

Improving Pediatric Therapeutics Through the Best Pharmaceuticals for Children Act of 2002

**Obstetric and Pediatric Pharmacology Branch
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Introduction and Workshop Goals

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Dr. Mattison—Director of the Best Pharmaceuticals for Children Act (BPCA) Program—welcomed attendees and thanked them for their participation. He explained that the goals of the workshop are to answer the following questions:

- Are there gaps in pediatric pharmacoepidemiology and therapeutic knowledge?
- How has NIH implemented BPCA?
- How can BPCA impact pediatrics?
- How can you become involved in BPCA activities?

The Best Pharmaceuticals for Children Act of 2002 is a law mandating performance of pediatric clinical trials of off-patent and on-patent drugs. The goal of BPCA is to provide better medicines for children, including:

- Evidence-based dosing recommendations
- Improved efficacy, safety information
- Improved information in medication labels
- Enhanced pediatric therapeutics.

BPCA highlights include:

- NIH/Food and Drug Administration (FDA) collaboration on scientific, clinical, study design, weight of evidence, ethical, and labeling issues to improve pediatric therapeutics
- Collaboration among NIH Institutes and Centers in BPCA
- Improving ability to identify pediatric public health gaps in drug labeling
 - Frequency of use and conditions
 - Existing knowledge and literature
- Special activities directed toward neonates, pediatric formulations, and childhood cancer.

Dr. Mattison described the usual steps for preclinical and clinical drug development:

- Discovery
- Preclinical development
- Application for Investigational New Drug (IND) status
- Exploratory development (phases I and IIa)
- Full development and life cycle management (phases IIb and III)
- Submission of New Drug Application (NDA)

- Launch (phase IV).

Given that most of the drugs of interest to BPCA are “old” (that is, generic or off-patent), Dr. Mattison said that many experts in pediatrics and pharmacology thought that most BPCA activity would occur at the end of the drug development process (that is, phase IV); unfortunately, that is not the case. He then provided the following information on the developmental status of BPCA “listed” drugs:

- Preclinical development (animal toxicity, pharmacokinetics [PK], efficacy; 3.5 years; \$335 million)
 - Lindane
 - Ketamine
 - Dopamine
 - Dobutamine
- Phase I (PK, toxicity, extremely preliminary efficacy; 22 months; \$15 million)
 - Dopamine
 - Dobutamine
 - Bemetanide
 - Furosemide
 - Spironolactone
- Phase IIa (small clinical trial of patients with disease of interest; 26 months; \$42 million)
 - Azithromycin
 - Baclofen
 - Rifampin
 - Lithium
 - Lorazepam
 - Nitroprusside
 - Metoclopramide
 - Meropenem
 - Vincristine
 - Dactinomycin
 - Ampicillin
 - Isoflurane
 - Pip/tazobactam
 - Amp/sulbactam
 - Metolazone.

Dr. Mattison described the basic steps in the BPCA process for off-patent drugs:

- List
- Written Request (WR)
- Request for Proposal (RFP)
- Contract
- Clinical study
- Label change.

Current information on the BPCA Program is available at <http://www.nichd.nih.gov/oppb/bpca/index.htm>

Dr. Mattison explained that the workshop is composed of two panels. Panel 1 answered the question: How Is the BPCA Program Currently Organized? Presentation titles and presenters were as follows:

- NICHD Perspective, Yvonne T. Maddox, Ph.D., Deputy Director, NICHD, NIH, DHHS
- FDA Perspective, Dianne Murphy, M.D., Director, Office of Pediatric Therapeutics, FDA, DHHS
- Clinical Perspective, Robert M. Ward, M.D., University of Utah Health Sciences Center
- The BPCA List Process, Perdita Taylor-Zapata, M.D., CRMC, NICHD, NIH, DHHS.

Panel 2 answered the question: How Can You Become Involved With the BPCA Program? Presentation titles and presenters were as follows:

- Issues in Pediatric Clinical Trials, Sam Maldonado, M.D., M.P.H., Johnson and Johnson Pharmaceutical Research and Development
- Conducting BPCA Clinical Studies, Anne Zajicek, M.D., Pharm.D., CRMC, NICHD, NIH, DHHS
- Becoming Principle Investigator (PI) of a Clinical Study: Improving your Chances for Success, George Giacoia, M.D., CRMC, NICHD, NIH, DHHS
- Implementing BPCA Within NICHD and CRMC, Anne Willoughby, M.D., M.P.H., Director, CRMC, NICHD, NIH, DHHS.

Panel 1: How Is the BCPA Program Currently Organized?

In their presentations, members of panel 1 reviewed:

- NICHD research initiatives and objectives to improve therapeutics for mothers and their children
- The FDA's role in pediatric clinical trials and in the BPCA Program
- The issues for improving pediatric therapeutics through the BPCA Program from a clinical perspective
- The drug prioritization and listing process in the BPCA Program.

NICHD Perspective

Dr. Maddox, Deputy Director, NICHD, NIH, DHHS

In this presentation, Dr. Maddox provided a brief overview of NICHD research initiatives and objectives to improve therapeutics for mothers and their children. She began her presentation with the following quote:

“When we are alone at night caring for a sick child, we trust HHS to ensure that the medicine we give her is effective.”

—Mike Leavitt, Secretary of Health and Human Services, in a statement to the U.S. Senate Finance Committee in Washington, DC, during his confirmation hearing on January 19, 2005

Dr. Maddox said that current obstetric and pharmacology research initiatives at NICHD include:

- Pediatric Pharmacology Research Unit (PPRU) Network
 - Established in 1992 to build pediatric pharmacology infrastructure
 - Fosters collaboration for pediatric therapeutics among industry, academia, and health care providers
 - Supports 13 sites with access to more than 150,000 pediatric inpatients and 2 million pediatric outpatients
- Obstetric Pharmacology Research Units (OPRU) Network
 - Established in 2004 to develop obstetric pharmacology infrastructure
 - Supports four sites, which include thought leaders in obstetric pharmacology
 - Describes basic and clinical mechanisms of drug disposition and effect during pregnancy
- BPCA
 - Enacted in 2002 to enhance pediatric therapeutics and improve label information to guide drug use in children
- OPPB
 - Established in 2004 to foster enhanced research and training in obstetric and pediatric pharmacology.

Dr. Maddox noted that as early as 1998, researchers were interested in studying the influence of drugs during pregnancy. The three main areas of research were:

- Antihypertensives
- Anticonvulsants
- Antidepressants.

Dr. Maddox commented that the effects of these drugs were of great interest to women's health organizations, and it was at their urging that NICHD began to develop its maternal-child research initiatives. However, since establishment of the PPRU and OPRU Networks, researchers have begun to explore the effects of other drugs during pregnancy.

In addition to its research initiatives, NICHD's commitment to improving therapeutics for mothers and children includes the following objectives:

- Evidence-based dosing recommendations
 - Drug disposition in pregnancy and childhood
- Improved efficacy and safety information
 - Maternal, placental, and developmental characterization
- Improved information in medication labels
 - Guidelines for appropriate, safe, and effective therapeutics
- Enhanced clinical outcomes.

Dr. Maddox said that future NICHD research initiative would focus on topics such as:

- Maternal-placental transfer of drugs
- Effects of drugs on the embryo and fetus
- Fetal antecedents of developmental processes.

NICHD research initiatives will help develop better health care guidelines for the American public. Successful research initiatives will help build trust in the biomedical community by providing better information and transforming this information into helpful guidelines for appropriate, safe, and effective use of drugs. The ultimate goal of programs such as BPCA is to enhance clinical outcomes so that every child can be treated appropriately. Dr. Maddox reminded the participants that children cannot simply be considered as “little adults” and that all subpopulations of children need to be included in federal research initiatives in order to address diversity issues as well as health disparities and gaps in various racial and ethnic communities in relation to drug treatments.

In concluding, Dr. Maddox emphasized that NICHD stands ready to fully support the BPCA Program, both financially and intellectually. NICHD is committed and dedicated to the success of this program.

FDA Perspective

Dr. Murphy, Director, Office of Pediatric Therapeutics FDA, DHHS

In this presentation, Dr. Murphy provided a brief overview of FDA’s role in pediatric clinical trials, and she reviewed FDA’s role in the BPCA Program. FDA pediatric initiatives include:

- 1979—Pediatric subsection
- 1992—Proposed label changes
- 1994—Finalized label changes
- 1997—Food and Drug Administration Modernization Act (FDAMA)
- 1998—Pediatric Rule
- 2002—BPCA
- 2003—Pediatric Research Equity Act (PREA).

Dr. Murphy commented that BPCA and PREA will both “sunset” in 2007. She explained that WRs are the main mechanism (“the fundamental building block”) through which FDA implements the BPCA program. The drug industry occasionally specifies the types of pediatric studies it wants to conduct. In such cases, FDA generally negotiates for studies that are in the best interest of public health.

Dr. Murphy described “the problem”:

- 1973—*Physician’s Desk Reference* (PDR): 78 percent of drugs without sufficient pediatric drug labeling
- 1984–1989—New Molecular Entities (NMEs): 80 percent of NMEs without pediatric drug labeling
- 1991—PDR: 81 percent of drugs without disclaimers or age restrictions
- 1992—NMEs: 79 percent of potential pediatric use unapproved
- 1991–1994—NMEs: 71 percent without pediatric labeling.

(The just-cited material is from *FDA Report to Congress*, page 2, January 2001; available at www.fda.gov/cder/pediatric/reportcong01.pdf.)

Dr. Murphy elaborated that the smaller and younger the population, the larger the problem. She cited the following information for neonates:

- The average numbers of drugs given to newborns (by birth weight) are
 - <1,000 grams, 15–20
 - >2,500 grams, 4–10.
- More than 90 percent of drugs used in the neonatal intensive care unit are off-label.
- As of October 2004, pediatric studies for drug with exclusivity:
 - WRs issued for 295 products
 - Submitted studies for 113 products
 - Only 18 of 113 drugs with data submitted for exclusivity were studied in neonates.

Dr. Murphy described BPCA:

- Became law on January 4, 2002
- Is an important “engine” for pediatric drug development
- Reauthorizes exclusivity incentive program under FDAMA for products with remaining patents or exclusivity marketing rights (on-patent)
- Authorizes FDA to determine needed studies and to issue WRs for on-patent products
- Is a major force resulting in new studies, new prescribing information, and new labeling for pediatrics
- Mandates that FDA and NIH collaborate in the study of both off- and on-patent drugs that industry does not want to study. A WR is issued for all products.
- Establishes an additional mechanism for obtaining information in the pediatric populations for off-patent drug, which involves contracting activities by NIH
- Mandates public dissemination of studies conducted as result of exclusivity
- Mandates public review of safety reporting on products granted exclusivity.

The FDA/NIH partnership for off-patent products:

- Develops a list of drugs for which pediatric studies are needed
- Is a long, iterative process
- Uses input obtained from a federal advisory committee, FDA divisions, NIH divisions, the American Academy of Pediatrics (AAP), the U.S. Pharmacopoeia (USP), and experts.

The history of the listing of drugs for which pediatric studies are needed is as follows:

- An initial list of 12 drugs was published in the *Federal Register* on January 21, 2003.
- A second list of 8 drugs was published in the *Federal Register* on August 13, 2003.
- In February 2004, 5 more drugs were added, and the status of prior 20 was updated (<http://www.fda.gov/cder/pediatric/69FR7243.htm>).
- In January 2005, 7 more drugs “for study” were listed in the *Federal Register* (<http://www.fda.gov/cder/pediatric/70FR3937.txt>).

NIH contracts are developed from this list. FDA issues a WR to the drug’s innovator, and if rejected, the WR is sent to NIH. The goal is an on-patent exclusivity process and an off-patent process that lead to new pediatric information in the label. The WR is a legal document sent by FDA to sponsors requesting studies in the pediatric population, the specifics of which include:

- Indication

- Population
- Type of studies
- Safety parameters
- Longer term follow-up
- Timeframe for response.

Exclusivity results, as of March 2005, include:

- Products issued WRs, 299
- Total number of studies, 692
- Products with submitted studies, 120
- New labels with pediatric information, 89
- Number of children involved (not including 40,000 in the Ibuprofen study), >43,400.

Exclusivity outcomes, as of March 2005, include:

- Products with new labels, 89
 - New dosing recommendations, 17
 - New safety information, 22
 - Effectiveness not established, 11.

FDA's pediatric requirement under PREA includes the following:

- FDA requires pediatric studies for the indication for which an adult application is to be submitted as strategic part of the application process.
- These studies are usually submitted by a sponsor and are not involved in an NIH contracting process.
- This process is separate from the off-patent contracting and exclusivity process. PREA studies may be different from the exclusivity studies, although PREA and exclusivity studies can be the same.
- Between June 1999 and December 2002, there were 47 product labels with new pediatric information obtained from studies conducted under PREA.

Pediatric trials have taught (that is, “what we were doing before we knew better”) the following:

- Unnecessary exposure to ineffective drugs
- Ineffective dosing of an effective drug
- Overdosing of an effective drug
- Undefined unique pediatric adverse events (AEs)
- Effects on growth and behavior.

According to Dr. Murphy, scientific trials issues include:

- Extrapolation
- Bridging studies
- Safety studies, both length and type
- Endpoint and validation issues.

Dr. Murphy presented and explained the decision tree for pediatric studies. There are some outstanding issues, including:

- Ethical constraints of placebo controlled trials (rapid-rescue?)
- Standard of care using nonpharmacologic therapy (sucrose)
- Need for pain assessment scales for ongoing and/or chronic pain
- Need for longer term outcomes for studies (18–24 months).

Dr. Murphy presented an organizational chart depicting FDA’s six centers and presented another chart depicting FDA’s pediatric structure. In concluding, Dr. Murphy described the pediatric links on FDA’s Web site, displayed FDA’s Office of Pediatric Therapeutics Web page, and listed relevant Web links and contact information, including:

- www.fda.gov
 - <http://www.fda.gov/oc/gcp/default.htm>
- www.fda.gov/oc/opt
 - <http://www.fda.gov/cder/pediatric/index.htm>
 - <http://www.fda.gov/cder/pediatric/wrlist.htm>
- http://www.fda.gov/cder/pediatric/wr_template.htm
- Office of Pediatric Therapeutics
 - 301-827-1996
 - 301-827-1017 (fax)
- Office of Counter-Terrorism and Pediatrics
 - 301-827-7777
- Division of Pediatrics
 - 301-594-PEDS
- E-mail
 - opt@fda.gov
 - pdit@cder.fda.gov.

Clinical Perspective

Dr. Ward, University of Utah Health Sciences Center

In this third presentation, Dr. Ward reviewed the issues for improving pediatric therapeutics through the BPCA Program from a clinical perspective. According to Dr. Ward, drug treatment for children is a neglected, but not forgotten, aspect of clinical research. He cited the following:

“There is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents.”
 —AAP Committee on Drugs, *Pediatrics* 1995; 95:286

Dr. Ward listed the following federal and legislative efforts to increase the study of drugs in children:

- 1979—Pediatric subsection in label required
- 1994—Final Rule allows extrapolation of efficacy from adults if the disease is similar
- 1997—FDAMA, exclusivity stimulates studies
- 2001—Subpart D—Final Rule: Additional safeguards for children in FDA-regulated clinical investigations
- 2002—BPCA

- 2003—PREA.

Dr. Ward characterized pediatric drug therapy as clinical practice without adequate study. He cited the following:

- From 1968 to 1997, 75 percent of approved drugs lacked complete pediatric prescribing information in the label.
- Pediatricians base prescribing on experience, drug handbooks derived from limited evidence, peers, and textbooks.
- Newer drugs enter pediatric practice slowly, usually from older to younger/smaller patients.
- Newborns are the last to be studied, if studied at all.

Dr. Ward asked: Have these laws and regulations improved pediatric drug therapy? He described the types and numbers of studies implemented under FDAMA and BPCA, from November 21, 1997, to March 31, 2005.

<u>Type of Study</u>	<u>Number</u>	<u>Percentage</u>
Efficacy and safety	245	35
PK and safety	202	30
PK/pharmacodynamics (PD)	61	9
Safety	106	15
Other	78	11
All types of study	692	—

These studies will potentially involve more than 43,399 pediatric subjects. Although the number of pediatric studies has increased, Dr. Ward questioned the gains. He noted that studies have identified unrecognized dosing problems. Dr. Ward cited the following:

- Gabapentin—higher doses need in children under 5 years of age to control seizures; identified new AEs of hostility and aggression in children under 12 years of age
- Midazolam—lower starting doses needed in children with congenital heart disease or pulmonary hypertension to avoid respiratory compromise
- Fluvoxamine—inadequate dosing of adolescents lead to ineffective therapy for obsessive-compulsive disorder; girls 8–11 years may need lower doses.

Other studies have identified previously unrecognized AEs. Dr. Ward cited the following:

- Propofol—increased mortality when used as sedative in pediatric intensive care unit population, although causality not determined; concomitant treatment with fentanyl may cause bradycardia
- Sevoflurane—potential for causing seizures in children without a prior history of seizures
- Ribavirin—increased evidence of suicidal ideation or attempts 2.5:1 in children versus adults; reduced linear growth and weight gain
- Betamethasone—Hypothalamic-pituitary-adrenal suppression systemically; local skin atrophy, not recommended in younger patients under 12 years of age for Diprosone and Diprolene or under 17 years of age for Lotrisone

- Pimecrolimus—indicated for atopic dermatitis in immunocompetent children older than 2 years of age; not recommended for under 2 years of age due to safety issues (infection, fever, diarrhea).

Dr. Ward characterized the BPCA study of off-patent drugs:

- Many drugs do not reach pediatric therapy until their patents have nearly expired (no exclusivity).
- BPCA provides for study of off-patent drugs in children to fill therapeutic voids:
 - List of drugs prioritized for study
 - FDA with the NIH defines in a WR what studies are needed to improve the health of children.

The study of off-patent drugs has been refined since the implementation of BPCA. In 2002, prioritization relied heavily on expert opinions from AAP, USP, and NIH PPRU Network sites. An expert panel met in December 2002 to discuss candidate drugs, using telephone conferences with outside experts in the therapeutic area. From these deliberations, the following drugs were among the first to be listed (*Federal Register* 68:2789, 2003):

- Azithromycin
- Baclofen
- Bumetanide
- Dobutamine
- Dopamine
- Furosemide
- Heparin
- Lithium
- Lorazepam
- Rifampin
- Sodium nitroprusside
- Spironolactone.

In reviewing off-patent drugs, 38 were prioritized (3 for two indications) for study. Some factors that lead to their listing in the *Federal Register* include:

- Treatment for serious disease
- Toxicities not well studied in pediatrics
- Widespread use based on hearsay, tradition, and limited or no systematic study
- Studies raise doubt about putative effects
- Pediatric populations understudied for safety, efficacy, PK such as: preterm newborns, oncology, behavioral disorders, and so on.

Dr. Ward explained that NIH and FDA decide which drugs and what studies to include in the WRs. WRs for study have been issued for:

- Azithromycin for prevention of bronchopulmonary dysplasia (BPD) through treatment of *Ureaplasma* sp.
- Azithromycin for treatment of chlamydia conjunctivitis and pneumonia
- Vincristine for children's cancer

- Lorazepam for status epilepticus
- Lorazepam for sedation in pediatric critical care units
- Nitroprusside for blood pressure control
- Dactinomycin for children's cancer.

Prioritization of off-patent drugs for special population led to the Newborn Drug Development Initiative. Dr. Ward characterized this NIH/FDA-developed initiative as:

- Responding to BPCA-identified need to study newborns
- Being led by Dr. Giacoia and Debra L. Birenbaum, M.D.
- Resulting in five working groups with NICHD/FDA facilitators
 - Neurology—seizures, hypoxic-ischemic encephalopathy
 - Cardiology—inotropes, postoperative cardiac support
 - Respiratory—apnea, BPD
 - Pain—sedation/analgesia during invasive mechanical ventilation, perioperative analgesia, procedural pain
 - Prioritization—criteria that indicate need for study.

The five working groups' recommendations will help identify the gaps in study of drugs in the newborn. The Newborn Drug Development Initiative report will be published in a future supplement to the journal *Pediatrics*, detailed reports from the working groups will be published in *Clinical Therapeutics* beginning in June 2005.

The benefits to pediatric therapeutics from FDAMA, BPCA, and PREA include the following:

- Systemic study of new drugs in pediatric patients increases their access to effective and safe treatment with new drugs.
- Labels based on systemic pediatric study disseminate information that improves pediatric treatment.
- Study of older, off-patent drugs is likely to reveal unrecognized gaps and misconceptions in the knowledge of how children respond to drug treatments.

The collateral benefits from FDAMA, BPCA, and PREA include an increased infrastructure for drug studies, which leads to:

- Physicians trained to study drugs in children
- PPRU Network sites and clinical research centers staffed and able to support drug studies in children
- Analytic methods for small samples to facilitate pediatric kinetic studies
- Application of population kinetics to children
- Collaborative studies for rapid completion.

Pertinent Web sites and talks include:

- <http://www.fda.gov/cder/pediatric/>
- <http://www.nichd.nih.gov/bpca/action.cfm>
- (Dr. Birenbaum) <http://www.fda.gov/cder/pediatric/presentation/dlb-DIA-Mar2003/dlb-DIA-Mar2003.PPT>
- (Dr. Mattison) http://www.nichd.nih.gov/bpca/documents/NICHD_and_the_BPCA.pdf

- (Dr. Murphy) <http://www.fda.gov/oc/opt/presentations/pedinitiatives.html>.

The BPCA List Process

Dr. Taylor-Zapata, CRMC, NICHD, NIH, DHHS

Dr. Taylor-Zapata reviewed the drug prioritization and listing process in the BPCA Program. She described the steps in the BPCA process for generic (that is, off-patent) drugs. These steps involve drug prioritization and listing, which results in:

- An annual list
- Improvements in pediatric therapeutics
 - Premise: Children deserve evidence-based medicine
 - Action item 1: Identify and combine useful databases
 - Action item 2: Estimate frequency of
 - Conditions affecting children (descriptive epidemiology)
 - Medications used by children (pharmacoepidemiology), both inpatient and outpatient
 - Action item 3: Determine availability and quality of the literature addressing PK/PD, safety, and efficacy.

The ultimate goals of the prioritization process are to make the best use of BPCA funds and to deliver the greatest benefit to America's children. The essentials of this process are to:

- Expand our knowledge base
 - Share information across agencies
- Expand input into the process
 - Outreach
 - Ensure that many voices and perspectives are heard
- Improve documentation
 - Share information, enlarge perspective
 - Transparency invites comment, expands input
 - Evaluation and continuous improvement to process.

In developing and prioritizing the list, BPCA legislation asks NIH/FDA to consider:

- Availability of information concerning safety and efficacy
- Whether additional information is needed
- Potential health benefits in the pediatric population
- Need for reformulation.

The list process for year ending in January 2005 resulted in the following *Federal Register* listings:

- Express Scripts of outpatient data
- Feedback from 19 organizations, and 3 federal agencies
- Pilot assessment of literature for 64 high-frequency drugs
- Preliminary list release in August 2004
- Scientific meeting on October 25 and 26, 2004
- *Federal Register* announcement on January 27, 2005.

According to Dr. Taylor-Zapata, the October 25 and 26, 2004, scientific meeting:

- Brought together experts from infectious disease, neonatology, emergency care, dermatology, psychiatry, nursing, pharmacology
- Allowed the exchange of diverse viewpoints and perspectives
- Provided greater depth to scientific discussion of pediatric therapeutics.

The off-patent drugs listed in January 27, 2005, issue of the *Federal Register* and recommended for clinical studies included:

- Ivermectin for scabies
- Hydrocortisone valerate ointment and cream for dermatitis
- Hydrochlorothiazide for hypertension
- Ethambutol for tuberculosis
- Griseofulvin for tinea capitis
- Methadone for opiate addicted neonates
- Hydroxychloroquine for connective tissue disorders.

The off-patent drugs listed in January 27, 2005, issue of the *Federal Register* and recommended for systematic literature review and/or further consultation with scientific community included:

- Cyclosporine for heart transplant patients
- Clonidine for autism, attention deficit disorder
- Flecainide for life threatening ventricular arrhythmias.

The on-patent drugs listed in *Federal Register* January 27, 2005, and recommended for clinical studies included:

- Sevelamer for renal failure
- Morphine for analgesia.

The on-patent drugs listed in *Federal Register* January 27, 2005, and recommended for systematic literature review and/or further consultation with the scientific community included:

- Bupropion for depression.

Dr. Taylor-Zapata listed the milestones for coming year:

- Outreach mailing in February 2005
- Receive input through April 30, 2005
- Preliminary list in the *Federal Register* in August 2005
- Scientific meeting on November 8 and 9, 2005
- *Federal Register* announcement in January 2006.

Improvements in pediatric pharmacoepidemiology and understanding of medication use in children include:

- Inpatient databases from hypothesis-testing observational studies of efficacy and outcomes of drugs used in inpatient setting
- Patterns by age, that is, neonates and adolescents
- Variations by race/ethnicity with ability to make inferences in patterns of disease occurrence, treatment, and severity.

Dr. Taylor-Zapata summarized her presentation:

- The annual list process is a transparent evidenced-based process that has led to increased opportunities for input from all sectors.
- Pharmacoepidemiology to inform the list process has generated quantitative, objective estimates of drugs and conditions affecting children in all ages, by sex and by racial/ethnic groups.
- Theist process has also generated information leading to wise use of BPCA funds to best serve needs of America's children as well as better practice and use of medications in all of America's children.

Panel 2: How Can You Become Involved With the BPCA Program?

In their presentations, members of Panel 2 reviewed issues regarding:

- Obstacles to pediatric drug development
- Developing a pediatric drug program
- Drug companies' perspective on pediatric clinical trials
- Conducting BPCA clinical trials
- Improving chances of success in becoming a principal investigator of a BPCA pediatric clinical study
- Implementing BPCA with NICHD and CRMC.

Issues in Pediatric Clinical Trials

Dr. Maldonado, Johnson and Johnson Pharmaceutical Research and Development

Dr. Maldonado reviewed issues in pediatric clinical trials from the perspective of drug companies. He acknowledged that BPCA a good tool. With BPCA, it is easier for a drug company to make a business case to develop a pediatric drug. However, advocacy is as important as BPCA. There are many pediatricians involved in drug development, and if there is a medical need, then practicing clinicians need to make the case. In this context, FDA's role is more than oversight: FDA becomes a champion of pediatric drug development.

Dr. Maldonado listed the following obstacles to pediatric drug development by drug companies:

- Business is small—BPCA alleviates by incentive
- Internal competition for resources
- Medical needs typically different in children
 - Most children are healthy
 - Those in need of medication do not have same illness (heart disease, cancer, etc.)
- Fewer patients to study
- Fewer qualified investigators and study sites
- Heterogeneous population/stages of development
- Lack of FDA-approved comparators.

The business case for not developing pediatric drugs includes:

- Smaller and healthier population

- Fewer chronic diseases than in adult population
- Requirement of a new formulation
 - FDA approves formulations (drug products)
 - There may be a need for several drug products to cover the entire pediatric age range
 - Formulations need maintenance
 - Technical and regulatory maintenance
 - Nonsolid formulations may be more difficult to produce
- Competing with unmet needs in adult populations.

However, if there is medical need and a business case, drug companies will develop a pediatric program. Dr. Maldonado outlined the steps for developing a pediatric drug program:

- Company's pediatricians proposal
 - Present to pediatric key opinion leaders (KOLs)
 - Present to pediatric practitioners
- Pediatric proposal redesign
 - Present again to pediatricians (KOLs and practitioners)
- Present to several stage gate reviews
 - Scientific, technical, and resource stage gate reviews
- Corporate, ethical, and legal oversight
- Propose pediatric study request
 - FDA issues a WR
- WR discussed with KOL and practitioners
 - Program may need modifications
 - If substantial modifications are made:
 - Stage gate reviews
 - Scientific review (protocol review committee)
 - Technical review (scientific merit and feasibility of program)
 - Request for resources (competing with other programs)
 - Corporate, ethical, and legal oversight
- Back to FDA for WR amendment
 - Negotiate amendment
 - Several rounds of negotiations may be necessary
- Execution of the program
 - Based on findings in the field (sites and institutional review boards [IRBs]):
 - Program may need further modifications
 - Modifications may trigger
 - Further stage gate reviews
 - WR amendment negotiations with FDA
- Pediatric supplemental NDA in response to WR
 - Exclusivity granting or denial
 - Review of data by FDA reviewing division
 - Label may or may not be modified even if exclusivity is granted; pediatricians may never see final product.
 - Pediatric formulation scale up may prove difficult or impossible; pediatricians may never see final product.

- Marketplace
 - Formulation may be available but not used (sold).
 - Decision to maintain the formulation needs to be made.

Regarding marketplace availability, Dr. Maldonado noted that companies might decide not to promote the drug product in the pediatric community. Dr. Maldonado cited the following caveats:

- This does not mean lack of availability.
- Availability of product in the absence of promotion does not decrease risks.
- Inappropriate uses may occur.
- There may be increasing regulatory and legal liability.
- Risk management and risk assessment in the pediatric population is an ongoing task even if the company does not promote or make money on the pediatric formulation.

Regarding children’s access to appropriate medications, Dr. Maldonado cited the following statement from AAP:

“The AAP believes it is unethical to deny children appropriate access to existing and new therapeutic agents. It is the combined responsibility of the pediatric community, pharmaceutical industry, and regulatory agencies to conduct the necessary studies; it is the responsibility of the general public to support the necessary research in order to assure that all children have access to important medications and receive optimal drug therapy.”
—AAP Committee on Drugs; *Pediatrics* 1995; 95:294

Dr. Maldonado explained that safe/effective pharmacotherapy in children requires clinical studies in children. The ethical imperative to obtain needed information in clinical studies must be balanced against the ethical imperative to protect each child in such studies. Thinking about “pharmacologic vulnerability” in children is driven by past therapeutic misadventures and by the very real ethical considerations about clinical studies in “vulnerable” populations. In fact, children are not always pharmacologically “at higher risk.”

Approaches that afford the best protection for studying pediatric therapeutics include:

- Knowledge of human pathways of metabolism and elimination, and their ontogeny
 - In vitro studies, adult human PK studies, developmental studies on pathways of drug clearance in children
 - Development of “ontogenetic maps” of clearance pathways to direct and target studies
- Routine immature animal screens fraught with validation issues—science needs better
 - Species differences in metabolism, ontogeny, sensitivity.

Regarding distributive justice, Dr. Maldonado said that information that can be obtained in a less vulnerable population should not be obtained in a more vulnerable population. He urged that researchers to not do studies in nonconsenting subjects that can be done in consenting subjects. In addition, studies in handicapped or institutionalized children should be limited to diseases or conditions found principally or exclusively in these populations or where the underlying

conditions of the patients would be expected to alter the disposition or PD effects of a medication.

Dr. Maldonado noted the following about alternative approaches:

- Pediatric Labeling Regulations (1994)
 - Published data had inadequate information for labeling
- Literature filled with small, underpowered, often inadequately designed studies that
 - Are often done with nonvalidated formulations with inadequate data on stability and bioavailability
 - Have multiple study designs and end-points
 - Are “unsalvageable” by meta analysis
 - Are ultimately of little service to patients.

Regarding studies in juvenile animals as pediatric models, Dr. Maldonado said that there is no parallel of human development in the animal world. He cited the following:

“All animal models are wrong.”
—Steve Pelton, M.D., Children’s Hospital, Boston

Dr. Maldonado said that if studies in adults exist, they might be better predictors of efficacy and safety. Children (even adolescents) and adults are the same species.

Dr. Maldonado presented two graphs:

- Time to develop adult characteristics in rats and humans (percentage adult status versus age in years)
- Relationship between extent of maturation in rats and humans (percentage adult status versus physiologic time).

Regarding the relevance of adult data, Dr. Maldonado cited the following:

“When paediatric patients are included in clinical trials, safety data from previous adult human exposure would usually represent the most relevant safety data and should generally be available before paediatric clinical trials are started.”
—David R. Jones, Senior Toxicologist at the Medicines and Healthcare Products Regulatory Agency, United Kingdom

Dr. Maldonado explained that each formulation is a new drug product. In addition:

- It needs to be developed as an entity by itself
 - Physicochemical properties (solution, suspension, etc.)
 - Palatability and color preferences
 - PK, including bioavailability.
- Once developed for clinical trials, it needs to be scaled up for commercial distribution; scale up may fail.
- It needs to be tested for appropriate stability.
- It requires a dedicated line production.

- It needs to comply with all good manufacturing practices.
- It needs dedicated technical, scientific, and regulatory resources.

Dr. Maldonado listed the following ethical considerations:

- Is it ethical to conduct clinical trials in non-consenting populations?
 - Surrogate consent is usually obtained in pediatric studies
- Is it ethical to continue using drugs that have not been adequately studied in children?
 - Risk of repeating therapeutic misadventures of the past
- Risk of unintended harm will always be present
 - Minimize risk
 - Explain risk
 - Distribute risk.

Dr. Maldonado cautioned that pediatric clinical studies often generate unfounded criticism. He cited the following examples from a variety of publications:

- “The Guinea Pigs Demand Justice”
—*Financial Times*, December 2001
- FDA and Pharmaceutical Researchers and Manufacturers of America (PhRMA) as targets of tabloid drama
“FDA Considers Drugging Healthy Kids for Science”:
“Is it ethical in the name of science to give a healthy child as young as 9 a controlled substance?”
—Associated Press, September 3, 2004
- In reference to fluoroquinolones
“Strong Antibiotics to be Tested on Kids: FDA Urges Trials Despite Side Effects”:
“Companies that produce a group of powerful antibiotics are being encouraged by the federal government to move into the pediatrics market, even though the drugs' use for children has been discouraged for a decade because of severe side effects.”
—Jeff Nesmith, *The Atlanta Journal-Constitution*, August 15, 2004
- PhRMA (and more recently FDA) are suspects
“Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin”
—*Pediatric Infectious Disease Journal* 2002; 21:525
“We wonder if this research would have been published had the authors come to the opposite conclusion. The whole dilemma of publication bias and industry-based research makes our joints—as well as our heads—ache.”
—*AAP Grand Rounds*, L. First and E. Marcuse; September 2002.

In reference to BPCA as “a carrot,” Dr. Maldonado asked: Do you really want that carrot? He concluded his presentation by characterizing pediatric drug development, which is a

- Scientifically complex endeavor
- Technically demanding task
- Commercially challenging case
- Regulatory risky business
- Corporate conundrum.

However, because the alternative is unthinkable, Dr. Maldonado explained that, as a science, pediatric drug development “cannot go back.” It must move forward to maximize the benefits and minimize the risks to children.

Conducting BPCA Clinical Trials

Dr. Zajicek, CRMC, NICHD, NIH, DHHS

Dr. Zajicek provided an overview of the processes for conducting BPCA clinical trials. She began her presentation by describing “the big picture” and listing the initial steps in the BPCA process for identifying off-patent drugs to be studied. She noted the following progression in the list process:

- All off-patent drugs
- All off-patent drugs that lack pediatric labeling
- All off-patent drugs that lack pediatric labeling for which additional information would provide a health benefit.

Once the off-patent drugs are identified, listed, and prioritized, the WR process begins for drugs that are placed on the prioritization list. FDA writes a letter with input from NIH, to the holder of the NDA or abbreviated NDA (aNDA). The WR describes what is not known about the drug during human development (for example, safety, efficacy, PK/PD) and describes the studies and/or data development or gathering that FDA is requesting for a single drug and indication, including patient population, numbers of patients, and types of studies (for example, safety, efficacy, PK/PD). The holders of the NDA or aNDA may accept or decline the WR. If the WR is declined, then it is referred to NIH to begin the contracting process.

The steps in the contracting process include:

- WR referred to NIH
- RFP developed
- RFP listed in FedBizOpps
- Proposals submitted and peer-reviewed
- Contract(s) awarded.

The RFP includes a Statement of Work (SOW) and describes the technical evaluation criteria. The SOW is based on the WR and includes a description of specific elements that must be contained in the proposal. Dr. Zajicek provided the following example of studying oral azithromycin for the treatment of *Chlamydia trachomatis*:

- Diagnostic criteria
- Azithromycin dose(s) to be used
- PK sampling strategy
- Assay methods
- PK data analysis
- Safety assessments.

Dr. Zajicek explained that the technical evaluation criteria differ for each RFP. The offerers’ proposals are reviewed by a specially convened panel of outside experts and scored according to

the technical evaluation criteria contained in each RFP. Dr. Zajicek listed technical evaluation criteria and the total potential score for each:

- Understanding project requirements, 25 points
- Organizational experience and staff qualifications, 20 points
- Technical approach, 20 points
- Recruitment plan, 25 points
- Facilities, 10 points.

Contract negotiations are conducted with RFP respondent(s) with the highest score(s). This process allows protocol finalization. The final step is a contract award with PI(s). Projects may have multiple PIs and multiple prime contractors; most projects will have multiple sites (subcontracts).

The next step in the process is initiation of the clinical study, which begins with project start-up that includes:

- Meetings
 - Kick-off meeting with PI(s), NICHD, Coordinating Center
 - Investigator meeting with PI(s) and subcontracting sites, NICHD
- Protocol finalization.

IND submission occurs after project start-up and includes:

- Pre-IND meeting with FDA to discuss protocol design
- IND package including final protocol submitted to FDA
- IND approved by FDA.

The contract for the BPCA Coordinating Center was awarded in September 2003 to Premier Research, of Philadelphia, PA. The Coordinating Center reports to NICHD, the government-contracting officer, and the government project officer; and it interacts with the various clinical study sites. Responsibilities of the Coordinating Center include:

- Data management
 - Web portal
 - Electronic case report forms
- Statistical support
- Randomization
- Regulatory support–IND submission
- Drug supply
- Monitoring of studies
- Management of Data and Safety Monitoring Board (DSMB)
- Safety reporting to FDA.

Ethical and safety oversight of BPCA clinical studies includes:

- IRB submission and approval of a single protocol for all sites
- DSMB review of protocol.

The ultimate goal of BPCA clinical studies is better medicines for children, including evidence-based dosing recommendations; improved efficacy, better safety information; improved information in medication labels; and enhanced pediatric therapeutics.

Becoming Principal Investigator of a Clinical Study: Improving Your Chances of Success

Dr. Giacoia, CRMC, NICHD, NIH, DHHS

Dr. Giacoia reviewed the process of responding to BPCA RFPs in order to improve offerers' chances of contract award. Responses to RFPs include:

- Technical (scientific) proposal
 - Proposal in response to NICHD's SOW
 - Additional technical proposal information
 - Reviewed by peer-reviewers
- Business proposal.

Dr. Giacoia's presentation dealt with only technical (scientific) proposals. He explained that additional technical proposal information often describes:

- Offerers' knowledge and experience
- Clinical trials experience
- Laboratory capabilities
- Administrative expertise.

Problems and common pitfalls in responding to RFPs include:

- Applicant PIs may lack experience in directing large efficacy trials
- Limited number of pediatric trialists
- Role of proposed coinvestigators not clearly stipulated
- Not involving key coinvestigators in the planning of the protocol early in the process
- Assuming that PI is responsible for filing IND.

Dr. Giacoia elaborated on the common pitfalls:

- Lack of understanding of the role of PI's clinical trials office
- Misunderstanding the role of the BPCA Coordinating Center
 - Assignment of BPCA Coordinating Center tasks to applicant clinical trials office/organization
 - Data management
 - Drug randomization schemes
 - Drug distribution
- Overestimation of the number of patients available for study
 - Use of *International Classification of Diseases* (9th edition) to estimate patients available for study (that is, to estimate disease prevalence)
 - Underestimation of the number of sites needed
- Ignoring feasibility issues.

Responsibilities of the BPCA Coordinating Center include:

- Regulatory functions
- Data management
- Interaction with FDA, NIH, and pediatric off-patent drug study site (PODS)
- Statistical support
- Randomization process
- Pharmacy support
- Sites monitoring
- Final study report.

Responsibilities of the PODS' Clinical Trial Office, Network Coordinating Center, and Site Management Organization include:

- Administrative support for PIs
- Management of clinical sites
- Day-to-day operation of protocol implementation
- Facilitation of interaction among PIs and Coordinating Center
- Recruitment of additional sites.

According to Dr. Giacoia, feasibility issues include:

- Estimation of the number of patients likely to enroll
- Support from other physicians (within and across specialties)
 - Local practice standards that are in conflict with the proposed study design
- Nursing staff experience in pediatric drug trials
 - Nursing and ancillary personnel support.

Common pitfalls in protocol development include:

- Misinterpretation of
 - NICHD SOW
 - FDA's WR
- Ignoring stipulations of WR
 - The WR is incorporated into the NICHD SOW.
 - WR is always attached as appendix to the RFP.

Dr. Giacoia strongly urged offerers to respond to the SOW with knowledge and awareness of the WR. The SOW incorporates the WR as an appendix and lists the WR's requirements in the text of the SOW.

Other common pitfalls in protocol development include:

- Lack of specificity in the response
- Ignoring NIH policies as stated in the SOW
- Inaccurate estimation of amount of blood drawing
- Inappropriate inclusion/exclusion criteria
- Lack of stopping rules
- Research team not separate from patient care staff
- Prespecifications stated in the SOW not incorporated into the protocol
- Safety outcome variables not clearly defined

- Lack of distinction between drug-specific toxicity and condition-related abnormalities
- Methodology for protocol specific biochemical studies not specified
- Laboratory not identified
- Validation of biochemical studies or PD measurements not available
- Plan for the collection, processing, storage, and analysis of PK specimens not available
- Misunderstanding of contract award process
 - Roles of program officer and contract officer
 - Review process
 - Negotiation
- Confusing requirements for grants and contracts
 - The processes for awarding a contract are different from those of a grant.

Dr. Giacoia suggested the following as potential BPCA add-on studies:

- Diagnostic biomarkers
 - Biomarkers of disease progression
 - Biomarkers of toxicity or effectiveness
- Pharmacogenetic studies
- Outcome measurements
- PD measurements and/or scales.

Some of the regulatory issues in responding to BPCA RFPs include:

- Limited knowledge of regulations governing the conduct of trials to support FDA labeling of drugs (for example, Good Clinical Practices and Good Laboratory Practices)
 - NICHD and the Coordinating Center will work with successful offerers to implement
- Lack of understanding of regulatory requirements for reporting AEs
 - Use of “academic” definition of AEs instead of FDA definitions
 - Will be addressed in detail in the IND protocol
 - Offerers need to be aware of FDA guidance on AE definitions.

Other common pitfalls and problems with offerers’ responses to BPCA RFPs include:

- Technical proposals are often incomplete.
- Proposals are not presented in an organized fashion.
- The final statistical plan is developed by Coordinating Center after contract award.
- Accurate statistics on patient population, as required by RFP, are not available.

Dr. Giacoia characterized successful proposals:

- The proposed study has high scientific value.
- The proposed protocol is feasible and can be completed in the anticipated time period.
- The offerers demonstrate an understanding of BPCA clinical trials process.
- The proposal includes all the required elements, as listed in the RFP.

In concluding, Dr. Giacoia listed the stages of protocol development:

- PODS PI stage
 - Initial protocol developed by PI and Co-PIs
 - NICHD peer review

- NICHD site visit (high-score proposals)
- Revised proposal (final offer)
- Post-award protocol development
 - PI PODS plus Coordinating Center plus NICHD staff (statistical, data management regulatory issues)
- FDA stage
 - Pre-IND and IND meetings
 - Protocol changes and submission of IND
- Post-IND revisions
 - PODS steering committee revisions.

Implementing BPCA Within NICHD and CRMC

Dr. Willoughby, Director, CRMC, NICHD, NIH, DHHS

Dr. Willoughby briefly reviewed the way in which BPCA is implemented. She noted that various government agencies and private organizations and entities are collaborating to bring the vision of BPCA to fruition. She said, “It’s all about how we can work together.” Dr. Willoughby first described the process of developing the list of drugs to be studied:

- Queries to professional societies and advocacy groups
- Notice requesting input
- Collating results
- Weighting information for specialized epidemiologic data sets
- Day-long meeting with consultants.

The next step in the process is soliciting proposals. The RFP:

- Is a legal and scientific document that invites qualified offerers to perform one of the BPCA clinical trials or activities related to BPCA clinical trials
- Includes an SOW that outlines what the offerer needs to do
- Includes the WR—the backbone of the RFP—that describes
 - What studies are to be done
 - What drug is to be studied
 - The study population
 - The indication.

Dr. Willoughby reminded meeting participants that the BPCA program has already established a data and study Coordinating Center to support all aspects of the BPCA clinical studies. After the RFP is released, offerers submit an application to NIH, which is peer-reviewed. Upon contract award, both the government contracting officer and the government program officer play vital roles in implementing the clinical studies. Dr. Willoughby concluded by explaining that the goal of all BPCA clinical studies is to produce information relevant to the labeling of the study drug for use in children.

Question-and-Answer Session

Dr. Mattison and panel members

Dr. Mattison noted that the BPCA process is intended to be an open, transparent one, as all federal processes are intended to be. The overarching goal of the BPCA process is to produce information that improves pediatric therapeutics. During this session, Dr. Mattison and the panel members responded to questions and comments. They answered, addressed, and discussed the following issues and concerns:

- **Availability and Sources of Funding.** Kanwaljeet Anand, M.B.B.S., D. Phil., Arkansas Children's Hospital, asked the panel members to explain the discrepancy between a Congressional mandate to conduct BPCA studies and the lack of appropriation of funds to conduct such studies. Dr. Mattison explained that, through BPCA, Congress allowed the spending of funds for research on pediatric pharmaceuticals but did not appropriate the necessary funding for this research. To date, approximately 22 Institutes and Centers at NIH have contributed to BPCA funding through their existing budgets. These contributions are proportional to the Institutes' and Centers' interests in pediatric diseases and conditions. Although Congress recommended annual spending of up to \$250 million per year, the various contributions to BCPA clinical and preclinical trials total about \$25 million per year.
- **Stopping Rules/Data Monitoring.** Daniel K. Benjamin, M.D., M.P.H., Ph.D., Duke University Clinical Research Institute, submitted two questions. First, he asked whether BPCA proposals should provide tentative plans for the roles and responsibilities of DSMBs, including stopping rules. Dr. Benjamin said that because members are preselected, and because DSMBs are freestanding and autonomous groups, they will review BPCA study plans according to their own rules and regulations. Dr. Mattison replied that he expects all protocols to be reviewed by DSMBs and that each will have its own stopping rules. Regardless, DSMB plans should be outlined in all proposals. Dr. Zajicek said that the Program Office understands that each protocol will have its own stopping rules. Second, Dr. Benjamin asked whether applicants are encouraged to provide a way to assess a site's performance during onsite visits without necessarily being responsible for assessing FDA Part 11 compliance (that is, monitoring the data collected from the patients), which is the Coordinating Center's responsibility. Dr. Giacoia answered that data monitoring is intended to be a complementary process: Contractors should collect performance data but forward the information to the Coordinating Center for centralized analysis.
- **Clinical Drug Supplies.** Jon B. Bruss, M.D., M.S.P.H., Pediamed Pharmaceuticals, asked about the sources of clinical drug supplies at the study sites and the randomization scheme. He also asked: If a particular organization had all the necessary regulatory capabilities, would the services of FDA and NICHD offices involved in BPCA still be needed? Dr. Zajicek replied that the contractor for the Coordinating Center (Premier, Inc.) is supplying all drugs for the studies through a subcontract with McKesson Corporation. Sites may need to provide some ancillary drugs if they are not available through McKesson. Dr. Zajicek said that randomization is implemented through the Interactive Voice Response System, which is provided by Life Tree through another subcontract. The data monitoring has also been contracted to Premier, Inc. Dr. Zajicek explained that the statement of work for the Coordinating Center is included as an attachment to the RFPs. Dr. Giacoia emphasized the

importance of knowing and understanding the roles and responsibilities of the Coordinating Center before submitting a proposal.

- **Drug Development Process.** John DeVincenzo, M.D., University of Tennessee, Memphis, observed that, under BPCA, new drugs for children are being developed “in retrospect,” that is, drugs originally developed for adults are now being tested in children. Dr. DeVincenzo asked: What new processes are being implemented to specifically develop new drugs for childhood diseases? Dr. Mattison explained that there are two ways in which this issue is being addressed. First, FDA is instituting new regulatory strategies to ensure pediatric testing for new drugs as they enter the marketplace. Second, several Institutes within NIH, particularly NICHD, are very interested in investigator-initiated proposals to characterize the targets of disease or the receptors responsible for modulating disease responses. Government entities such as NICHD are actively encouraging academia to more fully understand the developmental-specific pathways of disease progression in children. Dr. Murphy commented that FDA encourages sponsors of new products or new indications to fully assess their products for pediatric applications. The Research Equity Act gives FDA the authority to request that new drug applicants conduct pediatric studies, if the new product is deemed relevant to a pediatric indication and it is determined that there is pediatric need for the new product. Dr. Murphy elaborated that there may be timing issues for the testing of new products (for example, new molecules) in children. It may be advisable to wait until sufficient adult research has been conducted before testing a new product in children. To encourage sponsor-funded research in such situations, FDA may combine an extension of product exclusivity with the requirement for pediatric testing. FDA’s regulatory strategies are intended to develop a full range of studies, not just those for a specific indication.
- **Information Dissemination.** Alicia Bazzano, M.D., M.P.H., University of California, Los Angeles, asked: How will drug information such as label modifications be disseminated and communicated to practicing pediatricians? Dr. Mattison replied that NICHD and FDA collaborate with the Agency for Research on Health Quality (AHRQ). One of AHRQ’s responsibilities is to disseminate appropriate practice parameters and standardization. To the extent possible, NICHD and FDA will conduct public education sessions on label modifications. In addition, NICHD and FDA will work with other NIH Institutes and Centers, as well as various pediatric professional organizations and associations, to disseminate important pediatric information. The Office of Pediatric Therapeutics posts information to FDA’s Web site that extracts the specific, new drug labeling changes. In addition, Congress has mandated the posting of pediatric study summaries for all products being studied under exclusivity. Eventually, all clinical data for potential pediatric products will be made publicly available. Dr. Ward noted ongoing discussions about a joint United Kingdom/AAP publication of a pediatric drug handbook that would provide both on- and off-label prescribing information that has been agreed upon by experts. This handbook could potentially become the document that pediatricians rely upon for prescribing medicines for children. In response to another question from Dr. Bazzano, Dr. Mattison acknowledged that there is no information dissemination or publication requirement under BPCA. All information will be publicly available but only as a function of available resources. Both NICHD and FDA continue to explore mechanisms and strategies to disseminate new drug information and change pediatricians’ practices with regard to pharmaceuticals.

- **Effects of Foreign Study Sites.** Dr. Benjamin asked whether the inclusion of foreign sites negatively impact a technical score if the investigators believed that such inclusion would facilitate enrollment and timelines. Dr. Mattison said he could not answer this question conclusively. Scoring would depend on whether the sites could be justified based on sample size calculations that are needed and if the investigators can demonstrate that the study cannot be conducted within the United States.
- **Timeline for drug studies.** A workshop participant inquired about the timeline for studies of off-patents drugs that have already been listed and are “in consultation with experts.” Dr. Mattison explained this situation: Drugs that are being evaluated through consultation with experts indicates that officials in the BPCA program have been frustrated with a range of factors. Essentially, there is a hitch in some aspect of the normal process. For example, there may be a problem with the development of the WR or the design of the clinical trials. In some cases, a preclinical study may be warranted; in other cases, there may be a lack of agreement among experts about how the drug acts. In such circumstances, clinical trials cannot be designed with amorphous or nondescribed endpoints. The participant asked specifically about furosemide and spironolactone. Dr. Mattison said that a working group that includes experts from FDA and the National Heart, Lung, and Blood Institute has been formed to address issues of studying typical antidiuretics and antihypertensives. This group will focus on strategies for diagnosing and treating pediatric hypertension. It will also examine the ways in which antidiuretics and antihypertensives fit into current practices and determine how these drugs can be evaluated in clinical trials. Dr. Mattison commented that this working group is part of a specific pediatric hypertension initiative. In response to another query, Dr. Mattison explained that each clinical trial would study only single indications for pediatric drugs. If a drug has multiple indications, then separate clinical trials will be necessary to study each indication.
- **Clinical Trial Design.** A workshop participant reported that drug companies often approach clinical researchers to perform clinical trials, and the drug companies will stipulate the trial design for the studies. When researchers ask the drug companies why they chose the particular clinical trial design, the companies will reply that FDA assigned the trial design. The participant asked whether trial design assignment by FDA could be revealed and/or verified. Dr. Murphy replied that, although FDA is legally restricted from revealing certain contractual elements, researchers can, and should, ask the drug companies to provide FDA’s WR for the clinical trial. WRs are an open part of this process. Researchers do not have to conform to the trial designs described in the WRs; they can request modifications. Researchers can contact the FDA division that issued the WR for any available, supplemental information. Dr. Mattison commented that all BPCA WRs are open and available, and in the public domain. The BPCA Program Office will provide copies of all WRs, upon request. In addition, WRs are posted on the BPCA Web site.
- **Information Dissemination.** A workshop participant suggested that the BPCA program aim its information dissemination efforts at the next generation of pediatricians, which are today’s pediatric residents. To this end, the participant further suggested that AHRQ purchase two pages in the *Harriet Lane Handbook* and post information on the Harriet Lane WWW Links Web site.

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