Center, Director, Pediatric Comprehensive Sickle Cell Clinic, Division of Hematology/Oncology, Department of Pediatrics, Duke University Medical Center

The working group focused on the use of anticoagulants for pediatric venous thrombosis. Although thrombosis occurs most frequently adults, it occurs in children across all age groups. Peak incidence is in neonates to 2 years of age and in adolescents 13–16 years of age. Incidence has increased significantly from 2001 to 2007 in all age groups. The risk factors for pediatric thrombosis include abnormalities in the vessel wall, aberrations of blood flow, and alterations in the constituents of the blood. Endothelial damage due to intravascular catheters accounts for 80–90 percent of pediatric venous thrombosis. Children are less likely than adults to have idiopathic thrombosis. Arterial thrombosis is less common than venous thrombosis. Patient types include general pediatric patients, infants in NICUs, and children and adolescents in PICUs with diseases that are high risk for thrombosis. Age groups range from younger than 1 year to 18 years.

Eleven anticoagulant drugs are licensed for adults in the United States. All pediatric anticoagulants are used off-label and are often used for indications that are different than those labeled for in adults. Pediatric-specific guidelines for antithrombotic therapy are based on adult guidelines and expert opinion. Drugs used for pediatric thrombosis include:

- Anticoagulants—unfractionated heparin, low molecular weight heparins, warfarin, and new anticoagulants (oral and parenteral) such as direct thrombin inhibitors and anti-Xa inhibitors
- Thrombolytics—tissue plasminogen activator (t-PA)
- Antiplatelet agents—aspirin and clopidogrel.

The working group identified three areas of concern: safety (bleeding risk and effects on bone density due to aluminum loading), efficacy optimization, and implementation. Gaps in knowledge and research needs are in the areas of epidemiology, prevalence, and pathophysiology; therapeutic outcomes; safety monitoring of long-term therapies; and drug dosing. In determining priorities, the working group considered available evidence, different pediatric populations, and potential impact of their recommendations. The working group agreed on four priority areas.

Epidemiology and Pathophysiology of Thrombosis in Children. There are large and expanding vulnerable pediatric populations that are at high risk of thrombosis. Epidemiologic and pathophysiologic data are needed to guide drug-dosing studies and clinical trials to determine the dose response linked to optimal outcome, the incidence of the outcomes, and source of patients that can be effectively recruited.

Drug-Dosing Studies. Studies of off-patent drugs, tPA, and pharmacogenetics are needed. For t-PA for stroke, the working group proposed the following:

- Adult PK studies to determine the target therapeutic concentration achieved with current dosing—These can be performed in patients who are receiving the drug as standard of care for treatment of stroke. About 15–20 adults would be required.
- Pediatric PK/safety studies—A dose escalation study should be performed based on adult dosing and PK.
- RCTs of optimal dose versus placebo are needed to determine safety and efficacy.

The working group also proposed the following:

- PK and dose-ranging studies in the largest patient populations (for example, hematology/oncology patients, children with long-term indwelling IV catheters, and pediatric cardiology patients)
- PK/PD studies in unique populations known to be at risk for undertreatment (for example, neonates and obese children)
- Studies of reversal agents, particularly for new anticoagulants
- Treatment and prevention trials, both RCTs and quasi-experimental.

Outcomes. Laboratory studies are needed to establish pediatric therapeutic ranges, indexes, and biomarkers of response. Best assays need to be identified (for example, activated partial thromboplastin time versus heparin level versus thrombin generation). Optimal therapeutic ranges need to be determined. Clinical studies are needed to determine what outcomes should be used as clinical endpoints for clinical trials. Studies are needed to establish the quantitative relationship between laboratory measures of the degree of anticoagulation and clinical outcomes.

Long-term safety. Two issues concerning long-term safety are the bleeding risk associated with anticoagulants in different populations of children with thrombosis and the impact of heparins on bone density. Some barriers to conducting these long-term safety trials are smaller pediatric patient populations compared with adult populations, diversity of pediatric populations, critical illness in these populations, and venous access for blood samples. Without new data and better

guidelines and labeling for existing anticoagulants, clinicians may begin using new anticoagulants under the assumption that the new drugs are better, which is a safety concern.

In summary, there is a need for further study of venous thrombosis epidemiology and tailored treatment for high-risk and unique pediatric populations. As part of the research, investigators need to define ideal measures of responses that result in optimal safety and clinical outcomes.

Questions and Discussion

The following issues and topics were discussed:
- The importance of the laboratory component to the priorities
- Mechanism-specific assays and comparisons across classes of agents
- Expanding clotting-time assays to differentiate the diversity among pediatric populations
- Lack of common therapeutic range for low molecular weight heparins
- Need for specific, well-defined biomarkers that are correlated to outcomes
- Need for ADME studies
- Databases to determine anticoagulant use patterns
- Mechanisms to look at anticoagulant AEs in children
- Utility of data registries
- Asymptomatic screening in children who had catheters
- Anticoagulant monitoring issues
- Need for more information on oral anticoagulants.

Pulmonary Therapeutic Working Group: Summary of Findings 2011

Heber C. Nielsen, M.D. (Working Group Leader), Professor of Pediatrics, Professor of Anatomy and Cell Biology, and of Physiology, Cell and Molecular Developmental Biology, Graduate Program, The Sackler School of Graduate Biomedical Sciences, Tufts University

The working group focused on therapeutic components of pulmonary hypertension, asthma, and cystic fibrosis.

Pulmonary Hypertension. Although the working group recognized the need for more pharmacologic information of new therapeutics, they decided to focus on the use of sildenafil to treat pulmonary hypertension (PH) associated with bronchopulmonary dysplasia (BPD). Because of the diverse etiologies of BPD-associated PH in different pediatric age groups, the working group also recognized that there may be different types of PH that may require different treatment approaches and discriminatory biomarkers.

Issues of sildenafil use are as follows:
- Up to 20 percent of infants with BPD develop pulmonary artery hypertension (PAH).
- Up to 40 percent of infants with PAH that complicates BPD die.
- Studies of inhaled nitrous oxide for BPD have been inconclusive and had conflicting results.
- Dose-response studies of sildenafil conducted in term neonates with PAH show altered PK parameters compared with adults.

- A retrospective study of enteral sildenafil in 25 premature infants with lung disease showed no hemodynamic benefit in 22 infants. Of those 22, there were 5 deaths in follow-up. There was no PK analysis in this study.

Sildenafil research needs are as follows:
- Development of blood spot technology to measure sildenafil concentrations
- Development of an an enteral liquid formulation of sildenafil
- Trials for sildenafil PK/PD in preterm infants
- A clinical pharmacology plan for phase I–III trials to determine optimal dose and effectiveness.

Biomarker issues are as follows:
- Childhood disease is layered on the backdrop of developmental programming, which is a significant, though little recognized feature of PH in neonates and children compared with adults.
- There is a lack of validated classification schemes to discriminate the types of PH in children and facilitate the study of PH treatment options in children.
- Children and neonates with PH have differences in etiology, disease progression, genetic associations, and treatment responses compared with adults.

Biomarker research needs are as follows:
- Development of physiology-based biomarkers—alternatives to 6-minute walk for ambulatory age (less reliable) and nonambulatory age (not useful)
- Determination of the reliability of pulmonary vascular resistance index in pediatric or neonatal populations
- Development of plasma-based biomarkers—several are validated for adults; none for pediatrics/neonates
- Validation of identified plasma biomarkers against new physiology-based biomarkers
- Development of genetic-based biomarkers—genetic risk factors for BPD and PAH.

Asthma. The working group focused on the pharmacology of existing three therapeutic agents: inhaled corticosteroids, IV beta agonists, and omalizumab.

Issues of inhaled corticosteroid use are as follows:
- Inhaled corticosteroids are commonly used in children younger than 5 years old, which is outside the age range of scientific evidence and FDA approval.
- Inhaled corticosteroids are usually delivered in these children by metered dose devices with spacers (MDI) but with no data on drug delivery to the lung.
- Safety in these growing children is unknown. Also unknown are systemic absorption and incidence of AEs.
- Evidence of efficacy in these children is limited.

Research needs for inhaled corticosteroid use in children younger than 5 years old are as follows:
- PK studies comparing nebulizer with MDI/spacer delivery, including dose-response and systemic absorption

- Efficacy-safety analyses of inhaled corticosteroids in this age group
- Development of improved outcome measures relevant to this age group
- Development of improved technologies for pulmonary function testing.

Issues of IV beta agonist use are as follows:
- IV beta agonists are commonly used in PICUs for severe refractory asthma.
- Important gaps in clinical pharmacology of beta agonists in the pediatric population exist.
- There is uncertainty of efficacy.
- There is variability in clinical application (dose, indications).
- Dose-related risks of cardiovascular side effects are unknown.
- There is a lack of appropriate pediatric formulations.

Research needs for IV beta agonist use are as follows:
- Development of age-appropriate formulations of IV terbutaline
- Development of asthma assessment tool(s) appropriate to age and disease severity—for severe unstable asthma cared for in the ICU and correlation with physiologic parameters and robust measure of outcome
- Age-related PK/PD studies of IV terbutaline
- Age-related efficacy and safety studies of IV terbutaline.

Issues of omalizumab use in children younger than 5 years old are as follows:
- There are no therapies for disease modification or prevention in children.
- Omalizumab (anti-IgE antibody) is only approved for children older than 12 years with IgE-triggered environmental antigen sensitivity.
- Experimental data suggest use of omalizumab early in childhood may prevent or modify the course of asthma.
- Omalizumab has the potential for serious AEs including delayed anaphylaxis and malignancies.

Controlled clinical trials of omalizumab use in children younger than 5 years for developing safety and efficacy data are highly desirable. Safety data would include immunologic effects and long-term outcomes. Efficacy data would include prevention or amelioration of asthma and genetic markers. Successful studies are needed for a validated asthma predictive index, age-appropriate physiologic pulmonary function testing, and age-appropriate immunologic testing.

Cystic Fibrosis. The working group focused on the pharmacology and use of existing drugs: antibiotics, antifungals, colistin/colistimethate, ibuprofen, and proton pump inhibitors (PPIs).

Issues for antibiotics use include:
- There is a need for more effective antibiotic regimens for multi-drug resistant *Pseudomonas.* With increasing minimum inhibitory concentrations in multi-drug resistant strains, traditional intermittent dosing—even high doses—may be suboptimally effective. There are few PK and/or safety data on high-dose infusions of beta lactams, third- and fourth-generation cephalosporins, carbapenems, and monobactam.

- New regimens of extended (more than 4 hours) or continuous infusions are being tried with insufficient data.
- Current continuous infusion studies of beta lactams and third- and fourth-generation cephalosporins are not specific to the cystic fibrosis population.
- The cystic fibrosis population is known to have different PK characteristics.

Research needs for antibiotics are as follows:
- Studies to be carried out with beta lactams, third- and fourth-generation cephalosporins, carbapenems, and monobactam—PK, efficacy, and safety comparisons of high-dose, extended infusion and continuous infusion; evaluation of potential interference with clearance of aminoglycosides
- Development of a uniform clinical assessment tool for clinical response.

Issues for the use of antifungals include:
- Fungal endobronchitis and allergic bronchopulmonary aspergillosis (ABPA) are emerging serious problems in cystic fibrosis related to increased use of inhaled, oral, and IV antibiotics.
- There are particular problems in younger age groups because these antibiotic regimens are being extended into these children.
- Voriconazole and itraconazole are currently used, but they have not been approved for children younger than 12 years old and have not been approved for use in cystic fibrosis.

Research needs for the use of antifungals are as follows:
- Establishing therapeutic ranges in children with cystic fibrosis
- Establishing conditions that make enteral absorption more reliable and predictable
- Establishing long-term safety in children with cystic fibrosis—recommendations for drug and safety monitoring
- Efficacy studies in both endobronchitis and ABPA—reduction in exacerbations and reduction in prednisone use during exacerbations.

Issues for colistin/colistimethate use include:
- The number of multi-drug resistant gram negative pathogens in cystic fibrosis is increasing.
- Although there is sensitivity to IV colistin/colistimethate, IV PK studies in younger children has been inadequately studied.
- It is a common practice to deliver colistin/colistimethate via nebulized/aerosolized/inhaled route using IV formulations.
- There are no data PK, safety, or efficacy data of this mode of delivery.
- Serious colistin/colistimethate toxicity is possible.

Research needs for colistin/colistimethate are as follows:
- PK, safety, and efficacy of colistin/colistimethate in children younger than12 years old with cystic fibrosis—IV use and aerosolized/nebulized/inhaled use
- Standardized clinical assessment tool(s) for efficacy.

Issues for ibuprofen use include:

- There is strong evidence that high-dose long-term ibuprofen slows the progression of cystic fibrosis.
- Age-associated adverse effects on high-dose long-term therapy in cystic fibrosis are not known.
- Possible protective effects of adjuvant therapy are not known.
- Ibuprofen is used with invasive/intense monitoring to optimize dosing.

Research needs for ibuprofen are as follows:

- Development of dose scheme requiring less intensive ibuprofen therapeutic monitoring
- Data on safety of high-dose ibuprofen relative to the age of treatment initiation across the pediatric age spectrum
- Determination of whether concurrent acid-suppressive therapy benefits ibuprofen efficacy, safety, and PK.

Issues for the use of PPIs include:

- PPIs have the potential value as adjuvant therapy with enzyme replacement drugs to enhance their bioavailability.
- There is a need for episodic treatment of gastroesophageal reflux disease (GERD), but there is a lack of approved product labeling for GERD in neonates and young infants.
- The potential value of normalizing duodenal pH to reduce intestinal permeability and stress on the exocrine pancreas is not known.
- PPI PK is, however, well studied in pediatric populations.

Research needs for PPIs are as follows:

- Development of an exposure-controlled paradigm (that is, a target area under the curve) to evaluate value of concomitant PPI therapy on bioavailability and bioactivity of enzyme replacement therapy
- Determination of cystic fibrosis phenotype and CYP2C19 phenotype on PPI treatment-response relationships in cystic fibrosis
- Determination of effect of PPIs on magnesium metabolism.

Barriers to Information Acquisition. In order to acquire needed information to formulate age-appropriate treatment plans for children, investigators need to be invested in and involved with pediatric protocols. Instead of soliciting protocols, clinical research center directors could initiate protocols or organize a group of investigators to initiate pediatric studies through existing research networks. The clinical research centers could provide resources and collaborate with the NICHD to implement such studies. To continue progress in developing pediatric therapeutics, recommendations from the BPCA working groups needs to be disseminated and acted on.

Questions and Discussion

The following issues and topics were discussed:

- Reduced bone density associated with the use of inhaled steroids
- Reduced bone density associated with long-term use of PPIs in adults with cystic fibrosis

- Challenges to defining PH and determining most appropriate diagnostic criteria
- Diagnostic and predictive criteria for asthma in children
- Importance of early communication about pediatric protocols with the appropriate FDA divisions
- WRs as outcomes of working group recommendations
- Funding information in Requests for Applications
- Role of CTSAs and pediatric research networks in organizing and initiating new studies
- Prioritization of proposed studies and implementation through the PTN
- Oral formulation for a cystic fibrosis gene-modifier drug
- Industry motivation to develop pediatric cystic fibrosis drugs
- Health consequences and adverse effects of long-term, continuous drug therapies.

Renal Disease Therapeutic Working Group

The Renal Disease Therapeutic Working Group focused on four areas:
- Anemia management of pediatric patients with stages II–V chronic kidney disease (CKD)
- PK of life-saving medications in critically ill children with acute kidney injury (AKI) receiving continuous renal replacement therapy (CRRT)
- Anticoagulation in children with kidney disease
- Reduction of future cardiovascular (CV) risk and management of dyslipidemia/hyperlipidemia in children with CKD.

Anemia Management of Pediatric Patients with Stages II–V CKD

Frederick Kaskel, M.D., Ph.D. (Working Group Leader), Professor of Pediatrics, Vice Chairman for Affiliate and Network Affairs, Chief, Section of Nephrology, Department of Pediatrics, Albert Einstein College of Medicine at Yeshiva University, Children's Hospital at Montefiore

Background. Anemia affects more than half of the 10 million Americans with CKD. Anemia is associated with increased mortality, hospitalizations, risk of progression of CKD, left ventricular hypertrophy, and adverse effects on quality of life in adults and children/adolescents. Treatment with erythropoiesis-stimulating agents (ESAs) has ameliorated many of the adverse effects of anemia in CKD. A recent RCT in CKD in adults showed increased risk of ESAs and cardiovascular events and mortality at higher hemoglobin (Hgb) targets (>11 g/dL). A Black Box warning issued by the FDA called into question the safety of these agents in adults and children. The investigators recommended starting ESA treatment for Hgb <10g/dL in order to avoid the need for red blood cell transfusion; no target Hgb goal was defined.

Gaps in Knowledge. The safety concerns upon which the revised targets were based came from studies only in adults with CKD/ESRD with outcomes (severe cardiac events, mortality) that may not be applicable to pediatric patients with CKD/ESRD. Pediatric patients with CKD may need higher doses of ESAs and different target Hgb values in order to achieve optimal outcomes for growth, neurocognitive development, and cardiovascular function. No clinical trials assessing the optimal dosing and safety of ESAs in children with CKD have been performed. Increased risk for hospitalizations and mortality is associated with Hgb <10 g/dL. There are no data on the impact of gender/age, weight, stage of CKD, use of concurrent medications, and PK and

pharmacogenetic (PG) measurements on ESA's dosing and effect despite their use in 95 percent of children with CKD. Determination of the appropriate target Hgb levels of these agents in children with CKD is unknown.

Research Needs. Short-term outcomes of anemia treatment with ESAs need further investigation in children. Proposed studies include the following:

- Prospective studies of the safety/efficacy of dosing strategies for age-/gender-specific Hgb levels >95th percentile based on stage of CKD
- Determination of target Hgb levels required to achieve maximal growth, neurocognitive development, and avoidance of cardiovascular risks
- PK/PG on ESA dosing and medication interactions.

Proposed ancillary studies are as follows:

- Identification of new biomarkers to assess the efficacy and safety of ESA dosing in CKD/ESRD.
- Outcome and comparative effectiveness of therapies including determination of quality of life assessments in children with CKD/ESRD receiving ESAs.

Collaborators. Potential collaborators include the following:

- North American Pediatric Renal Trials and Collaborative Studies
- The NIH Chronic Kidney Disease in Children Longitudinal Cohort Study (CKiD)
- The PTN
- Investigators from other disciplines (cardiology, endocrinology, neurology, epidemiology).

Renal Disease Therapeutic Working Group: PK of Life-Saving Medications in Critically Ill Children with AKI Receiving CRRT

Stuart L. Goldstein, M.D., Director, Center for Acute Care Nephrology, Cincinnati Children's Hospital Medical Center (CCHMC); founder and principal investigator of the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry Group

AKI in children is often the result of another systemic or organ illness or its treatment. In hospitalized children, only 7 percent of AKI is primary renal disease. There is increasing incidence/prevalence AKI in ICU populations. Current treatment approaches are mostly supportive. CRRT is the most common renal replacement therapy modality provided to children. Mortality is still very high for children with AKI who receive CRRT despite technological advancements. There are no comprehensive, validated data to guide dosing of most medications in children who receive CRRT. The knowledge to treat these critically ill children comes from *in vitro* data, extrapolated data from patients with end-stage renal disease, and extrapolated data from adult AKI studies. AKI patients have other chronic illnesses.

The CCHMC has designed a pilot study of meropenem population PK to assess medications in CRRT. The study model will include clearance, volume of distribution, volume overload, age, albumin, modality, and sepsis versus nonsepsis. The short-term goals to address knowledge gaps are to devise highly predictive computerized drug disposition models, validate models *in vivo*, and refine models with *in vivo* PK/PD validation profiles.

Meropenem use parameters will be abstracted from the literature, and the derived model will be used to estimate meropenem clearance. The model will be applied to 372 children in the ppCRRT Registry Group database who received CRRT. The database includes CRRT settings, residual renal function, age, and weight. The preliminary data will be used to determine an adequate dosing regimen by using clinical trial simulations.

This study will be a pilot to set up the paradigm for a multicenter study. The network is in place (13 ppCRRT centers). Four centers are invested in the current project. The PK/PD expertise is in place.

Future directions include determining appropriate dosage for medications in this patient population. For medications with unknown PK, samples can be analyzed for any child, anywhere with AKI receiving CRRT. Clinician collaborator can access Web-based sampling requirements and collect samples and send to them to the CCHMC for PK analysis. For medications with validated PK, samples can be analyzed for any child, anywhere with AKI receiving CRRT (or not). Clinicians can access a Web-based dashboard and enter patient-specific parameters to guide dosing.

Anticoagulation in Children with Kidney Disease

Drs. Goldstein and Kaskel

The three main areas where hypercoagulation affects children with kidney diseases are:

- Pediatric end-stage renal disease (ESRD)—catheter thrombosis and fistula/graft thrombosis, which prevents delivery of maintenance dialysis and is associated with increased morbidity
- Pediatric acute kidney injury—catheter/CRRT circuit thrombosis in patients on dialysis, which prevents delivery of life-saving therapy
- Nephrotic syndrome—hypercoaguable state and rarely venous and arterial thrombosis, which can lead to limb loss and stroke.

No medication is approved to prevent or treat vascular access thrombosis in children. No medication is approved for CRRT to anticoagulate CRRT circuits. There are few data that describe the best thrombosis prophylaxis or treatment regimens for nephrotic syndrome states.

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee met November 2, 2011, in order to identify strategies to encourage and facilitate studies of anticoagulants in children that will result in informative pediatric labeling, appropriate endpoints for studies of anticoagulants in pediatric patients, and the role of PK/PD studies to support a pediatric indication for anticoagulants.

The working group identified the following anticoagulation medications for the three patient populations:

- Citrate and heparin ESRD children receiving maintenance hemodialysis
- Citrate and prostacyclin for children with AKI receiving CCRT
- Low molecular weight heparins for children with nephrotic syndrome.

Studies are needed in the following areas:

- Epidemiology/surveillance of AKI, CKD/ESRD and nephrotic pediatric cohorts to identify the effects of age, gender, weight, stage of CKD, and use of other medications on the incidence/prevalence of thrombosis
- Prospective clinical trials aimed at determining the ideal anticoagulation in children with AKI, CKD/ESRD, and nephrotic syndrome as determined by safety and efficacy metrics
- Performance of PK/pharmacogenomics (PGen) measurements for determination of optimal dosing strategies of anticoagulation therapies in AKI, CKD/ESRD, and nephrotic children.

Ancillary studies include:

- Identification of new biomarkers to assess the efficacy and safety of anticoagulation therapies in AKI, CKD/ESRD, and nephrotic children
- Impact of unique PK/PGen characteristics on the efficacy and safety of anticoagulation therapies to prevent and lower the risk for thrombosis
- Reduction of future CV risk and management of dyslipidemia/hyperlipidemia in children with CKD.

Reduction of Future CV Risk and Management of Dyslipidemia/Hyperlipidemia in Children with CKD

Jeffrey M. Saland, M.D., Chief, Pediatric Nephrology, Mount Sinai School of Medicine

Children with moderate CKD progress to ESRD in a relatively short amount of time: 50 percent in 5 years and 70 percent in 10 years. CV events (frequently stroke) are the number one cause of death in young adult survivors of ESRD. Data from the CKiD showed that 45 percent of children with CKD have persistent and severe dyslipidemia. Other studies have shown that lowering lipid levels is beneficial (that is, fewer major atherosclerotic events) in adults with CKD.

With regard to short-term safety/dosing of lipid-lowering drugs for children, there is a need to systematically identify potentially unknown issues. No PK or safety data have been derived directly from children with CKD. Statins or simva+ezetimibe are currently labeled for children with familial hypercholesterolemia (FH) and CKD in adults. No drugs are currently labeled for treatment of dyslipidemia/hyperlipidemia in children with CKD. The lower safe limits of lipid levels by children are not known. Little or no data have been derived directly about how therapeutic agents interact with other agents commonly used in children with CKD.

The working group recommended short-term studies of PK, PGen, and safety in children with CKD or ESRD. Study drugs should be broadly inclusive (begin with simva+ezetimibe, other statins, omega-3s, and sevelamer). Studies need to define efficacy targets. Inclusion criteria should not be based on lipid levels. The mechanisms of dyslipidemia in pediatric CKD are different than those for FH (only pediatric labeling currently). Studies of dyslipidemia mechanisms can be built into PK studies. Better understanding of these mechanisms will increase prospects of best directed therapy.

The long-term safety concerns of dyslipidemia/hyperlipidemia treatment in children with CKD are potentially unknown and need to be systematically identified. Whether cancer is associated with long-term treatment is also unknown. Studies of long-term safety should consider effects on development (for example, neurocognitive or pubertal effects) and coexisting issues (for example, hypertension, acidosis, and bone disease). There are several impediments for the study of long-term effects of lipid-lowering drugs. Surrogate/intermediate markers of clinical efficacy are needed. Lipid levels are a starting point but not sufficient. The atherosclerotic event "risk horizon" is distant; CV risk at ages 10–30 years is a log-scale lower than ages older than 40 years. The time course of treatment benefit is unknown.

The goals of long-term studies are to validate surrogate markers of future CV disease and define the risk horizon of atherosclerotic and nonatherosclerotic events. Subjects should be profiled at regular intervals over 10, 20, and 30 years. The studies should track CV and non-CV outcomes. The focus should not be on any particular stage of CKD, but rather the individual who over time might pass through multiple stages of CKD or ESRD. The CKiD could be extended to meet study goals. Currently, the CKiD does not follow children after ESRD. This is a lost opportunity to study CV event outcomes and to quantify atherosclerotic burden in a group where pediatric status is extremely well recorded. The CKiD could begin yielding data within a few years.

Questions and Discussion

The following issues and topics were discussed:

- Heparin use in ESRD and risk of aluminum loading due to contaminated heparin
- Heparin treatment of children on hemodialysis
- Lack of assessment of citrate protocols in chronic hemodialysis
- NHLBI panel recommendation to treat children with CKD and renal transplant with statins to achieve LDL cholesterol level of <100 mg/dL
- Off-label use of statins in children with CKD and renal transplant; lack of safety and efficacy studies of statin use in this population
- Application of adult safety data to children
- Retrospective study of young adults who developed ESRD as children (10–20 years prior to study)
- Timing of treatment initiation relative to the need for CV treatment
- Inclusion of pregnant women with CKD in studies or registries
- Conducting studies in countries with national medical care data sets; international collaboration
- Use of Medicaid, Medicare, and private data sets to determine statin use in children
- Early treatment of anemia, hyperlipidemia, inflammation, and other conditions that are risk factors for cardiac disease in patients with CKD.

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.

PFI Workshop Overview, November 1–2, 2011

Dr. Giacoia

The PFI was formed by the OPPB/NICHD in 2005 to address the lack of appropriate formulations in pediatrics as mandated by the BPCA of 2002 and 2007. The purpose of the PFI is to identify and address the scientific, regulatory, and economic barriers that prevent the development of pediatric formulations and review current gaps in knowledge. The PFI facilitates interactive discussions, data sharing, and feedback between industry, academia, regulatory, and funding agencies. The overall goal of the PFI is to develop a blueprint to address issues related to pediatric formulations needs including gaps in knowledge, solutions to identified problems, and types of research innovations needed. The blueprint will serve as a guide for future interactions (both national and international), development of research initiatives and programs, identification of funding needs and sources, and recommendations to policy makers. Specific objectives to achieve the overall goal will be determined by technical focus groups that will analyze the issues, determine priorities, and develop a set of individual recommendations and action items. The PFI currently has five working groups. Four of them convened at the November PFI Workshop and presented their findings and recommendations. The Economics Working Group did not convene at the workshop.

Biopharmaceutics Working Group. This working group reviews new approaches to pediatric formulations development by transforming an empirical process to a science-based platform, identifies taste-masking technologies appropriate for children, and evaluates new concepts in pediatric formulation design. The working group's findings and recommendation are as follows

- Excipients
  - Potential pharmaceutical–excipient interactions in different types of pediatric formulations have not been studied.
  - Clinical consequences of excipient exposure are largely unknown.
  - Accepted daily and cumulative intake of excipients has not been established in pediatrics.
  - Acceptable daily intake recommendations in the pediatric literature are mostly based on adult studies.
  - Scientists from the U.S. PFI need to interact with their EU PFI counterparts to ensure that needed information is captured in a joint excipients database.
- Pediatric platform development
  - Transfer technology from adult formulations development
  - Explore development of pediatric platform technology that is capable of providing age-related formulations across the range of pediatric groups (neonates to young adults) to contain appropriate doses without major formulation changes

  - Explore development of public–private partnership with participation of industry and academia with the proviso that these platforms would become available to the broader scientific community while retaining proprietary information.
- Use of computational tools
  - Modeling and computation can be used to predict molecular properties, including solubility, membrane permeability, stability, and taste.
  - Prediction of crystal structure, mechanical strength, surface energy, and other particle properties, in addition to the fundamental molecular properties, can significantly facilitate formulation and dosage form design and manufacturing processes.
  - Prediction of the taste of a drug compound and *in silico* design of novel taste inhibitors can advance pediatric drug development.

Biopharmaceutical Classification System (BCS) Task Specific Group. This working group focuses on the development of a framework to close the knowledge gap on the effects of developmental changes on drug disposition for selected BDDCS/BCS Class 1–4 drugs in pediatrics. The objective is to (1) assess whether a pediatric BCS that is scaled in a simple fashion from the adult BCS accurately predicts fraction dose absorbed in pediatric patients, (2) assess whether drugs that are well absorbed in adults are well absorbed in pediatric patients, and (3) explore the application of the BDDCS to pediatrics. The working group recommended the following:

- Determine essential requirements for classification of representative pediatric medicines; select the compounds for which a large amount of preclinical and clinical data is available (particularly PK/PD data in both children and adults)
- Identify developmental factors influencing absorption, distribution, and elimination of drugs in children younger than 2 years old
- Using the BCS, develop *in silico* database construction for predictive modeling and simulation of population-based PK/PD at different stages of development
- Classify pediatric drugs according to the BCS and BDDS
- Develop a pediatric classification system extended to transport and metabolism
- Classify drugs according to transporters and metabolic pathways
- Evaluate PK/BA simulation for representative drugs
- Identify and incorporate missing information in Gastroplus and Symcyp simulation programs.

New Technology and Drug Delivery Systems Working Group. This working group stimulates the development or application in pediatrics of new methods of drug delivery, the adaptation to pediatrics of new technologies, and the development of pediatric-specific devices. The working group's findings and recommendation are as follows:

- Parenteral route (dendrimers/nanotechnology)
  - There is a need to know molecular weight, range of variation, polydispersity, and toxicity profiles in developing systems. In addition, there is a lack of validated models for pediatrics and a need for multiple dose studies.
  - Studies in different age groups are needed.
  - Studies of the biodisposition by glucuronidation are needed.
  - Indications in pediatrics need further definition.

  - If nanocarrier materials are not biomimetic, biocompatible, or biodegradable, then toxicity can increase considerably.
  - Many nanocarrier materials in research are not biomimetic, biocompatible, or biodegradable.
- Dermal route
  - Because of its ability to overcome first-pass effects, the transdermal delivery route may reduce toxic effects.
  - There is need to apply in pediatrics physical transdermal delivery techniques such as iontophoresis, electroporation, sonophoresis, and transdermal patches with microscopic projections; other technologies under development include thermal poration, magnetophoresis, and photomechanical waves.
- Ocular route—Suggested ways to address barriers and/or knowledge gaps on ocular formulations and drug dosage forms in children are:
  - Develop more efficient formulations and drug delivery systems
  - Develop appropriate animal models and *in silico* models for pharmacologic studies in the developing eye
  - Organize collaborative studies to allow sampling or banking of intraocular tissues or fluids whenever dictated by clinical indication
  - Develop and evaluate micro-needle, ultrasound and iontophoresis-based ocular drug delivery system in newborns and pediatric populations.
- Inhalation route
  - Develop new devices that work across pediatric patient age and size
  - Develop effective interfaces that are designed for use for each age and size
  - Improve uniformity and standards for *in vitro* testing
  - Develop rational guidelines for demonstrating efficacy and safety in the smallest patients
  - Develop a novel technology for the efficient delivery of pharmaceutical aerosols that minimizes depositional losses in the delivery system and nasal airways and maximizes drug delivery to the lungs.

Taste and Flavor Working Group. This working group summarizes current knowledge of drug palatability and promotes the development and/or harmonization of age-appropriate standardized psychophysical methods for testing drug formulations in children and adult panels; proposes the development of *in vitro* and animal models to predict the degree of bitterness likely to be sensed by children; and recommends research aimed at increasing understanding of the intracellular mechanisms of bitter taste signaling. The working group's recommendations are as follows:

- Develop age-appropriate standardized psychophysical methods for testing drug formulations in children and adult panels and validate and determine the reliability of these psychophysical methods.
- Determine the types of adult sensory panels and psychophysical methods that are most appropriate for predicting acceptance/compliance in the pediatric population.
- Conduct studies of different textures, granularities, and smells of dosage forms in the acceptability of pediatric formulations.
- Evaluate the value of the electronic tongue and nose to quantify bitterness and taste masking efficiency in the development of pediatric formulations.

- Conduct studies aimed at increasing understanding of the intracellular mechanisms of bitter signaling to assist in discovery of novel bitterness blockers.
- Incorporate environmental and family support as co-factors in studies of the relationships between taste sensitivity and noncompliance in children.
- Develop partnerships among academics, government, and industry to gain access on existing, yet proprietary, data on taste masking, bitter and irritant blocking, and drug palatability to determine successful approaches identify major obstacles.

Economics Working Group. This working group identifies economic barriers, reviews reasons for the failure of pharmaceutical companies dedicated to reformulation of off-patent drugs, and identifies possible economic incentives. This group explores possible funding mechanisms and the development of academic and industry partnerships to create cost-effective and appropriately formulated products for orphan and off-patent drugs and ensure their distribution and availability.

Future Steps. Future steps for the PFI are to (1) continue working groups' activities, (2) create ad hoc groups drawing from membership in established working groups, (3) work with the World Health Organization and EU PFI on areas of common interest, and (4) develop close interactions with professional organizations and foundations that support development of pediatric formations. Possible outcomes include publications, research initiatives, and compilation of factual public information on pediatric formulations. Other possible outcomes are a prioritized approach for essential age-appropriate drug formulation and a blueprint to support manufacturing and distribution of off-patent formulations.

Pediatric Formulations Update

Mansoor A. Khan, Ph.D., Director, Division of Product Quality Research, Center for Drug Evaluation and Research (CDER), FDA

FDA-NIH Collaboration. The FDA and the NIH have collaborated to develop a priority list of legacy products with pediatric needs that the pharmaceutical industry was not interested in developing. The collaboration identified some acute global needs for pediatric formulations and considered taste, solubility, stability, and other technical challenges. The priority list of legacy products included active pharmaceutical ingredients amenable to certain well-established platforms. By an appropriate consideration of chemistry, PC and PK properties, and use of computational models, the FDA-NIH collaboration will group the products into appropriate platforms and start developing case studies. The findings will be discussed, presented, and published for worldwide dissemination.

The Biopharmaceutics Classification System (BCS). The BCS is a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability. In conjunction with dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from immediate release solid oral dosage forms: solubility, permeability, and dissolution. Products are classified as BCS Class 1, 2, 3, and 4. BCS Class 1 drugs have high solubility and high permeability. BCS Class 2 drugs have low solubility and high permeability. BCS Class 3 drugs have high solubility and low permeability. BCS Class 4

drugs have low solubility and low permeability. Compounds that have high solubility (for example, BCS Class 3 drugs) can be easily made into oral solutions.

Challenges of Oral Solutions. The main challenges of oral solutions are solubility, stability, taste masking, accurate dosing, and appropriate selections of excipients and packaging material. Typical excipients include solubilizers, stabilizers, viscosity builders, sweeteners, colorants, flavors, and complexing agents. Excipients can affect a drug's solubility. Excipients must be carefully chosen to have extemporaneous formulations with consistent properties. Pediatric oral formulations are not readily available for some of the drugs, and often "adult formulations" are used for this purpose. This includes splitting a tablet or opening up a capsule and solubilizing the contents in a sweetened vehicle.

Case Study. The objective of the study was to evaluate the feasibility of preparing a pediatric friendly levothyroxine (a thyroid drug) with high assurance of dose uniformity for pediatric use. An orally disintegrating tablet (ODT) formulation with a dose range of 5 and 25 micrograms was proposed as a pediatric-friendly formulation. The methods for this study included coating of levothyroxine sodium on mannitol; superdisintegrant evaluation for ODTs; optimization of ODTs by use of Design of Experiments; and evaluation of ODTs by disintegration time, friability, hardness, weight variation, and content uniformity. The results showed that low-dose formulations for pediatric patients might have content uniformity issues if prepared by conventional technology. In this study, levothyroxine ODTs were found to have the potential for pediatric use with high assurance of dose uniformity and other desired product quality attributes.

Questions and Discussion

The following issues and topics were discussed:

- Feasibility versus cost in developing pediatric formulations
- FDA guidance on pediatric formulations development (for example, taste masking)
- Scalability of different dosages (that is, multiple strengths)
- Liquid formulation testing in adults for liquid formulations that are going to be used in children; appropriateness of extrapolation
- Regulatory requirements for pediatric formulation testing
- Reporting of pediatric formulations used in clinical trials in the published literature
- Formulation data of generic drugs
- Need for data to support clinical use of pediatric drugs.

NICHD Training in Pediatric Clinical Pharmacology

Dr. Giacoia

Pediatric clinical pharmacology is not a formally recognized subspecialty of adult clinical pharmacology. Pediatric pharmacologists have adapted adult methodologies and tools to pediatrics. The National Institute of General Medical Sciences (NIGMS) T32 Post-Doctoral Program is a vehicle for adding a pediatric clinical pharmacology training component. Co-funding by the NIGMS and the NICHD adds a pediatric clinical pharmacology position to eight selected currently funded programs. The program goals are to (1) provide training in pediatric

clinical pharmacology; (2) stimulate interdisciplinary collaboration among clinical, translational, and basic researchers in pediatric therapeutics; and (3) enable the development of a pediatric pharmacology section within the adult clinical pharmacology department. Institutions participating in the NIGMS-NICHD T32 Programs in pediatric clinical pharmacology are:

- Duke University/University of North Carolina at Chapel Hill
- Mayo Clinic
- Thomas Jefferson University
- University of California, Los Angeles
- University of California, San Francisco
- University of Chicago
- University of Pennsylvania/Children's Hospital of Philadelphia
- Vanderbilt University.

Institutions participating in the NICHD T32 Programs in pediatric clinical pharmacology are Children's Mercy Hospital Kansas City, University of Indiana, and University of Cincinnati.

Program fellows participate in a harmonized pediatric clinical pharmacology core curriculum and interact with fellows in other T 32 programs. They have access to educational material developed by the NICHD and participating programs, and they have exclusive access to the dedicated pediatric clinical pharmacology Web site PedPharmHub. They also have access to experts in other programs for individual queries or as member of a research team. The fellows participate in across-center special interest groups. They interact and collaborate with other pediatric pharmacology fellows in the same pediatric subspecialty. Pharm.D./Ph.D. fellows can interact and collaborate with other fellows and faculty to respond to NICHD initiatives (for example, developmental pharmacology and pediatric formulations). These fellows have a forum to discuss their own research and present at professional organization meetings in programs sponsored by the NICHD. They also have the possibility of using PedPharmHub tools to develop research protocols or review articles across programs.

The PedPharmHub is an interactive Web site that is a resource for the pediatric pharmacology and therapeutics community. It facilitates training and collaboration in the field of pediatric pharmacology and provides a platform for the NIGMS-NICHD Pediatric Clinical Pharmacology T32 Training Programs to interact. The site features each program's overview and contact information. T32 programs and fellows can use the PedPharmHub to interact, collaborate, and store trainings and lectures. The PedPharmHub provides a forum for online network-based pediatric pharmacology training programs in different therapeutic areas using lectures, slides, videos, and course materials. In addition, the PedPharmHub houses multimedia and other training resources.

Questions and Discussion

The following issues and topics were discussed:

- Collaboration with international training programs
- Need for pediatric psychiatric subspecialists
- Need for pharmacology support/pharmacologists in pediatric clinical trials

- Need for pharmacologists and statisticians in the PFI working groups.

Future Directions for BPCA and Pediatric Research Equity Act (PREA): 2011 and Beyond

Mark Del Monte, J.D., Director, Department of Federal Affairs, AAP

Several regulatory and legislative initiatives have moved the study of drugs for children forward, beginning with the FDA Proposed Rule on pediatric labeling and extrapolation in 1992. In 2002, the BPCA was passed into law, and in 2003, PREA, codifying the pediatric rule, was passed. BPCA and PREA were viewed as enormously successful at generating pediatric information and were reauthorized in 2007, extending them until October 1, 2012. The BPCA Program has resulted in 424 drugs being relabeled with pediatric information. With PREA as an integrated part of drug approval process, 227 drugs have been labeled with pediatric information. The 2007 BPCA and PREA programs will sunset October 1, 2012.

Innovations to BPCA and PREA in 2007 are as follows:
- Retention of 6-month market exclusivity despite proposals to limit "blockbusters"
- Increased transparency by making WRs and FDA reviews publicly available and posting BPCA- and PREA-related information on the FDA Web site
- Centralized review of all WRs and PREA study plans by new internal review committee: Pediatric Review Committee (PeRC)
- Addition of pediatric study information in all drug labels regardless of outcome
- Annual monitoring of AEs after approval for drugs studied under BPCA or PREA.

In 2012, there will be a second opportunity to reauthorize BPCA and PREA together and create a better integrated pediatric program. The legislation can be improved by considering changes recommended by the AAP, other pediatric groups, expert reviewers, the Government Accountability Office, and the Institute of Medicine. There will be a new and different political environment, with two parties in control of Congress and new Senate champions. BPCA and PREA reauthorizations will be included as components of the User Fee Act reauthorizations.

Potential areas for improvements to the 2012 legislation are to:
- Increase the transparency of the operation of BPCA and PREA processes and data generated
- Better coordinate and streamline the independent BPCA and PREA operations into a coordinated pediatric program, with an increased use and role of the PeRC
- Induce pediatric program planning earlier in the drug development cycle
- Address the unique challenges of neonates and pediatric cancers
- Further pediatric research on off-patent drugs
- Address issues of PREA deferrals of pediatric drug studies.

In discussions of the 2012 reauthorizations of BPCA and PREA, Congress will consider how to evaluate the impact of BPCA, PREA, and Section 409I (which authorizes and guides the NIH's work in the BPCA Program), whether the benefit is worth the cost, and whether this federal policy is working such that regular evaluations should be automatically triggered. Other considerations are pediatric devices, drug shortages, medical countermeasures for man-made or

natural disasters, polypharmacy of psychopharmaceutic drugs, and the "cost" of BPCA incentives.

Questions and Discussion

The following issues and topics were discussed:
- Consequences of incomplete/pending studies deferred by PREA
- Pediatric components in electronic medical records
- Impact of BPCA and PREA on building pediatric clinical trials infrastructure
- Partnership with clinical research organizations
- Numbers and costs of "blockbuster" drugs
- Need for improved FDA transparency and information sharing
- Evolution of NIH-FDA cooperation in conducting pediatric trials and studies.

Next Steps and Closing Remarks

Dr. Anne Zajicek

Next steps for the BPCA Program in 2012 include:
- Submitting information to the FDA docket for hydroxyurea, meropenem, nitroprusside, and lorazepam for sedation (pre-IND meetings have been held)
- Convening meetings with the FDA to discuss labeling of capsule preparations (for example, extemporaneous compounding)
- Convening pre-IND meetings for baclofen, vincristine, actinomycin-D, daunomycin, isotretinoin, and ampicillin and submitting data for WRs
- Publishing BPCA program processes, findings, and study results
- Continuing the partnership with the FDA
- Continuing development of the NIH-FDA formulations platform
- Continuing the prioritization process
- Integrating dried blood spot technology
- Posting additional program announcements and grant opportunities
- Incorporating and involving the academic community.

Participants

John Alexander, M.D., M.P.H., CDER, FDA, HHS
Ravinder Anand, Ph.D., The EMMES Corporation
Jacob Aranda, M.D., Ph.D., F.R.C.P.C., F.A.A.P., State University of New York Downstate Medical Center
Stephanie Archer, M.A., NICHD, NIH, HHS
Jeffrey Barrett, Ph.D., F.C.P., Children's Hospital of Philadelphia
Peter Belamarich, M.D., Albert Einstein College of Medicine of Yeshiva University
Danny Benjamin, M.D., Ph.D., M.P.H., Duke Clinical Research Institute
Katherine Berezny, M.P.H., Duke Clinical Research Institute
Carol Blaisdell, M.D., NHLBI, NIH, HHS
Diane Brandt, The EMMES Corporation

Charlie Bruetman, M.D., The Lewin Group
Barbara Buch, M.D., M.B.A., Center for Biologics Evaluation and Research, FDA, HHS
Marcia Buck, Pharm.D., F.C.C.P., F.P.P.A.G., University of Virginia Health System
Gilbert Burckart, Pharm.D., CDER, FDA, HHS
Edmund Capparelli, Pharm.D., University of California, San Diego
James Chamberlain, M.D., Children's National Medical Center
Allison Chung, Pharm.D., Auburn University
Catherine Connor, J.D., Elizabeth Glaser Pediatric AIDS Foundation
Judith Cope, M.D., M.P.H., Office of the Commissioner, FDA, HHS
Jonathan Davis, M.D., Tufts University School of Medicine
Mark Del Monte, J.D., AAP
Linda Duffy, Ph.D., M.P.H., National Center for Complementary and Alternative Medicine, NIH HHS
Elizabeth Durmowicz, M.D., Office of New Drugs, FDA, HHS
Oluchi Elekwachi, Pharm.D., M.P.H., CDER, FDA HHS
Tiffany Farchione, M.D., CDER, FDA, HHS
Jane Filie, M.D., CDER, FDA, HHS
Joseph Flynn, M.D., M.S., Seattle Children's Hospital
Jacqueline Francis, M.D., M.P.H., Center for Devices and Radiological Health, FDA, HHS
George Giacoia, M.D., NICHD, NIH, HHS
Roberta Glass, M.D., CDER, FDA, HHS
Stuart Goldstein, M.D., Cincinnati Children's Hospital Medical Center
James Gorman, Ph.D., M.D., Healthcare Innovation Laboratory
Gilman Grave, M.D., NICHD, NIH, HHS
Thomas Green, M.D., Northwestern University
Tamar Haro, AAP
Barrie Harper, B.S.M.T., Duke Clinical Research Institute
Ethan Hausman, M.D., CDER, FDA, HHS
Rosemary Higgins, M.D., NICHD, NIH, HHS
Elora Hilmas, Pharm.D., B.C.P.S., Alfred I. du Pont Hospital for Children
Steven Hirschfeld, M.D., NICHD, NIH, HHS
Jeffrey Jacot, Ph.D., Rice University
Tammara Jenkins, M.S.N., R.N., NICHD, NIH, HHS
Lisa Kaeser, J.D., NICHD, NIH, HHS
Alyson Karesh, M.D., CDER, FDA, HHS
Abraham Karkowsky, Ph.D., M.D., CDER, FDA, HHS
Frederick Kaskel, M.D., Ph.D., Albert Einstein College of Medicine of Yeshiva University
Gregory Kearns, Pharm.D., Ph.D., Children's Mercy Hospitals and Clinics
James Keim, M.S.W, L.C.S.W., Bay Area Oppositional and Conduct Clinic
Mansoor A. Khan, R.Ph., Ph.D., CDER, FDA, HHS
Gordon Klein, M.D., M.P.H., University of Texas Medical Branch
Renee Kozloff, Ph.D., KAI Research, Inc.
Katie Lapides Coester, M.P.P., Elizabeth Glaser Pediatric AIDS Foundation
Matthew Laughon, M.D., M.P.H., University of North Carolina at Chapel Hill
Marie Ann Leyko, Ph.D., CCS Associates, Inc.

Donald P. Lombardi, Institute for Pediatric Innovation
Lolita Lopez, M.D., CDER, FDA, HHS
Lori Luchtman-Jones, M.D., Children's National Medical Center
Diane Maloney, J.D., Center for Biologics Evaluation and Research, FDA, HHS
Kimberly Martin, D.O., CDER, FDA, HHS
Marva Moxey-Mims, M.D., National Institute of Diabetes and Digestive and Kidney Diseases, NIH, HHS
Yeruk "Lily" Mulugeta, Pharm.D., CDER, FDA, HHS
Mary Dianne Murphy, M.D., F.A.A.P., Office of the Commissioner, FDA, HHS
Sharon Murphy, M.D., Institute of Medicine of the National Academies
Pamela Murray, M.D., M.P.H., West Virginia University School of Medicine
Robert Nelson, M.D., Ph.D., Office of the Commissioner, FDA HHS
Christopher Newth, M.D., Children's Hospital Los Angeles
Heber Nielsen, M.D., Tufts University
Amy Odegaard, M.P.H., Office of the Commissioner, FDA, HHS
Maura O'Leary, M.D., Center for Biologics Evaluation and Research, FDA, HHS
Uptal Patel, M.D., Duke Clinical Research Institute
Ian Paul, M.D., M.Sc., Pennsylvania State College of Medicine
Hanna Phan, Pharm.D., B.C.P.S., University of Arizona
Denise Pica-Branco, Ph.D., Office of New Drugs, FDA, HHS
DeWayne Pursley, M.D., M.P.H., Beth Israel Deaconess Medical Center
Mary Purucker, M.D, Ph.D., National Center for Research Resources, NIH, HHS
Natella Rakhmanina, M.D., Ph.D., F.A.A.P., A.A.H.V.S., Children's National Medical Center
Michael Reed, Pharm.D., Children's Hospital Medical Center of Akron
J. Routt Reigart, M.D., Medical University of South Carolina
Zhaoxia Ren, M.D., Ph.D., NICHD, NIH, HHS
Charles Reynolds, M.D., Ph.D., Texas Tech University Health Sciences Center
William Rodriguez, M.D., Ph.D., Office of the Commissioner, FDA, HHS
Ellen Rosenberg, B.S.N., M.H.A., NHLBI, NIH, HHS
Michelle Roth-Cline, M.D., Ph.D., Office of the Commissioner, FDA, HHS
Allen Rudman, Ph.D., CDER, FDA, HHS
Hari Cheryl Sachs, M.D., CDER, FDA, HHS
Daniel Safer, M.D., Johns Hopkins School of Medicine
Jeffrey Saland, M.D., Mount Sinai School of Medicine
Victor Santana, M.D., St. Jude Children's Research Hospital
Nita Seibel, M.D., National Cancer Institute, NIH, HHS
Daiva Shetty, M.D., CDER, FDA, HHS
David Siegel, M.D., NICHD, NIH, HHS
Elaine Siegfried, M.D., Saint Louis University Medical School
Douglas Silverstein, M.D., CDER, FDA, HHS
P. Brian Smith, M.D., M.P.H., M.H.S., Duke University Medical Center
Thomas Smith, M.D., CDER, FDA, HHS
Kristen Snyder, M.D., CDER, FDA, HHS
Michael Spigarelli, M.D., Ph.D., University of Utah
Peter Starke, M.D., CDER, FDA, HHS

Janice Sullivan, M.D., University of Louisville
Melissa Tassinari, Ph.D., CDER, FDA, HHS
Amy Taylor, M.D., M.H.S., F.A.A.P., CDER, FDA, HHS
Perdita Taylor-Zapata, M.D., NICHD, NIH, HHS
Courtney Thornburg, M.D., Duke University Medical Center
Ekaterini Tsilou, M.D., NICHD, NIH, HHS
Johannes Van Den Anker, M.D., Ph.D., Children's National Medical Center
Surendra Varma, M.D., F.A.A.P., Texas Tech University Health Sciences Center
Benedetto Vitiello, M.D., National Institute of Mental Health, NIH, HHS
Kelly Wade, M.D., Ph.D., Children's Hospital of Philadelphia
Philip Walson, M.D., University Medical Center Göttingen
Robert Ward, M.D., University of Utah
Tasmeen Singh Weik, Maternal and Child Health Bureau, HRSA, HHS
Pamela Weinel, M.S., M.B.A., R.N., Office of the Commissioner, FDA, HHS
Steven Weinstein, M.D., Cornell University
Thomas Wells, M.D., M.B.A., University of Arkansas for Medical Sciences
Teri Woo, Ph.D., R.N., C.N.L., C.P.N.P., University of Portland
Anne Zajicek, M.D., Pharm.D., NICHD, NIH, HHS
Julie Zito, Ph.D., Pharm.D., University of Maryland, Baltimore