

**Drug Prioritization Meeting
Best Pharmaceuticals for Children Act
National Institute of Child Health and Human Development
National Institutes of Health
November 8–9, 2005
Holiday Inn Select Bethesda
Bethesda, MD**

This workshop was sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS).

DAY 1

Welcome, Introductions, and Goals for the Meeting

Robert M. Ward, M.D., Chair, Best Pharmaceuticals for Children Act (BPCA) Drug List Prioritization Experts; Professor of Pediatrics, University of Utah Health Sciences Center

Dr. Ward welcomed the participants and described the meeting goals:

- Review of existing drug listing process, challenges, and successes
 - Provide NIH an opportunity to do a mid-course review of drugs identified for study and progress in conducting needed studies
 - Describe challenges and opportunities noted by NIH in designing and initiating preclinical and pediatric clinical studies
- Consider alternative processes for identifying drugs and conditions for study
 - Alternative approaches have been proposed by the European Union and a group of neonatologists.
 - NICHD, the U.S. Food and Drug Administration (FDA), and the National Heart, Lung, and Blood Institute (NHLBI) are collaborating in an evaluation of pediatric hypertension.
- Discuss drugs under consideration for hypertension, attention deficit/hyperactivity disorders (ADHD), parasitic diseases, pertussis, influenza, and poisoning.

Dr. Ward said that drug treatment for children has been neglected but has not been forgotten, and with BPCA, it is now advancing. To date, about 75 percent of drugs have not been fully labeled for treatment of pediatric patients. Dr. Ward noted that:

“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,” American Academy of Pediatrics (AAP) Committee on Drugs (*Pediatrics* 1995;95:286).

Dr. Ward reviewed past, present, and future efforts to improve pediatric drug therapies. Two legislative acts were passed by Congress to address deficits in pediatric studies:

- 1997 Food and Drug Administration Modernization Act (FDAMA)
 - Incentives increase study of on-patent drugs

- 2002 Best Pharmaceuticals for Children Act (BPCA; PL-107-109)
 - Continues incentives for study of new drugs
 - Mandates study of off- and on-patent drugs that industry will not study that are prioritized
 - Studies specified in a Written Request by FDA.

From FDAMA (November 21, 1997) to BPCA (March 31, 2005), almost 700 pediatric studies of on-patent drugs have been implemented, potentially involving more than 43,399 pediatric subjects:

Type of Study	Number	Percentage
• Safety and efficacy	245	35
• Pharmacokinetics (PK) and safety	202	30
• PK and pharmacodynamics (PD)	61	9
• Safety	106	15
• Other	78	11
• All types of studies	692	

Dr. Ward described the role of off-patent drugs in pediatrics:

- New drugs reach pediatric therapeutics slowly.
- Pediatric therapy often relies on older drugs that are familiar to pediatricians.
- Treatment with these older drugs is often based on studies and experience in adults or small, uncontrolled pediatric studies.
- Drug doses are often not appropriate for all ages, which may produce adverse effects.

BPCA provides for pediatric study of off-patent drugs that “will provide a health benefit,” which Dr. Ward characterized as a vague concept. Other aspects of BPCA’s approach for off-patent drugs include:

- NIH creates a prioritized list of drugs for pediatric study.
- FDA and NIH collaborate to develop Written Requests and contract for studies.
- The Foundation for the National Institutes of Health (FNIH) funds studies with “\$200 million for fiscal year 2002; and such sums as are necessary for each of the five succeeding years.”
- No funds were appropriated by Congress, so NIH has funded studies to date.

BPCA’s mandate to prioritize off-patent drugs has lead to “The List.” To this end, NIH is to:

- Develop a list of drugs for which pediatric studies are needed
- Gather input from AAP, the U.S. Pharmacopeia, the FDA Pediatric Advisory Committee, NIH divisions, and experts
- Conduct discussions that frequently focus on drugs used in pediatrics without pediatric study to demonstrate optimal dosing, efficacy, and safety.

Dr. Ward summarized BPCA listings since January 2002:

- First listing (2003)
 - Expert consultation (FDA, NIH, pediatric experts)
 - December 2002 listing meeting

- February 2003 *Federal Register* publication of 12 drugs needing study
- August 2003 second *Federal Register* publication of 8 drugs needing study
- Second listing (2004)
 - Expert consultation (FDA, NIH, pediatric experts)
 - November 2003 listing meeting
 - January 2004 third *Federal Register* publication of 5 new drugs; 20 others updated
- Third listing (2005)
 - Public outreach and expert consultation in spring 2004
 - October 2004 listing meeting
 - February 2005 fourth *Federal Register* publication of 7 new drugs.

Dr. Ward listed the steps in current process:

- Identify generic (off-patent) drugs
 - Track patent status
 - Remove those currently listed
 - Track discontinuations
- Consider approved indications—relevant for pediatric conditions
- Solicit expert and public opinion to identify those of greatest interest
- Convene expert panel for discussion and recommendation
- Select drug/indication for development of Written Request—study.

Because BPCA “sunsets” in 2007, Dr. Ward noted that 2005 is an appropriate half-way point in this important endeavor. It is a time to celebrate accomplishments and to strategize the next steps. Dr. Ward summarized the accomplishments to date:

- | | |
|---|----|
| • Drug-indication pairs listed | 51 |
| • Written Requests at NICHD | 21 |
| – Generic, off-patent | 11 |
| – On-patent, through FNIH | 10 |
| • Requests for proposals, collaborations prepared/published | 13 |
| • Clinical studies initiated | 9 |
| • Preclinical studies initiated | 4 |
| • Grants initiated | 1 |

In reviewing the current problems and challenges, Dr. Ward commented that an appropriate question to ask is whether BPCA is being implemented in the most effective manner. Current discussions of individual drug-indication pairing should fully consider:

- Condition being treated
 - Public health impact
 - Severity of condition
 - Therapeutic intensity
 - Similarities to adult condition (for example, pathophysiology)
- Therapeutic options available
 - Other generic drugs

- Diversity of drug classes available or under consideration
- Available and emerging on-patent drugs.

Dr. Ward listed some emerging resources that may better inform the BPCA process:

- Neonatal drug prioritization
- European Medicines Agency (EMA) evaluation of drugs
 - Pain
 - Rheumatology
 - Cardiovascular
- Frequency of use of medications in pediatrics
- Frequency of conditions leading to outpatient visits, hospitalizations, and mortality
- Effective consultations with pediatric experts (for example, the Children’s Oncology Group [COG], which has an excellent record of conducting pediatric clinical trials).

To evaluate potential modifications to the process, Dr. Ward suggested that those involved in BPCA should examine the next steps in the process, including:

- Use data on frequency of pediatric conditions to set priorities for evaluation of therapeutic options
 - How to weight frequency versus severity of illness to provide the greatest health benefit for children
 - How to define/measure health benefit for children
 - Severity must be considered with feasibility for study
 - Consider alternate study designs to allow studies in small populations
- Within pediatric conditions requiring care, describe or define various therapeutic options and determine how often they are used along with their risks and benefits—when known
- Incorporate knowledge of use, efficacy, safety, and so on for generics within that condition among the available therapeutic options
- Define selected conditions/options for discussion and public input
- Select conditions/treatments for study based on above steps
 - Develop Written Request
 - Subsequent process is similar to current activity.

Dr. Ward explained that feasibility is perhaps the most important criterion for pediatric studies. Because of feasibility issues, pediatric studies often require alternate approaches. He concluded his presentation by noting the two key goals for the meeting participants:

- Define strategy for the second half of BPCA
- Refine the process for studying off-patent drugs.

NICHD Listing Activity Progress

Donald R. Mattison, M.C., Captain, U.S. Public Health Service; Senior Advisor to the Directors of NICHD and CRMC; Chief, OPPB, CRMC, NICHD, NIH

Dr. Mattison welcomed the participants and said that, because the BPCA process has reached the midpoint, it is important for all of those involved to determine the next steps and to consider

more effective and efficient processes. This meeting will allow experts to provide input to help NIH select the next drugs for study. NIH has worked closely with the FDA on BPCA and will continue to collaborate in this important project. During this collaboration, many questions have arisen, and they will be presented for consideration by the meeting's experts. Dr. Mattison asked the assembled experts to think creatively about future BPCA processes. Dr. Mattison briefly summarized BPCA listings to date and described the steps in the current process. He noted that:

- Nine clinical studies have been initiated for:
 - Dactinomycin
 - Hydroxyurea
 - Lithium
 - Lorazepam
 - Methylphenidate
 - Nitroprusside
 - Vincristine
- Four preclinical studies have been initiated for:
 - Ketamine
 - Vincristine
 - Dactinomycin
 - Methylphenidate
- A grant has been initiated to study morphine.

Dr. Mattison listed the BPCA drug-indication pairings as follows:

Drug	Indication
• <i>Acyclovir</i>	<i>Herpetic infections</i>
• Ampicillin	Infection
• Ampicillin/sulbactam	Infection
• Azithromycin (request for proposal [RFP])	Prevention of bronchopulmonary dysplasia (BPD) in neonates colonized with <i>Ureaplasma urealyticum</i>
• Azithromycin (RFP)	Prevention and pneumonia, treatment of <i>Chlamydia conjunctivitis</i> and pneumonia
• <i>Baclofen (RFP)</i>	<i>Oral treatment of spasticity from cerebral palsy</i>
• Bumetanide	Diuresis
• <i>Bupropion</i>	<i>Treatment of depression</i>
• <i>Bupropion</i>	<i>Treatment for smoking cessation</i>
• Clonidine	Autism
• Clonidine	Attention deficit disorder
• Cyclosporine	Organ transplant rejection
• Dactinomycin (National Cancer Institute [NCI], COG)	Cancer
• Daunomycin (Daunorubicin)	Cancer
• <i>Dexrazoxane</i>	<i>Prophylaxis from cardiotoxicity of Adriamycin</i>
• Diazoxide	Hypoglycemia

Drug	Indication
• Dobutamine	Hypotension, low cardiac output in neonates
• Dopamine	Hypotension, low cardiac output in neonates
• <i>Eletriptan</i>	<i>Migraine headaches in adolescents</i>
• Ethambutol	Tuberculosis
• Flecainide	Ventricular arrhythmia
• Furosemide	Diuresis
• Griseofulvin	Tinea capitis
• Heparin (labeled ≥ 1 kg)	Anticoagulation
• Hydrochlorothiazide	Hypertension
• Hydrocortisone valerate ointment and cream	Dermatitis
• Hydroxychloroquine	Connective tissue disorders
• <i>Hydroxyurea (NHLBI Baby HUG)</i>	<i>Sickle cell disease</i>
• Isoflurane	Maintenance of general anesthesia
• Ivermectin	Scabies
• Ketamine (National Center for Toxicological Research [NCTR])	Sedation, preclinical toxicology studies with FDA
• Lindane	Second line treatment of scabies
• Lithium (contract with Case Western Reserve University)	Treatment of mania in bipolar disorder
• Lorazepam (contract with Children's National Medical Center [CNMC])	Treatment of status epilepticus
• Lorazepam (contract with Case Western Reserve University)	Sedation in the intensive care unit for children on respirators
• Meropenem (RFP)	Infection
• Methadone	Neonates with opioid withdrawal
• Methotrexate	Cancer
• <i>Methylphenidate (National Institute of Environmental Health Sciences [NIEHS], NCTR)</i>	<i>Attention deficit disorder, hyperactivity</i>
• <i>Metoclopramide</i>	<i>Gastroesophageal reflux</i>
• Metolazone	Diuresis
• <i>Morphine (grant to CNMC)</i>	<i>Analgesia</i>
• Piperacillin/tazobactam	Infection
• Promethazine	Nausea and vomiting
• Rifampin	Methicillin resistant <i>Staphylococcus aureus</i> endocarditis
• Rifampin	Central nervous system (CNS) shunt infection

Drug	Indication
• <i>Sevelamer</i>	<i>Hyperphosphatemia in chronic renal failure</i>
• Sodium nitroprusside (contract)	Control of blood pressure
• Spironolactone	Diuresis
• Vincristine (NCI, COG)	Cancer
• <i>Zonisamide</i>	<i>Partial seizures</i>

Bold = Written Request at NICHD; *italics* = on-patent.

Dr. Mattison listed the status of the 11 Written Requests for generic off-patent drugs that are currently at NICHD:

Drug	Status
• Azithromycin (BPD; ureaplasma)	Proposals being evaluated
• Azithromycin (chlamydia conjunctivitis and pneumonia)	No proposals received
• Baclofen (spasticity)	Proposals being evaluated
• Dactinomycin (cancer)	Partnership with NCI and COG
• Hydroxyurea (sickle cell disease)	Partnership with NHLBI and Baby HUG Investigators
• Lithium (mania in bipolar disorder)	Contract with Case Western Reserve University
• Lorazepam (status epilepticus)	CNMC
• Lorazepam (sedation in intensive care)	Contract with Case Western Reserve University
• Meropenem (infection)	Proposals received
• Sodium nitroprusside (control of blood pressure)	Contract with Stanford and Duke Universities
• Vincristine (cancer)	Partnership with NCI and COG

Dr. Mattison briefly reviewed the current problems and challenges, as well as the emerging resources, and summarized the proposed modifications to the BPCA listing process:

- Use data on frequency of conditions to prioritize
- Consider data on frequency of use, efficacy, safety, and so on for generics and on-patent drugs within that condition and among available therapeutic options
- Define selected conditions/options for discussion and public input
- Select conditions/treatments for study based on above proposal.

Frequency of Conditions

Norma I. Gavin, Ph.D., Senior Research Economist, RTI International

Dr. Gavin began her presentation by noting that RTI International and the Department of Epidemiology, University of North Carolina, provide scientific support to NICHD for BPCA activities. RTI was contracted to study the frequency of pediatrics conditions and produce tables

of demographic characteristics including mortality, hospitalizations, physician visits, and chronic conditions in children. The study objectives are to:

- Develop estimates of the number of children nationally who could potentially use a specific drug or a category of drugs to (1) prioritize drugs for study and (2) assess the feasibility of accruing adequate sample sizes to study the drug and indication
- Determine the relative severity of conditions treatable by medications by synthesizing information on (1) mortality rates, (2) hospitalization rates, (3) physician visit rates, and (4) prevalence.

The first step in this study was to identify appropriate data sources. Dr. Gavin listed the database requirements for the data sources, which must:

- Be representative of the U.S. pediatric population
- Report age, gender, and race/ethnicity of the children with the medical events
- Report medical events for a comprehensive range of pediatric medical conditions treatable by prescription medications
- Be of adequate size to stratify the medical events by condition and the selected demographic characteristics
- Code conditions or disease categories similarly enough to enable cross-file syntheses by condition.

Pediatric mortality rates can be determined from the Multiple Causes of Death Public Use Files from the National Vital Statistics System. This system:

- Is nationally representative—includes data from all death certificates recorded in the United States
 - Consistently coded data are available for 1999–2002.
 - The 2003 data will be available in January 2006.
 - There are small changes to the death certificates in five states.
 - The 2002 files contain 46,572 observations for children (younger than 18 years of age) from the 50 states plus the District of Columbia.
- Provides demographic information
 - Age (in days for infants) and gender are known for all decedents.
 - Race and ethnicity if known. Hispanic ethnicity and single race are recorded. The National Center for Health Statistics (NCHS) provides “bridged” population estimates for the race/ethnicity categories on death certificates.
- Includes condition coding
 - The coding includes multiple causes of death.
 - Each record includes an underlying cause of death—the disease or injury that initiated the train of morbid events leading directly or indirectly to death or the circumstances of the accident or violence that produced the fatal injury.
 - Codes are presented in 5-digit ICD-10 format.
 - When the underlying cause of death is an injury or poisoning, it is typically coded with V, X, Y, or Z codes for the cause of the injury (for example, traffic accident, shooting) rather than the ICD-10 code for type of injury (for example, spinal cord injury, fracture of upper limb).

- No study was found validating the cause of death for children, but this is believed to be better than for adults.

The following data sources were considered for hospitalizations:

- National Hospital Discharge Survey, a annual national probability survey of records from a sample of nonfederal short-stay hospitals
- Healthcare Cost and Utilization Project Nationwide Inpatient Sample, a compilation of discharge records from a sample of community hospitals in 37 states.

These data sets were not designed to be valid for children, and as a consequence, the sample of children’s hospitals included varied widely from year to year. The study also considered the Kids’ Inpatient Database (KID) from the Agency for Healthcare Research and Quality’s (AHRQ) Healthcare Cost and Utilization Project. Dr. Gavin characterized KID as follows:

- Only all-payer inpatient care database specifically for children in the United States
- Currently available
 - 1997 KID—data from 22 states, children younger than 19 years of age
 - 2000 KID—data from 27 states, children younger than 21 years of age
- Available in November 2005
 - 2003 KID—data from 37 states, children younger than 21 years of age
- Sample of pediatric discharges from short-term general and specialty hospitals in 27 State Inpatient Databases
 - Geographic representation disproportionate; sample included
 - 90 percent of hospitals in Northeast
 - 77 percent of hospitals in West
 - 63 percent of hospitals in South
 - 30 percent of hospitals in Midwest
- Systematic random sample of discharges from these hospitals
 - 10 percent of uncomplicated in-hospital births
 - 80 percent of complicated births and other pediatric cases
- Weighted to national totals based on American Hospital Association survey data
- 2,039,244 discharges for children (younger than 18 years of age)
 - 207,186 were for normal uncomplicated birth (DRG 391), accounting for 45 percent of all weighted pediatric discharges
 - Remainder weighted to 3.5 million discharges nationally
- Demographic Information
 - Age in days is missing for 27 percent of discharges for infants.
 - 19 percent had ICD-9-CM codes V30–V39 and therefore were assigned to the “birth-to-28-days” age group.
 - 8 percent were assigned to the “29-to-364-days” age group.
- Race and ethnicity are missing on 17 percent of discharges and coded as “other” on 4 percent of discharges, precluding the estimation of accurate hospitalization rates by race/ethnicity from KID.
- Condition coding
 - Includes principal and multiple secondary diagnoses

- Codes are presented in 5-digit ICD-9-CM format.
 - E-codes are not used to code principal diagnoses but are included in separate injury variables.

The following data sources were considered for physician visits:

- National Ambulatory Medical Care Survey (NAMCS)/National Hospital Ambulatory Medical Care Survey (NHAMCS)
 - Nationally representative data on physician visits
 - Conducted annually since 1989
 - 2004 files will be available in December
 - NAMCS is a weighted national sample of physician visits to nonfederal office-based physicians
 - Three-stage probability sample based on geographic location, physician specialty, and visits during a specified 1-week period
 - NHAMCS is a weighted national sample of patient visits to emergency departments (EDs) and outpatient departments (OPDs) of non-federal short-stay hospitals
 - Four-stage probability sample based on geographic location, hospital, ED/OPD, and visits in a specified 4-week period.
- NAMCS/ NHAMCS, 2000–2002
 - Combined NAMCS/NHAMCS files for 2000–2002
 - 61,710 observations for children (younger than 18 years of age)
 - Demographic information
 - Age (in days for infants) and gender is known for all visits.
 - Ethnicity is missing for 20 percent of the visits.
 - Sample is too small for races other than white and black to reliably compute condition-specific rates.
 - Condition coding
 - Multiple variables
 - Three reason for visit variables coded using a survey-specific coding system
 - Three diagnostic variables coded in 5-digit ICD-9-CM
 - Three injury variables coded in E-codes
 - Diagnoses are missing or could not be matched to AHRQ clinical classification system (CCS) categories in 3 percent of visits.
 - For almost 20 percent of physician visits among children, the first-listed diagnosis is for well-child care, general administration, and screening.
 - Results suggest that sampling frame may be missing many mental and reproductive health providers.
- 2002 NAMCS
 - Pediatric specialties (excludes providers whose main activity is teaching, research, administration, or hospital-based care)

- Adolescent medicine	- Neonatal-perinatal medicine
- Allergy	- Nephrology
- Cardiology	- Neurodevelopmental disabilities
- Critical care pediatrics	- Neurology
- Developmental-behavioral	- Ophthalmology

- | | |
|--------------------------------|-------------------|
| pediatrics | – Orthopedics |
| – Emergency medicine | – Otolaryngology |
| – Endocrinology | – Pediatrics |
| – Gastroenterology | – Psychiatry |
| – Hematology/oncology | – Pulmonology |
| – Infectious diseases | – Rheumatology |
| – Internal medicine/pediatrics | – Sports medicine |
| – Medical toxicology | – Surgery |

The following data sources were considered for prevalence:

- National Health and Nutrition Examination Survey (NHANES), national probability survey designed to estimate the prevalence of selected diseases
 - Covers only 24 broadly defined diseases, some of which are adult only
- National Health Interview Survey (NHIS), household survey on the health of the civilian, noninstitutionalized U.S. population
 - Respondents are asked to identify the limiting conditions for family members with previously reported activity limitations from short lists of conditions on flash cards.

Neither survey covered a comprehensive range of pediatric conditions treatable by medications.

The Medical Expenditure Panel Survey (MEPS) was considered as a data source for prevalence.

Dr. Gavin characterized MEPS as follows:

- Nationally representative household survey of health care use, expenditures, sources of payment, and insurance coverage in the civilian, noninstitutionalized U.S. population.
- Sample of households surveyed is drawn from households that participated in the prior year's NHIS.
- Each household is interviewed five times over a 2½-year period; thus, each year's data are taken from two overlapping panels of households.
- Annual files are currently available for each year from 1996 to 2002.

Dr. Gavin characterized MEPS 2001 as follows:

- The 2001 file had 9,627 children (younger than 18 years) representing 72,787,924 million children in the United States.
 - Small numbers suggests pooling over years is desirable.
- Demographic information
 - Age
 - Measured as of December 31, 2001. Age in days is not available.
 - In the 2001 file, there were only 34 infants younger than 1 month of age as of December 31, 2001.
 - Gender and race/ethnicity are known for all children.
- Condition coding
 - Physical and mental health conditions are enumerated from responses to open-ended questions
 - Parents' verbatim responses are recorded

- Subsequently coded to 3-digit ICD-9-CM format and CCS disease categories by medical coders
- Comparison of MEPS and NAMCS/NHAMCS conditions
 - Correlation on ranks of prevalence of CCS disease categories = 0.85 with $P < 0.0001$
 - NAMCS/NHAMCS codes were more specific.
- Since 2000, additional information has been collected on priority conditions, including:
 - Whether a medical person has been consulted for the condition
 - When the condition was first noticed
 - The condition's severity
 - Current status of the condition
 - Any treatments received.

Dr. Gavin listed the MEPS 2002 priority conditions:

- Long-term, life-threatening
 - Cancer (of any body part)
 - Diabetes
 - High cholesterol
 - HIV/AIDS
 - Hypertension
 - Ischemic heart disease
 - Emphysema
 - Stroke
- Chronic, manageable conditions
 - Arthritis
 - Asthma
 - Gall bladder disease
 - Stomach ulcers
 - Back problems (of any kind)
- Mental health issues
 - Alzheimer's disease and other dementias
 - Depression and anxiety disorders.

The RTI study attempted two cross-file syntheses. Dr. Gavin described the first cross-data analysis. She noted that some conditions are not comparable across data files, making cross-file synthesis difficult:

- Injuries and poisonings in the mortality database
- Normal newborns in the hospital database
- Well-child care in the physician visits database.

Dr. Gavin described the second cross-data analysis, noting that the most frequent conditions varied significantly across data sets and across age groups:

- For children younger than 2 years of age (see Tables 1 and 2)
 - Conditions originating in perinatal period dominated mortality and hospital stays when complicated births are included.

- Respiratory conditions were the leading reason for physician visits and hospital stays when complicated births are excluded.
- For children 2–11 years of age (see Table 3 and 4)
 - Injuries and poisoning were the leading causes of mortality, whereas respiratory conditions were the leading cause of hospital stays and physician visits.
- For children 12–17 years of age (see Table 5)
 - Injuries and poisonings become an even more dominant underlying cause of death.
 - Mental disorders and conditions related to pregnancy and childbirth take on prominence in hospitalizations.

Table 1. Most Frequent Conditions for Age Younger Than 2 Years (I)

Group	Number of Deaths	Number of Discharges Including Complicated Births
Group 6: Diseases of the nervous system and sense organs	2	2
Group 8: Diseases of the respiratory system	3	16
Group 14: Congenital anomalies	22	3
Group 15: Certain conditions originating in perinatal period	54	63
All other groups	19	16

Table 2. Most Frequent Conditions for Age Younger Than 2 Years (II)

Group	Number of Discharges Excluding Complicated Births	Number of Visits
Group 6: Diseases of the nervous system and sense organs	5	23
Group 8: Diseases of the respiratory system	37	31
Group 14: Congenital anomalies	8	2
Group 15: Certain conditions originating in perinatal period	14	2
All other groups	36	42

Table 3. Most Frequent Conditions for Ages 2–4 Years

Group	Number of Deaths	Number of Discharges	Number of Visits
Group 2: Neoplasms	12	4	0.5
Group 6: Diseases of the nervous system and sense organs	8	7	22
Group 8: Diseases of the respiratory system	6	36	37
Group 16: Injury and poisoning	48	11	10
All other groups	26	42	31

Table 4. Most Frequent Conditions for Ages 5–11 Years

Group	Number of Deaths	Number of Discharges	Number of Visits
Group 2: Neoplasms	19	5	1
Group 6: Diseases of the nervous system and sense organs	8	7	15
Group 8: Diseases of the respiratory system	5	22	33
Group 16: Injury and poisoning	45	15	14
All other groups	23	51	37

Table 5. Most Frequent Conditions for Ages 12–17 Years

Group	Number of Deaths	Number of Discharges	Number of Visits
Group 5: Mental disorders	0.5	16	10
Group 8: Diseases of the respiratory system	3	7	23
Group 11: Complications of pregnancy, childbirth, and puerperium	0	25	3
Group 16: Injury and poisoning	69	16	18
All other groups	27	16	18

Frequency of Use

James Korelitz, Ph.D., Senior Epidemiologist, Westat

Dr. Korelitz began his presentation by noting that Westat provides scientific support to NICHD for BPCA activities. Westat was contracted to study medication usage in the U.S. pediatric population. The objective of the study is to provide estimates of the frequency of medication use in pediatric populations. Dr. Korelitz described the study design:

- Populations specified by type of insurance:
 - Medicaid (25 percent)
 - Commercial/Health Maintenance Organization (HMO; >60 percent)
 - Uninsured (15 percent)
- Current analysis restricted to Medicaid and commercial/HMO populations
- Time period
 - Most recent calendar year available
 - 2000 Medicaid
 - 2004 commercial/HMO
- Eligibility
 - Enrolled in plan at any time during year
 - Younger than 18 years old at start of year.

Dr. Korelitz provided the following study definitions:

- Pediatric population
 - Up to 18 years of age
- Prescription medication
 - Drug claim
 - Outpatient use
- Medication use
 - Fill date
- Frequency
 - Number of subjects
- Prevalence
 - Percentage of subjects
 - Percentage of children who had a particular medication filled at any time during the study year
 - Includes subjects who were enrolled in the plan for only a portion of the year.

The study data sources were:

- Medicaid
 - Centers for Medicare and Medicaid Services
 - Medicaid Analytic eXtract (MAX) files
- Commercial/HMO
 - Caremark
 - Pharmacy benefits manager.

Dr. Korelitz characterized the Medicaid/MAX files:

- 40 million enrollees
- 20 million children (0–20 years old)
- Separate data files for each state
- Statistical sampling plan to select states
- 18 states selected
- 5.5 million children included in analysis.

Dr. Korelitz characterized the commercial/HMO data:

- Caremark; AdvancePCS
 - Administrative pharmacy claims data
 - 90 million covered participants throughout United States
 - Demographic profile representative of U.S. population overall
 - Commercial (non-HMO); HMO plans
 - 17.7 million children included in analysis.

The study used a stratified analysis of:

- Gender
 - Male
 - Female
- Age
 - 0 to <2 years
 - 0 to <28 days (neonatal)
 - 2 to <5 years
 - 5 to <12 years
 - 12 to <18 years
- Race (Medicaid only)
 - White
 - Black or African American
 - Hispanic or Latino
 - American Indian or Alaska Native
 - Asian.

Dr. Korelitz characterized the drug coding and grouping:

- Data files contain 11-digit National Drug Codes
- National Drug Codes are very detailed, but “details” are not necessarily relevant to the purpose of the study
- Algorithm developed to combine similar “entities” and to differentiate among different entities
 - Algorithm incorporates information on ingredients and route of administration.

The study generated a vast amount of data, but Dr. Korelitz presented only certain information for the Medicaid and commercial/HMO study populations (see Tables 6–9).

Table 6. Medicaid Study Population

	Medicaid 2000	
	Number	Percentage
• Total	5,527,397	100
• Continuously enrolled	3,070,177	55.5
• One or more dispensed	2,978,227	53

Table 7. Commercial/HMO Study Population

	Commercial/HMO 2004	
	Number	Percentage
• Total	17,762,142	100
• Continuously enrolled	8,777,236	49.4
• One or more dispensed	6,755,543	38

Table 8. Number of Children with a Dispensed Medication and Drug Prevalence:
Medicaid, 2000

Rank	Drug	Route	Unweighted Number of Children with a Dispensed Medication	Weighted Drug Prevalence (per 100 Children)
1	Amoxicillin	Oral	1,207,975	26.5
2	Azithromycin	Oral	445,330	10.3
3	Amoxicillin/Clavulanate	Oral	407,017	9.3
4	Albuterol	Inhalation	393,997	8.7
5	Ibuprofen	Oral	286,941	5.3
6	Cephalexin	Oral	207,893	4.8
7	Sulfamethoxazole/ Trimethoprim	Oral	186,558	4.4
8	Dextromethorphan/ P-ephedrine/Carbinoxamine	Oral	232,078	4.4
9	Loratadine	Oral	188,975	4.1
10	Prednisolone	Oral	198,771	3.9

Table 9. Number of Children with a Dispensed Medication and Drug Prevalence: Commercial/HMO, 2004

Rank	Drug	Route	Number of Children with a Dispensed Medication	Drug Prevalence (per 100 Children)
1	Amoxicillin	Oral	2,101,193	15.6
2	Azithromycin	Oral	1,209,168	9.3
3	Amoxicillin/Clavulanate	Oral	902,915	6.7
4	Albuterol	Inhalation	725,194	5.4
5	Cetirizine	Oral	497,243	3.5
6	Cephalexin	Oral	414,719	3.2
7	Cefdinir	Oral	402,447	3.0
8	Prednisolone	Oral	335,038	2.5
9	Montelukast	Oral	337,971	2.3
10	Codeine/Apap	Oral	268,709	2.1

Dr. Korelitz described the study's limitations:

- Secondary data source
- Subset of all drugs used
 - Prescription
 - Drug claim submitted
 - Outpatient use
- Some misclassification/data errors
- Features of insurance plan affect use/claims
- Medicaid reporting issues.

Dr. Korelitz described the study's strengths:

- Large study population (23 million children)
- Separate estimates for Medicaid and commercial/HMO populations
- Separate estimates by gender, age, race/ethnicity
- Continuous and noncontinuous enrollees included
- Drug coding algorithm used to define meaningful “drug entities.”

The challenges to the study are uses and flexibility of the data. It has not yet been determined how to present the data in an organized, useful way. The data could be:

- Ordered by prevalence
- Listed alphabetically by name
- Grouped by “relevant” class.

Dr. Korelitz provided the following examples of the American Hospital Formulary Service (AHFS) pharmacologic-therapeutic classification scheme and demonstrated how a non-AHFS classification of “antihypertensive drugs” could be derived from cardiovascular drugs:

- 4:00 Antihistamine drugs
- 8:00 Anti-infective agents
- 10:00 Antineoplastic agents
- 12:00 Autonomic drugs
- 16:00 Blood derivatives
- 20:00 Blood formation and coagulation
- **24:00 Cardiovascular drugs**
- 28:00 CNS agents
- 40:00 Electrolytic, caloric, and water balance
- 56:00 Gastrointestinal drugs.

Cardiovascular drugs (24:00) can be regrouped to include:

- 24:04 Cardiac drugs
- 24:06 Antilipemic agents
- 24:08 Hypotensive agents
- 24:12 Vasodilating agents
- 24:16 Sclerosing agents
- 24:20 α -Adrenergic blocking agents
- 24:24 β -Adrenergic blocking agents
- 24:28 Calcium-channel blocking agents
- 24:32 Renin-angiotension-aldosterone system inhibitors.

If cardiac drugs (24:04), antilipemic drugs (24:06), and sclerosing agents (24:16) are deleted from the 24:00 group, the following “antihypertensive” drugs remain:

- 24:08 Hypotensive agents
- 24:12 Vasodilating agents
- 24:20 α -Adrenergic blocking agents
- 24:24 β -Adrenergic blocking agents
- 24:28 Calcium-channel blocking agents
- 24:32 Renin-angiotension-aldosterone system inhibitors.

Hypotensive agents (24:08) would include:

- 24:08.16 Central α -agonists
- 24:08.20 Direct vasodilators
- 24:08.32 Peripheral adrenergic inhibitors
- 24:08.92 Hypotensive agents, miscellaneous.

Vasodilating agents (24:12) would include:

- 24:12.08 Nitrates and nitrites
- 24:12.12 Phosphodiesterase inhibitors

- 24:12.92 Vasodilating agents, miscellaneous.

The resulting AHFS class of “antihypertensive” drugs would include:

- 24:08 Hypotensive agents
- 24:20 α -Adrenergic blocking agents
- 24:24 β -Adrenergic blocking agents
- 24:28 Calcium-channel blocking agents
- 24:32 Renin-angiotension-aldosterone system inhibitors
- 40:28 Diuretics.

Dr. Korelitz explained that antihypertensive classes from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (the Fourth Report; *Pediatrics* 2004 Aug;114[2 suppl]:555–576) could be “mapped” onto the AHFS codes (see Tables 10–12).

Table 10. The Fourth Report (Table 9, Part 1)

<u>Antihypertensive Class</u>	<u>AHFS Code</u>
• ACE inhibitor	24:32.04
• Angiotensin-receptor blocker	24:32.08
• β -Blocker	24:24
• Calcium channel blocker	24:28.08
• Central α -agonist	24:08.16
• Diuretic	40:28
• Peripheral α -antagonist	24:20
• Vasodilator	24:08.20

Table 11. The Fourth Report (Table 9, Part 2)

AHFS Classification and Drug Name	Route	Number of Children with a Dispensed Medication	Drug Prevalence per 100 Children
ACE inhibitors (24:32.04)			
Benazepril	Oral	116	0.0019
Captopril	Oral	1,420	0.0259
Enalaprilat	Oral	1,973	0.0470
Fosinopril	Oral	120	0.0024
Lisinopril	Oral	1,109	0.0277
Quinapril	Oral	183	0.0049

Table 12. The Fourth Report (Table 9, Part 3)

AHFS Classification and Drug Name	Route	Number of Children with a Dispensed Medication	Drug Prevalence per 100 Children
Angiotension II receptor antagonists (24:32.08)			
Irbesartan	Oral	49	0.0010
Losartan	Oral	129	0.0034
β-Adrenergic blocking agents (24:24)			
Atenolol	Oral	2,161	0.0501
Bisoprolol/Hydrochlorothiazide	Oral	112	0.0021
Labetalol	Oral	359	0.0073
Metoprolol	Oral	747	0.0148
Propranolol	Oral	5,700	0.1388

Dr. Korelitz summarized the findings of the Westat study:

- Frequency/prevalence of use is an important component in the decision-making process.
- Medication claims data provide estimates of frequency of use (with appropriate caveats).
- Individual drug entities can be grouped and presented by meaningful drug classes.
- Frequency of use estimates can be examined by subgroups (for example, gender, age, race/ethnicity).
- Changes over time can be monitored.

Approaches to Prioritization

Anne Zajicek, M.D., Pharm.D., Pediatric Medical Officer, OPPB, CRMC, NICHD, NIH

Dr. Zajicek reviewed current prioritization process for off-patent drugs, alternative approaches, and future plans. The purpose of prioritizing is to:

- Focus on drugs with most pressing health need (health benefit) to study
- Develop a master list of all off-patent drugs that lack adequate pediatric labeling ($N = 200$)
- Consider for prioritizing:
 - Availability of safety and efficacy data
 - Whether additional data are needed
 - Whether new studies will produce health benefits
 - Whether reformulation is necessary
- Consultation with experts in pediatric practice and research, others
- Develop, prioritize, and publish an annual list ($N = 5-15$).

For off-patent drugs lacking pediatric labeling, the approach is to:

- Prioritize
 - Health benefit

- Need for further studies
- Therapeutic alternatives
- Feasibility.
- Define health benefit
 - Frequency of condition/use
 - Severity of illness
 - Therapeutic intensity
 - Therapeutic alternatives.
- Explore therapeutic alternatives
 - Drugs in class
 - Other therapies.
- Evaluate need for further studies
 - Literature review and analysis
 - Evidence-based medicine
 - Expert opinion.
- Determine feasibility
 - Frequency of condition/use
 - Study design: randomized clinical trial, observational, placebo versus active control
 - PK: assay, blood volume
 - Safety, efficacy, PD: measurements, follow-up
 - Ethical issues.
- Consider ethical issues
 - Should the study be done?
 - Can the study be done?
 - Consent
 - Feasibility.

If the study is not feasible, then it is not ethical.

Developing a new strategy for the BPCA process, Dr. Zajicek suggested the following:

- Prioritize drugs in a class
- Prioritize drugs for a therapeutic indication
- Create a parallel process with study design.

Regarding future plans, Dr. Zajicek suggested the formation of a subcommittee to formalize a plan for objectively prioritizing off-patent drugs that will incorporate (1) health benefit, (2) the need for further studies, (3), therapeutic alternatives, (4) feasibility, and (4) ethics.

Open Discussion

Dr. Ward, moderator

In this first open session, meeting participants discussed the following issues and topics:

- How alternate approaches will improve labeling
- Linking diagnoses with drug usage

- Prioritizing areas of therapies
- Pediatric information on drug labels but no pediatric indication
- Need for fundamental dosing and safety information
- Need for common use data and common dose data
- Different dosing for different conditions
- FDA clinical data requirements (FDA approves a drug for a specific indication)
- Perception of importance of drug label versus reality of day-to-day usage
- Inclusion of clinical trial data in labeling information
- Extemporaneous formulations
- Need for pediatric study models beyond placebo controlled trials
- FDA requirement for New Drug Applications (NDAs) for reformulated generic drugs
- Need for frequency of diseases and frequency of use to be included in decision making.

On-Patent Drugs: Collaboration Between FNIH and NIH

Stephen P. Spielberg, M.D., Ph.D., Board of Directors, FNIH; Dean, Dartmouth Medical School

Dr. Spielberg briefly described his role as an FNIH board member. He explained that FNIH is an effective forum to bring together public and private partners for important endeavors such as BPCA. Dr. Spielberg noted the following impediments to pediatric drug development:

- Fear of clinical trials in children
 - Nonvalidated use of medicines places more children at greater risk than participation in well-controlled, ethically conducted clinical trials.
 - After AAP Committee on Drugs, 1995
- Advocacy without validated science cannot succeed.
 - Formulation chemistry, analytical chemistry, population PK, safety/efficacy study designs.

Dr. Spielberg characterized the search for a legislative fix for the ultimate impediment:

- Most children are healthy
 - Those in need of medications do not have the same illnesses (disease density).
 - As opposed to adults with heart disease, cancer, and so on
 - Few patients to study: difficulty in conducting the clinical trials and developing age-appropriate formulations
 - Very small market once the medication is studied.

The legislative efforts to overcome risk, costs, and small market and to raise the priority of children in 1997 with FDAMA, which:

- Included pediatric provisions providing companies incentives to undertake pediatric studies
 - 6 months extended exclusivity
 - Supported broadly by AAP, NICHD, FDA, parent/children's groups, industry
- Provided
 - The power of positive reinforcement
 - Incentives to drive investment in pediatric research
- Was a 5-year experiment.

- Raised the priority of children
 - Among competing forces (new drugs for large adult populations in need) for resources (chemistry, formulation, clinical study personnel), FDAMA provides the needed incentive to assure timely implementation of pediatric studies
 - The focus of the legislation is children—and it works.

The pediatric provisions of FDAMA were reauthorized by Congress as BPCA, which was signed into law by the President on January 4, 2002, yielding a 6-year renewal of the provisions. BPCA:

- Offers 6-month exclusivity extension
- Introduced Prescription Drug User Fee Act of 1992 user fees
 - Funding for FDA and priority review
- Established formal Office of Pediatric Therapeutics (now Office of Counter-Terrorism and Pediatrics)
- Established new labeling and dissemination of information requirements
- Includes Institute of Medicine review of ethics, particularly “minor increase over minimal risk,” beginning March 2004.
- Has proven a success as an experiment for on-patent drugs
 - 307 Written Requests issued by FDA
 - 251 initiated by company proposals
 - 114 drugs in multiple therapeutic classes have been granted exclusivity extension
 - 93 labels with new pediatric information.
- Establishes an ongoing mechanism to assure pediatric studies for new compounds under development
- Provides funding (NIH and private contributions) to study off-patent drugs with major pediatric use and need for new data, and for medicines for which companies refused Written Requests
 - Need more data on bases for refusal, but often related to Written Requests that are considered “un-doable” due to study design, availability of investigators, time frames.

Dr. Spielberg noted the greater challenge of off-patent and refused on-patent, including:

- No primary industry sponsor
 - Of the 307 Written Requests, 312 Written Requests amendments were acted upon
- Learning curve for FDA, sponsor, and investigators on feasibility of pediatric studies
 - As well as for industry, but companies know their compounds well, and know good clinical practices
- When there is no company sponsor
 - There is less knowledge of the drug.
 - There is less knowledge of regulated clinical study design and protocols.
 - NICHD has little in-house experience in drug development.

Dr. Spielberg provided the following FNIH overview:

- FNIH was established by Section 499 of the Public Health Service Act, 42 U.S.C. paragraph 290(b), to support the NIH in its mission and to advance collaboration with biomedical researchers from universities, industry, and nonprofit organizations.

- Established at the direction of Congress in 1990, FNIH is a nonprofit, nongovernment, 501(c)(3) corporation (incorporated in 1996).
- FNIH is governed by an independent board of directors (the NIH Director and FDA Commissioner serve as ex officio members of the board of directors).

Dr. Spielberg described the on-patent BPCA process:

- The FDA Commissioner communicates to the Secretary of the Department of Health and Human Services (DHHS) whether a drug under market exclusivity should be tested in children, in which case the patent holder will be offered an additional 6 months of market exclusivity as an incentive to complete the needed studies.
- If the manufacturer of the on-patent drug declines to test the drug for use in children, the Secretary can refer individual drugs to FNIH (which can raise funds from the private sector to support the studies) and NIH, through NICHD (which can use appropriated funds to support these studies), in which case the offer of additional exclusivity is withdrawn to the patent holder.
- FNIH requests input from NICHD as to the prioritization of the drugs for which it has received referrals as well as an analysis as to the necessary tests and the costs and timeline for the required trials.
- FNIH must communicate to the Secretary of DHHS whether there are sufficient funds available to support the study of a given drug.
- If there are insufficient funds to conduct the study, the Secretary may refer the drug back to the patent holder and require the company to study the given drug in the pediatric population.

Dr. Spielberg proposed the following revised FNIH BPCA process:

- FNIH will request that the Pharmaceutical Research and Manufacturers of America (PhRMA) Pediatric Working Group review on-patent Written Requests as received and provide their feedback to FNIH on study design issues
- These comments will be shared with NICHD along with FNIH's request to NIH for a preliminary needs assessment and cost estimate.

To date, on-patent referrals have been received for:

- Baclofen (for spasticity)
- Bupropion (for depression)
- Dexrazoxane (used to block cardiac effects of the anticancer drug Adriamycin)
- Eletriptan (used for treating migraine headaches)
- Hydroxyurea (used to treat children with sickle cell disease)
- Morphine (for analgesia)
- Sevelamer (for renal failure)
- Zonisamide (an adjunctive medication for refractory partial seizures).

Dr. Spielberg reviewed FNIH BPCA fundraising/decision on allocation of funds:

- To date, FNIH has raised \$4,030,500 toward its BPCA program from 14 companies and one individual donor.

- In 2006, FNIH intends to determine whether to allocate its funds raised for the BPCA program to baclofen (NICHD's highest priority on-patent drug).

Dr. Spielberg reviewed future challenges and issues for the FNIH/BPCA collaboration:

- Difficulty raising funds from one company to sponsor study of another company's drug
- Difficulty having data generated without control of the company being added to company's label
- Continuing challenges to pediatric drug development
 - A paucity of well-trained pediatric clinical pharmacologists and clinical investigators
 - Lack of validated study designs and end-points to assess efficacy and safety
 - The antidepressants as a failure of study design and diagnostic precision rather than the drugs per se.
- Develop approaches that preclude the need to refer on-patent drugs
 - Need for better science to assure “do-able” and meaningful clinical studies to develop data to optimize safe/effective use of medicines in children
 - Early discussion of problematic Written Requests—use of pediatric expertise broadly
 - Prevent rejection of studies by sponsors.

Dr. Spielberg urged BPCA to focus on the needs for improved pharmacotherapy for children by considering the best use of resources, including:

- Training the next generation of pediatric clinical investigators
- Developing improved clinical trial methods including biomarkers
- Fitting with FNIH mission and activities
- Helping all investigators including industry to do better studies with higher probability of interpretable data
- Increasing likelihood of support by PhRMA
- Improving the Written Request process with better studies
- Placing children's need with comparable priority to adults
- Thinking of chronic disease in developmental context (diabetes, schizophrenia, bipolar disease)
- Working with PhRMA, NICHD, and FDA to continue studying selected drugs
- Working with all constituencies (AAP and other advocacy groups, FDA, NICHD, and PhRMA) in planning BPCA renewal to address critical needs of training pediatric investigators and of aligning investment in pediatric clinical investigation with cutting edge approaches in discussion at FNIH for adults.

Drug Development: On-Patent, Off-Patent, and AAP Research

Hari Cheryl Sachs, M.D., Pediatric Medical Officer, Division of Pediatric Drug Development, Office of Counter-Terrorism and Pediatric Drug Development, Center for Drug Evaluation and Research, FDA

Dr. Sachs reviewed the following aspects of pediatric drug development:

- Regulatory benchmarks: BPCA and Pediatric Research Equity Act (PREA)
- On- and off-patent processes

- The Written Request
- Patents and exclusivity
- Labeling.

Dr. Sachs listed the historic pediatric benchmarks:

- 1979, Labeling Requirement
- 1994, Pediatric Labeling Rule
- 1997, FDAMA
- 1998, Pediatric Rule
- 2002, BPCA
- 2003, PREA.

BPCA:

- Reauthorizes FDAMA exclusivity incentive
- Establishes a new process for studying “off-patent” drugs
- Requires collaboration between FDA and NIH in the development of
 - The list of drugs needed in the pediatric population
 - “Off-patent” Written Requests.

PREA:

- Mimics the Pediatric Rule
- Requires pediatric studies of certain drugs and biological products, unless waived or deferred, including
 - New indication
 - New dosage form
 - New route
 - New dosing regimen
 - New active ingredient.

Dr. Sachs compared BPCA and PREA:

BPCA	PREA
<ul style="list-style-type: none"> • Studies voluntary • Studies on entire active moiety (may include new indication) • Written Request may be issued for drugs and indications with orphan designation • Applies only to drugs • Sunsets October 1, 2007 	<ul style="list-style-type: none"> • Studies mandatory • Required studies only on drug/indication under review • Studies for drugs and indications with orphan designation are exempt • Applies to drugs and biologics • Sunsets October 1, 2007

Dr. Sachs summarized the process for the study of on-patent drugs:

- Industry submits a proposed pediatric study request
- FDA determines public health benefit to support pediatric studies
- FDA issues Written Request

- Industry has 180 days to respond
- Industry agrees to conduct studies
- Industry declines to conduct studies
- Referral to FNIH.

Dr. Sachs summarized the industry responses as of November 7, 2005:

- Proposals from Industry 395
- FDA-issued Written Requests 308
- Exclusivity determinations 125
- Exclusivity granted 114
- New labels 100

As a result, new pediatric labeling has been issued for:

- Ondansetron (March 2005)
 - Postoperative nausea/vomiting, 1 month–2 years
 - Prevention of chemotherapy-induced nausea/vomiting, 6 months–4 years
- Sodium ferric gluconate complex (August 2004)
 - Iron overload, 6–15 years
- Ertapenem (May 2005)
 - Multiple infections, older than 3 months
 - Not recommended for treatment of meningitis
- Norgestimate/ethinyl estradiol (May 2005)
 - No significant effect on bone mineral density for adolescent females with anorexia nervosa.

Dr. Sachs summarized the process for the study of off-patent drugs as follows:

- Priority list of off-patent drugs
- FDA issues Written Request
- Industry has 30 days to respond
- Industry agrees to conduct studies
- If industry declines to conduct studies, then referral to NIH/RFP.

Before issuing a Written Request, the FDA asks the following questions:

- Is there a public health benefit?
 - Does the request involve a serious life-threatening condition?
 - How frequently does the disease/condition occur?
 - How often is this drug or others like it used in children?
 - How frequent is off-label use?
 - Does the drug offer a meaningful therapeutic benefit?
 - Will there be significant improvement in the treatment, diagnosis, or prevention of disease compared with already approved drugs?
- Are there safety issues?
 - Is there adequate safety data to move into pediatrics?
 - Is there animal data?

- Were adult trials conducted?

If there is a public health benefit and the benefit-to-risk ratio is appropriate, the FDA then asks:

- What additional information is needed?
- For what age groups is the information needed?
- What studies are needed to obtain this information?

Dr. Sachs defined a Written Request as a legal document written and sent by the FDA to sponsors requesting studies in the pediatric population. The Written Request specifies:

- Indication
- Population
- Type of studies
- Safety parameters
- Longer term follow-up, if needed
- Timeframe for response.

The types of studies, and the questions asked, include:

- PK/PD studies:
 - Is the absorption, distribution, metabolism, and elimination (excretion) the same in the pediatric population?
 - What is the optimal dose (greatest effect with lowest toxicity)?
 - Safety information is always obtained in these studies.
- Efficacy
 - Are studies adequate and well-controlled?
 - Are they placebo-controlled or active controlled?
 - Is there dose-ranging?
- Can efficacy be extrapolated from adult studies and supported with smaller pediatric studies?
- Safety studies
 - All studies must assess safety for an appropriate timeframe.
 - Pediatric patients may not have the same adverse events as adults.
 - Potential adverse events must be specified in case report forms.
 - There must be consideration of a data monitoring committee.

As of November 7, 2005, off-patent Written Requests have been issued for the following drug-indication pairings:

- Azithromycin—BPD due to ureaplasma
- Azithromycin—chlamydia
- Dactinomycin—malignancy
- Lindane—scabies
- Lithium—bipolar disorder
- Lorazepam—status epilepticus
- Lorazepam—sedation
- Meropenem—abdominal infections
- Nitroprusside—reduction of blood pressure

- Rifampin—CNS shunt infection
- Rifampin—infective endocarditis
- Vincristine—malignancy
- Morphine—pain
- Baclofen*—spasticity
- Metoclopramide*—gastroesophageal reflux disease
- Ampicillin—neonatal sepsis/meningitis.

*Patent status changed after Written Request issued.

Dr. Sachs provided the following information regarding patents and exclusivity:

- Myth: If a generic is available, the drug is off-patent.
- False: Approval for a new formulation or indication can change exclusivity/patent status of a previously off-patent drug.
- Generics may be available for one formulation when another formulation (such as tablet for oral solution) is approved (for example, baclofen, and metronidazole).
- Off-patent Written Request is issued to active moiety (for example, hydrocortisone for hydrocortisone butyrate and valerate).
- Patent exclusivity status of entire range of formulations (for example, nasal spray, inhaler, tablet, topical) impacts ability to issue Written Request for a given active moiety (for example, Flovent HFA and Diskus, Cutivate, and Flonase for fluticasone).

Dr. Sachs compared active moiety and active ingredient:

Active Moiety	Active Ingredient
<ul style="list-style-type: none"> • The molecule or ion responsible for the physiological or pharmacological action • Excludes appended portions that cause the drug to be <ul style="list-style-type: none"> – An ester – Salt (hydrogen or coordination bonds) – Noncovalent derivative (for example, complex, chelate, or clathrate) 	<ul style="list-style-type: none"> • Entire active molecule: includes active moiety and appended portions

Dr. Sachs characterized drug labeling as follows:

- Labeling is part of drug packaging; it belongs to the sponsor.
- For an NDA, the sponsor submits draft labeling.
- FDA reviews the NDA.
- Final product labeling is negotiated between sponsor and FDA.
- Labeling is a summary of essential scientific information needed for safe and effective use of the drug.
- Labeling is informative, accurate, and neither promotional in tone nor false or misleading.
- Labeling is based on data derived from human experience (whenever possible).
- Order of contents (labeling sections) are specified as follows:
 - Description

- Clinical pharmacology
- Indications and usage
- Contraindications
- Warnings
- Precautions—subsections include pediatric use
- Adverse reactions
- Drug abuse and dependence
- Overdosage
- Dosage and administration
- How supplied
- Animal pharmacology and/or animal toxicology
- Clinical studies
- References
- Drug is approved (indicated) for a specific condition in a specified population
- Predicated on positive benefit-risk ratio for the condition and population; examples:
 - Fentanyl transdermal system—for management of persistent moderate to severe pain in opioid-tolerant patients older than 2 years
 - Ethinyl estradiol/norgestimate—moderate severe acne vulgaris in females 15 years or older who desire contraception and are unresponsive to topical antiacne medicines
- Unapproved or “off-label” use—different population or different indication.

Safety and efficacy are two bases for an indication:

- Safety
 - Systematically assessed by analysis of adverse events during clinical trial
 - Postmarketing surveillance:
 - Spontaneous adverse event reports
 - Phase IV clinical trials
 - Depending on the nature of event, described (in order of severity) in the contraindications, boxed warning, warnings, precautions and/or adverse events sections
- Efficacy
 - Two confirmatory multicenter trials
 - Exception: evidence robust enough for extrapolation; typically same indication, different population
 - Trial designs, clinically relevant primary endpoints, and appropriate statistical analysis agreed upon prior to submission of Phase III data.

Extrapolation is possible when FDA concludes that the course of the disease and the effects of the drug—both beneficial and adverse—are similar in the pediatric and adult population. Additional supporting information may be needed from PK/PD bridging studies and from pre- and postmarketing safety studies.

Dr. Sachs provided the following examples of pediatric use of extrapolation:

- Orlistat
 - “The safety and efficacy of Xenical have been evaluated in obese adolescent patients aged 12 to 16 years. Use of Xenical in this age group is supported by evidence from

adequate and well-controlled studies of Xenical in adults with additional data from a 54-week efficacy and safety study and a 21-day mineral balance study in obese adolescent patients aged 12 to 16 years.”

- Ertapenem
 - “Safety and effectiveness of Invanz in pediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from comparator-controlled studies in pediatric patients 3 months to 17 years of age with the following infections.”

Potential list drugs with approved adult indications include:

- Albendazole (neurocysticercosis, cystic hydatid disease)
- Amantadine, rimantadine (influenza)
- Furosemide, hydrochlorothiazide, labetalol, spironolactone (hypertension)
- Mebendazole (pinworm, whipworm, roundworm, hookworm)
- Pralidoxime (antidote for organophosphate poisoning).

Potential list drugs with new indications include:

- Azithromycin (pertussis)
- Bumetanide (hypertension)
- Clonidine (ADHD)
- Guanfacine (ADHD).

Dr. Sachs offered the following conclusions:

- Legislation has resulted in new pediatric labeling (100 and counting)
- Evidence indicates that dosing, safety, and efficacy of medications by children cannot always be predicted from adult experience.
- The off-patent Written Request process augments the ability to study “old” drugs.
- The work continues.

REVIEW OF ALTERNATE APPROACHES FOR CONSIDERING DRUGS/CONDITIONS

European Union Approach

Agnès Saint Raymond, M.D., Head of Sector, Scientific Advice and Orphan Drugs Paediatric Medicinal Products, Acting Head of Sector Safety and Efficacy, European Medicines Agency (EMA)

Dr. Saint Raymond described the experience of the EMA Paediatric Expert Group in its efforts to prioritize pediatric drug studies. This permanent expert group for the Committee for Human Medicines (CHMP) was created in 2002. It is composed of 13 experts in various domains and includes observers; it meets six times a year and often holds ad hoc meetings. The goals of the EMA Paediatric Expert Group are to (1) produce and participate in writing guidelines, (2) work

on definition of pediatric needs at European Union level, and (3) work on priorities for studies of older products (off-patent).

The EMEA Paediatric Expert Group works on priorities because:

- Previous attempts to draw up a list had not achieved the objective (United States, United Kingdom)
- There was a lack of expert consensus and “misuse” of the list.
- There was difficulty in agreeing on priority criteria.

The European Commission specifically requested:

- Preparatory work for future regulation
- Estimate of public funds required for clinical trials
- Need to refer to “existing” lists (United Kingdom, France, Germany, United States).

The process began with the request in July 2003 and ended in January 2004. It included the following steps:

- Prepare strategy
- Define criteria with Paediatric Expert Group
- Draft list (use existing lists)
- List “off-patent” products
- Consult Paediatric Expert Group
- Consult national authorities, learned societies, at European and national levels
- Compile comments and finalize.

The strategic steps for draft list included:

- List pediatric diseases/conditions
- Set priority criteria for conditions and priority criteria for products
- Propose criteria and rating (points)
- Check information from published literature (general reviews of therapeutics in the various domains) and textbooks
- Prepare database (Excel).

About 300 pediatric conditions were identified by therapeutic areas. The intent of the Paediatric Expert Group was to limit the number of conditions and keep the process simple. The proposed priority criteria included (1) seriousness (lethal or debilitating), (2) high prevalence (relative to children), (3) disease affects all age ranges, and (4) disease affects newborns. In addition, the disease has:

- No therapeutic options available (authorized)
- Some options but not fully satisfactory
- Full therapeutic options

Emerging diseases were included because of the likelihood of few or no therapeutic options.

For the pediatric products, however, the intent was to make the list as exhaustive as possible. The Paediatric Expert Group wanted to solve as many difficulties in prioritizing as possible (for example, products with multiple indications). Relying on evidence-based medicine would create a “win-win” situation. Regarding priority criteria, Dr. Saint Raymond listed the following:

- Availability of data on the product (evidence versus expectations)
- Positive points for evidence of efficacy
- Negative points for evidence of safety concern in children.

As the priority criteria were evaluated, points were assigned and added up as follows:

- Maximum of 9 points for condition (min 0)
- Maximum of 3 points for evidence (that is, randomized controlled trials) (min -2)
- Cutoff value for priority was set at 10.

The list produced 44 products with 10 or more priority points

- With a cutoff of 11 points, there were 4 products.
- With a cutoff of 9 points, there were 102 products.

Dr. Saint Raymond described the results of the experts’ consultation:

- Initial disbelief in the procedure
- No outcry in view of outcome
- Most comments included in the tables
- Large support of the exercise
- Reasonable agreement with priority list produced by NIH/FDA in 2003 (12 then 8 products).

The first critical analysis produced the following:

- Choice of frequent diseases (as orphan regulation implemented)
- Evidence for available treatment not assessed
- Emerging therapies as priority
- Evidence versus expectations
- Products of interest may actually be new ones
- No analysis of need for paediatric formulations
- Cutoff value.

The second critical analysis produced the following:

- Method not appropriate for cancer products
- Areas where no therapeutic agents have been assessed correctly are completely left out (for example, rheumatology)
- Exercise solely on old (off-patent) products and not on future developments needed in certain therapeutic areas.

Dr. Saint Raymond offered the following conclusions:

- Validation of method?
- Expert agreement!

- Outcome satisfactory
- Reasonable amount of products to be studied in the next years
- Public funding expected in the next years when the pediatric regulation comes into force (expected 2007).

Neonatal Drug Prioritization

Dr. Ward

Dr. Ward explained that a group of neonatologist consultants and FDA and NIH participants were charged 2½ years ago with prioritizing drugs for newborns. This neonatal drug development initiative examined five topical areas: pain control, pulmonology, cardiology, neurology, and ethics. The goal of the prioritization effort was to determine factors that identify which drugs are most important for study in neonates, especially when resources are limited. A secondary goal was to develop a list of criteria that would help to inform the NIH listing process. Dr. Ward reviewed the list of criteria used in the neonatal prioritization process.

Categories of criteria supporting study included (1) disease/indication, (2) drug, (3) current evidence, (4) feasibility of study, and (5) ethics. The criteria were evaluated and scored. Higher scores indicated greater need for study. Factors supporting study of a drug include:

- Drug—effects, duration of treatment, formulation, toxicity, interactions with other drugs or diseases, metabolism, off-label use, toxicity in animals, alternate treatments available
- Disease frequency, severity, variability
- Current evidence of efficacy
- Feasibility—adequate number of subjects for study, assay for drug, endpoints can be measured
- Ethics—Benefit versus risk of drug exposure, risk of study procedures, improves on current treatments.

Dr. Ward listed the following factors supporting neonatal study of a drug:

Disease/indication factors

1. Potential for adverse outcomes (morbidity, mortality, long term disability) based on studies in neonates
 - 0 = Studied without identified risk
 - 3 = Moderate risk (<10 percent frequency of morbidity, minimal risk of mortality or non disabling long term residua; studies of risk are incomplete)
 - 5 = High or frequent risk for known morbidity, mortality, disability
 - 5 = Risk not studied in neonates
2. Disease/indication is unique to neonatal population (for example, intraventricular hemorrhage, necrotizing enterocolitis).
 - 0 = Disease/indication is common in infancy beyond the neonatal period.
 - 3 = Disease/indication is unique to some neonatal populations.
 - 5 = Disease/indication occurs almost exclusivity in neonates.
3. Frequency in neonatal population(s) based on valid data base

- 0 = Disease/indication is rare in sick neonates (1–2/500 neonatal intensive care unit admissions; 100–1,000 cases/year).
- 3 = Disease/indication is relatively common in some neonatal populations (1,000–2,000 cases/year).
- 5 = Disease/indication is common in specific neonatal populations or moderately frequent in all neonatal populations (>2000 cases/year).
- 4. Evidence for treatment not established in neonates
 - 0 = Strong evidence (randomized clinical trial) for efficacy of treatment in neonates.
 - 3 = Some evidence suggests efficacy in neonates (case series, anecdotal reports).
 - 5 = No evidence available to support efficacy in neonates, although efficacy established in older populations for similar disorder.
- 5. Diversity of the severity or distribution/frequency of disease varies by gender, race, or ethnicity (genetic variation)
 - 0 = Disease does not vary by gender, race or ethnicity.
 - 2 = Disease is more common in a specific gender or racial or ethnic group.

Disease factors

- 6. Diversity of the severity or distribution/frequency of disease varies by gestational age or postnatal age
 - 0 = Disease frequency or severity is the same in term and preterm neonates.
 - 3 = Disease is more frequent or more severe in specific gestational age groups.
 - 5 = Disease frequency of severity is much more common in specific gestational ages of term and preterm neonates.

Drug factors

- 7. Duration of drug exposure
 - 0 = Anticipated duration of exposure is 1–7 days with minimal drug accumulation expected from existing PK information.
 - 3 = Anticipated duration of exposure is 8–28 days with drug accumulation expected from existing PK information.
 - 5 = Anticipated duration of exposure is >28 days with direct evidence that drug accumulation will occur.

Drug/evidence factors

- 8. Efficacy of treatment established in alternate populations for same disease/indication
 - 0 = Efficacy established in adults, but not in children younger than 12 years.
 - 3 = Efficacy established in children ages 3–11 years.
 - 5 = Efficacy established in infants and children age 1–24 months, but not in term or preterm neonates.

Drug factors

- 9. No appropriate formulation for neonatal populations
 - 0 = Appropriate formulations available for dosing 500 gm neonates without dilution or extemporaneous formulation.

- 3 = Formulations are available for dosing only neonates >1,500 gm without additional formulation.
 - 5 = Administration requires manipulation of existing formulation such as dividing existing powder by weight; pulverizing a tablet to put it into solution or suspension; subdividing existing liquid dose into smaller aliquots; using parenteral formulations orally.
10. Potential or known toxicity of the drug
- 0 = Used extensively in other populations without known toxicity.
 - 3 = Toxicity in other populations not related to factors that may be increased in neonates.
 - 5 = Toxicity in other populations due to factors such as reduced clearance or open blood brain barrier that are likely to be more frequent in neonates.

Drug/disease factors

11. Clinically relevant drug-disease interactions known
- 0 = No drug-disease interactions known for diseases that occur in neonates
 - 3 = Known interactions between drug and diseases that occur in neonates

Drug factors

12. Clinically relevant drug-drug interactions known
- 0 = No drug-drug interactions known for drugs that are used to treat neonates
 - 3 = Known interactions between drugs that are used to treat neonates
13. Drug disposition unknown or varies by gestational age, postnatal age, gender, race, or ethnicity (genetic variation)
- 0 = Drug disposition pathways known and do not vary by gestational age, postnatal age, gender, or race.
 - 3 = Drug disposition pathways known and may vary in neonates with changes in maturation, gender, race, or ethnicity.
 - 5 = Drug disposition pathways unknown or known and they vary with maturation of renal, hepatic, gastrointestinal, or other organ function that changes significantly during the neonatal period.
14. Frequent use of drug off-label
- 0 = Dosing and indications labeled for all subpopulations of neonates.
 - 3 = Dosing and indications labeled for some, but not all subpopulations of neonates, such as low birth weight versus term neonates.
 - 5 = Dosing and indications are not labeled for any neonates, yet the drug is used frequently in some neonatal subpopulation.
15. Preclinical evidence of toxicity
- 0 = No preclinical evidence of toxicity or evidence of toxicity involving physiology that does not occur in humans or neonates.
 - 3 = Preclinical evidence of reversible, non-life threatening toxicity that is not likely to occur in neonates.
 - 5 = Preclinical evidence of reversible, non-life threatening toxicity that is likely to occur in neonates.
16. Alternative similar treatment is available
- 0 = Alternate, similar drug treatment is safe and effective for treatment of the same disorder in all subpopulations of neonates; few advantages of new drug.

- 3 = Alternate, similar drug treatment is safe and effective for treatment of the same disorder in some, but not all, subpopulations of neonates.
- 5 = No alternate, similar drug has been studied and shown to be safe and effective for the proposed indication.
- 5 = New drug shown in other pediatric populations to increase safety or efficacy over existing treatments.

Feasibility/population factors

17. Adequate number of appropriate subjects likely available for study. Indication occurs with a frequency that could result in an adequate and representative study population for a multi-center trial in:
- 0 = 16+ sites
 - 3 = 6–15 sites
 - 5 = 2–5 sites

Feasibility/drug analysis factors

18. Assay available or can be readily developed
- 0 = Drug concentrations and safety labs cannot be studied within the volume limits set by the NIH guidelines/weight.
 - 3 = Drug concentrations and safety labs can be studied within the blood volume limits set by the NIH guidelines/weight.

Feasibility/endpoint factors

19. Clinically relevant endpoints identifiable and reliably measurable
- 0 = Endpoints indirectly relevant to the indication or require patient compliance and cooperation.
 - 3 = Endpoints directly relevant to indication and can be measured in some neonates (such as pulmonary function tests in intubated patients).
 - 5 = Endpoints directly relevant to indication and can be measured easily in neonates (such as sterilizing blood stream infections, achieving specific blood pressure).

Feasibility of studies in neonates

20. Disease can be studied in the neonatal population
- 0 = Disease can be studied only in limited/few neonatal subpopulations.
 - 3 = Disease can be studied in several subpopulations of neonates.
 - 5 = Disease can be studied in all populations of neonates.

Ethics/risk of drug exposure in neonates

21. Benefit or harm of drug exposure appropriate for study population
- 0 = No benefit and/or significant risk to neonates associated with drug exposure.
 - 3 = Risk may occur from exposure of neonates to the drug, but the risk is consistent with their level of clinical illness and procedures that comprise usual clinical care for the study indication.
 - 5 = Risk is low (≤ 10 percent frequency with minimal severity) and benefit is high (> 50 percent) from neonatal treatment.

Ethics of study methodology in neonates

22. Benefit or harm of study methodology is appropriate

0 = Study methodology poses significant risk to the study population.

3 = Study methodology poses some risk to the study population, but this risk is consistent with the risk of other procedures that are part of usual care for the study indication.

5 = Study methodology represents a risk of ≤ 5 percent frequency and minimal severity over the usual risks from usual care for the study indication.

Ethics of benefit from new drug for neonates

23. Benefit of new treatment relative to established treatment

0 = Current treatment with drugs in the same therapeutic class are safe and effective and the new drug does not offer significant therapeutic advantages (for example, single versus twice-a-day dosing).

3 = New drug offers potential improvement in safety and efficacy over existing treatments.

5 = New drug shown in other populations to significantly increase safety or efficacy over existing treatments.

Dr. Ward suggested that the following questions be answered during discussion of the issues:

- Do the criteria actually discriminate among drugs?
- Does the large number of factors obscure differences among drugs?
- How do we evaluate/prioritize drugs for different disease categories (dermatology versus cardiology versus respiratory versus infection)?

- Dr. Ward proposed testing the discriminatory value of the criteria against prioritization for study by a group of experienced neonatologists in the following manner:
- Twenty drugs ranked by neonatologists for their “need for study”
- Score each of the 20 drugs with the criteria
- Correlate similarities among criteria and agreement with prior ranks
- Expect to find several factors that correlate with each other and can be eliminated from the list to develop a shorter list that can establish priority among drugs for study.

Hypertension I

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

Dr. Taylor-Zapata provided a summary of the Pediatric Hypertension Working Group meeting. She explained that NICHD is considering a change in paradigm of how it lists the drugs that urgently need pediatric studies in order to improve the safety and efficacy of drugs used in children. The goals of changing the paradigm are to:

- Consider a condition-based or drug class-based approach to the BPCA prioritization of drugs that need pediatric studies instead of listing drugs and indications individually
- Determine how and whether evaluating drugs by class or condition may provide a positive impact to the progression of medical and public knowledge in the respective areas of medicine.

Dr. Taylor-Zapata described the process, noting that the catalyst was hydrochlorothiazide being listed as a prioritized drug in January 2005 for the indication of hypertension. The Pediatric Hypertension Working Group:

- Gathered background information on hypertension in children as an indication.
 - Major source was the Fourth Report (*Pediatrics* 2004 Aug;114[2 suppl]:565–576).
- Found that there is no treatment strategy for this disorder in children as there is in adults.
- Identified a list of experts in the field from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. This group of experts is responsible for the development of the Fourth Report.
- Contacted members of this consensus group to discuss the purpose of BPCA and NICHD's interest in looking at a disease-based approach to listing.
- Convened a subset of this consensus/expert panel in June 2005.

In the Fourth Report, pediatric hypertension is defined as:

- Systolic blood pressure and/or diastolic blood pressure that is, on repeated measurement (three occasions or more), ≥ 95 th percentile for gender, age, and height.
- Average blood pressure (systolic blood pressure or diastolic blood pressure) between the 90th and 95th percentile in childhood has been designated “high normal.” To be consistent with *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*, this level of blood pressure will be termed “prehypertensive” and is an indicator for lifestyle modifications.
- Do children have high blood pressure? Yes.
- Prevalence? Unclear.
- Outcome? Unknown.

Dr. Taylor-Zapata described the scope of the issues:

- Children with blood pressure >90 th percentile have 2.4 times the risk of having hypertension in adulthood (Mahoney et al., *Am J Hypertens* 1991; 4[Suppl]).
- Left ventricular hypertrophy has been reported in 34 percent to 38 percent of children and teenagers with mild, untreated blood pressure elevation (the Fourth Report).
- U.S. Preventive Services Task Force (July 2003) found good evidence that:
 - Blood pressure measurements can identify adults at increased risk for cardiovascular disease due to high blood pressure
 - Treatment of high blood pressure substantially decreases the incidence of cardiovascular disease and causes little major harm.
- However, the U.S. Preventive Services Task Force concluded that the evidence is insufficient to recommend for or against routine screening for high blood pressure in children and adolescents to reduce the risk of cardiovascular disease.
- Regarding treatment, the report states that “although the 95th percentile provides a blood pressure level that defines hypertension, management decisions about children with hypertension should be determined by the degree or severity of hypertension.”
- If pediatric patients have high blood pressure, what is the appropriate (safe and effective) treatment strategy for this population?

- How do we narrow the public health gap between what is or is not in the label of antihypertensive drugs and how the drug is actually used in practice?
- Prevention.

The goals of the Pediatric Hypertension Working Group meeting were to discuss:

- Where we are in the process of
 - Defining pediatric hypertension and its associated risks
 - Determining the natural history of hypertension in pediatrics
- What we need
 - Risk factors
 - Treatment strategies
- How to get what we need
 - Role and design of clinical trials
 - Outcome measures
- Who we contact/involve; who we target
 - Dissemination of information
- We do not need to discuss when—it is now.

Dr. Taylor-Zapata described the results of the meeting:

- Hypertension in children, for the most part, has been related to renal disease. The driving force behind the increase in pediatric hypertension in recent years is related directly to obesity.
- Repetitive screening is essential for accurate diagnosis of pediatric hypertension.
- In previous trials of antihypertensive agents in pediatrics, blood pressure reduction has been the only primary endpoint in determining efficacy and because of the short duration of most trials, safety information has been limited (see Table 9 in the Fourth Report).
- The long-term effects of untreated pediatric hypertension are still unknown.
- There is a need to delineate the mechanisms in developing organ systems that predispose a child to hypertension.
- Novel studies in pediatric hypertension need to be designed that answer some vital questions:
 - Effective treatment strategies in children
 - As well as expanding beyond determining whether a specific drug (or specific dosage) works in that patient population
- Suggestions:
 - “All-Hat” Trial: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (head-to-head comparison of four drug classes).
 - Include an approach that incorporates partnerships with private entities and pharmaceutical companies.
 - Determine how changes in drug labeling inform clinical practices.

The next steps are to develop partnerships with NICHD, NHLBI, FDA, AHRQ, and academia. Future developments include a second expert meeting in spring 2006, possible networks, possible clinical trials (head-to-head comparisons), and education.

Hypertension II

Rae-Ellen Kavey, M.D., M.P.H., Senior Medical Officer, Pediatric Cardiovascular Risk Reduction Program, Office of Prevention, Education, and Control, NHLBI, NIH

Dr. Kavey presented the NHLBI perspective on addressing pediatric hypertension. She described what is known and not known about hypertension in childhood. Defining “normal” pediatric blood pressure began with NIH/NHLBI Pediatric Task Force Reports:

- 1977, First Task Force: Normal blood pressure for age
- 1987, Second Task Force: Data from more than 70,000 children, revised standards; defined normal blood pressure for age and sex
- 1996, Third Task Force: Defined normal blood pressure tables for age, sex, and height
- 2004, the Fourth Report: 1999–2000 NHANES data added; included revised blood pressure tables for age, sex, and height.

Demographics of normal blood pressure curves were derived from:

- Nine pediatric data sets plus NHANES III, NHANES 1999–2000
- Two blood pressures taken, second used as representative blood pressure
- 51 percent male, 49 percent female
- Ethnic distribution:
 - White 54 percent
 - Black 29 percent
 - Hispanic 10 percent
 - Asian 3 percent
 - Native American 1 percent
 - Other 3 percent

The Fourth Report (*Pediatrics* 2004 Aug;114[2 suppl 2]:555-576) provided:

- Blood pressure interpretation by age, sex, and height percentile
- Tables with 50th, 90th, 95th, and 99th percentiles for systolic blood pressure (SBP)/diastolic blood pressure (DPB)
- Classification based on multiple measurements:

Classification	SBP ± DPB
– Normal	<90th percentile
– Prehypertension	90th–95th percentile or blood pressure >120/80 mmHg
– Stage 1 hypertension	95th–99th percentile + 5 mmHg
– Stage 2 hypertension	99th percentile + 5 mmHg

Issues in pediatric blood pressure measurement/interpretation include:

- Blood pressure \Rightarrow \Leftarrow Body size \Rightarrow normal blood pressure increases with growth throughout childhood. What are the relationships among age, body size, and blood pressure?
- Obesity epidemic \Rightarrow population of large children. What is normal blood pressure for a large child?
 - According to Centers for Disease Control and Prevention/NCHS, National Health Examination Survey, and NHANES data, the prevalence of overweight among children and adolescents ages 6–19 years rose more than 10 percent between 1963 and 2000.
- Blood pressure measurement problems: cuff size relative to arm size, variable physiologic state

- Auscultatory norms versus measurement in practice by automated device
- Role of white coat effect in “normal” blood pressure measurement
- Ambulatory blood pressure findings in establishing norms, making diagnosis, treatment of hypertension.

Dr. Kavey reviewed numerous studies on the outcome of hypertension diagnosed in childhood. The outcomes studied included:

- Coarctation of the aorta
- Target organ damage
- High-risk pediatric settings
- Primary hypertension
- Benefits of antihypertensive therapy
- Optimal time to initiate antihypertensive therapy.

Dr. Kavey compared known and unknown outcomes of hypertension diagnosed in childhood:

Known	Unknown
<ul style="list-style-type: none"> • In selected patient groups, early hypertension is associated with severe early cardiovascular disease. • Target organ damage is present and can be assessed noninvasively. 	<ul style="list-style-type: none"> • Outcome of mild primary hypertension • Benefits-risks of long-term therapy • Initiation of therapy

Dr. Kavey reviewed numerous studies on treatment of hypertension diagnosed in childhood and noted the following:

- Hypertension in childhood is usually asymptomatic.
- There is no evidence as yet that treatment beginning in childhood affects risk for future cardiovascular disease.
- Autopsies in normal children indicate that pre-morbid hypertension correlates with severity and extent of atherosclerosis.
- There is general consensus that treatment should be initiated for blood pressure >99th percentile.

In the reviewed studies, the treatments of hypertension diagnosed in childhood included:

- Diet change
 - Sodium reduction
 - Potassium supplements
 - Calcium supplements
- Weight loss
 - In obese adults and children, even small amounts of weight loss have been shown to significantly decrease blood pressure.
- Drug therapies.

FDAMA (1997) led to a significant increase in pediatric trials of relatively new antihypertensive medications. Twelve medications are now FDA-approved for use in pediatric hypertension, with

three medications being studied in ongoing trials. According to Dr. Kavey, there are limitations in the current trials:

- There are no trials of older medications with expired patent protection.
- All current reports are of short-term therapy.
- There are problems specific to recruitment of pediatric subjects.
- There are no trials to any endpoint except blood pressure itself.
- There are different mechanisms for hypertension in the pediatric age group, with very limited information on drug selection relative to pathophysiology.

Many studies suggest that a hyperkinetic hemodynamic state underlies primary hypertension with obesity in childhood. This state is characterized by:

- Increased resting heart rate
- Increased heart rate variability
- Increased 24-hour blood pressure variability
- Systolic hypertension alone without diastolic hypertension.

Dr. Kavey reviewed selection of the appropriate therapy:

- Beta blocker therapy should be ideal in this setting.
- Beta blockers have a long standing record of safety and efficacy for blood pressure control in other settings in children.
- By contrast, in adults, recent publications suggest that “the era of beta blockers for hypertension is over.”
- No data on beta blocker therapy for hypertension secondary to obesity in children.

Dr. Kavey listed “the knowns” of hypertension in childhood:

- Epidemiology of normal blood pressure throughout childhood is known.
- Obesity epidemic leads to increase in pediatric hypertension cases.
- In selected settings, devastating effects of hypertension in childhood are known.
- Target organ damage can be demonstrated with pediatric hypertension.
- Understanding of mechanisms for primary hypertension in childhood is evolving—not the same as in adults.
- Short-term therapy with a variety of agents is effective in reducing blood pressure.

Dr. Kavey listed “the unknowns” of hypertension in childhood:

- Best method for accurate blood pressure measurement
- Normal blood pressure range in obese children
- Role of diet change in blood pressure management
- Benefits of early treatment
- Risks of long-term therapy
- Appropriate drug selection/sequence for different settings.

Drug trial opportunities in pediatric hypertension include:

- Randomized trial of early intervention using surrogate endpoints, with long-term cohort follow-up to hard cardiovascular endpoints
- DASH diet versus beta-blocker in hypertension secondary to obesity with severely increased left ventricular mass index—minimum 1-year trial with blood pressure and left ventricular mass index as endpoints
- Randomized clinical trial of selected drugs for different settings, with rational staged approach to treatment (for example, in hypertension secondary to obesity; diuretic versus beta blocker versus combination)
- Randomized clinical trial with graded blood pressure goal in pediatric populations at established high risk for very early cardiovascular disease (for example, adolescents with end-stage renal disease: blood pressure target <75th percentile versus current goal [<90th percentile]; minimum 5-year trial with surrogate and hard endpoints).

Sickle Cell: Reflections on Protocol—Hydroxyurea

Duane R. Bonds, M.D., Sickle Cell Disease Coordinator, Blood Diseases Program, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI), NIH

Dr. Bonds briefly reviewed advances in sickle cell disease clinical research over the past 30 years. This review provided appropriate background information for the Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG). She listed the following studies:

- Cooperative Study of Sickle Cell Disease (CSSCD)
- Prophylactic Penicillin Trial I (PROPS I)
- Prophylactic Penicillin Trial I (PROPS II)
- Multicenter Study of Hydroxyurea (MSH)
- Perioperative Transfusion Trial
- Stroke Prevention in Sickle Cell Anemia (STOP I)
- Hydroxyurea in School-Aged Children (HUG KIDS)
- Hydroxyurea in babies (BABY HUG).

Dr. Bonds characterized observations from CSSCD, the first study of sickle cell disease:

- It began in 1979 as a large multi-institutional study.
- Until then, data in the literature were anecdotal and retrospective.
- The data suffered from selection bias—only the most severely affected patients were reported.

From 1979 to 1999, CSSCD recruited 3,200 subjects, 2,100 with hemoglobin (Hb) SS. Patients were from both rural and urban areas. Special interest groups included newborns and pregnant women. The goal of CSSCD was to identify major risk factors for disease severity. CSSCD revealed the epidemiology of the painful sickle cell crisis:

- 0.8 episodes per patient year (Hb SS)
- 4 episodes per patient year (Hb SC and S beta + thalassemia)
- 39 percent of Hb SS patients had 0 painful episodes per year
- 5.2 percent of Hb SS patients had 3–10 crises per year
- High pain rate associated with premature mortality.

CSSCD revealed the following organ dysfunction:

- Spleen damaged by 12 months of age (Hb SS)
- Leg ulcers—4.97 per 100 patient years (rate lower in alpha thalassemia)
- Osteonecrosis femoral head—9.8 percent; humeral head: 5.6 percent
- Brain—overt stroke rate varied with age; highest in children and adults older than 30 years (0.61 per 100 patient years overall)
- Brain—silent infarcts; risk factor for overt stroke and poor school performance
- Lung—acute chest syndrome; inverse relationship to age
 - 25.3/100 patient years 2–4 years of age
 - 8.8/100 patient years in adults
 - 12.8/100 patient years (Hb SS)
 - 5.2/100 patient years (Hb SC)
 - Risk factors: high white blood cell count; low Hb
 - Infectious event in children
 - Bone infarction/fat emboli event in adults.

CSSCD also revealed the following life expectancy information:

- Hb SS—median age at death is 42 years for males and 48 years for females
- Hb SC—median age at death is 60 years for males and 68 years for females
- 18 percent deaths secondary to organ failure (renal)
- 33 percent deaths in acute crisis (pain and/or acute chest syndrome)
- Early mortality risk inversely related to [Hb F].

Dr. Bonds explained that, as a child with sickle cell anemia grows, he or she may get:

- Stroke and/or lower brain function
- Painful attacks
- Acute chest syndrome
- Loss of spleen and/or kidney function
- Serious infections
- Early death.

Treatments available include:

- Daily penicillin to prevent infection
- Transfusion to prevent strokes
- Bone marrow transplantation—replaces body's sickle blood supply with nonsickle cell blood
- Hydroxyurea—benefit in children unknown.

In 1995, the results of MSH demonstrated that hydroxyurea for adults reduces:

- Chest syndrome
- Hospitalizations
- Need for blood transfusion
- Attacks of pain

- All of these symptoms by about 50 percent.

Dr. Bonds characterized BABY HUG as follows:

- It is a randomized, placebo-controlled, double-blinded clinical trial.
- Children with sickle cell anemia, 9–17 months old, are included at the start of the study.
- It is designed to test whether daily hydroxyurea taken by mouth can prevent organ damage in the spleen and kidney.
- Fetal hemoglobin is in the child’s blood before birth.
- Hydroxyurea raises fetal hemoglobin.
- People with higher fetal hemoglobin have fewer crises and lower risk of death.
- In a small pilot study, very young children given hydroxyurea with higher fetal hemoglobin also had better kidney function.
- In a small pilot study (HUSOFT), very young children taking hydroxyurea had more spleen function than a large group not taking hydroxyurea studied in the 1980s.

BABY HUG centers include:

- NHLBI and NICHD
- 14 clinical centers in the United States with expertise in sickle cell anemia in young children
- A medical coordinating center.

Dr. Bonds characterized the BABY HUG trial design as follows:

- Each one of the 14 clinical centers enrolls 20 children.
- All the children are given either hydroxyurea or a placebo for 2 years.
- The data are collected in the same way at all 14 centers and put together at the medical coordinating center.
- Each child will be assigned at random to take either hydroxyurea or a placebo.
- Hydroxyurea and placebo are given in identical-looking bottles that have a measuring dropper.
- Every child will have his/her blood tested every 2 weeks at first to make sure the hydroxyurea does not cause low blood counts.

The main trial measures include:

- Liver and spleen—a special picture at the beginning and at 2 years
- Kidney—glomerular filtration rate by DTPA, a radionuclide, and by serum creatinine and body length (height)
- Brain—transcranial Doppler, a special ultrasound picture of brain blood flow at the beginning, at 1 year, and at 2 years.

BABY HUG will study other characteristics in the children, including:

- Height, weight, and head circumference
- Neurology
- Development
- Blood counts

- Urine concentrating ability
- Genetics: chromosomes and DNA
- Immunologic responses to vaccinations.

Dr. Bonds concluded by commenting that one of the few problems noted so far with hydroxyurea is bone marrow suppression, which she said is reversible. Overall, however, the children taking hydroxyurea grow better because the calories that are usually used to make red blood cells help to increase linear growth and body weight. There is a high compliance with taking hydroxyurea because of its palatable taste.

Group Discussion of Alternative Approaches for Listing

Dr. Ward, moderator

Dr. Ward explained that the charge to the meeting participants was to take a comprehensive approach to the drug listing process and determine whether BPCA should adopt a new process or continue with the existing process. During this group discussion, meeting participants addressed the following issues and topics:

- Importance of label information but acknowledgement of alternate ways to disseminate drug information
- Publication of important drug information
- Stepwise labeling changes
- Inclusion of safety and efficacy data in package insert
- Better labeling versus better practice
- Importance of unpublished data (for example, data on safety of selective serotonin reuptake inhibitors in children)
- Dissemination of raw data
- Steps to change off-label usage
- Evidence-driven decisions
- Development of study approaches to provide FDA with objective information and having confidence to make label changes to benefit children
- Studying combination therapies
- Efficient use of limited time, focus, and funds to obtain level 1 data
- Inclusion of level 1 data in labels for both on- and off-patent drugs
- Consistency of evidence in published literature
- Inconsistencies in formulations used in studies
- Differences in scrutiny of data
- Large amounts of banked raw data at FDA (FDA has an enormous, unexamined database)
- Public access to FDA database of raw data
- Drug-indications pairings versus therapeutic category versus blended approaches
- Combining pediatric network databases
- Areas of most urgent needs for children (that is, severity, frequency)
- Areas where drugs will have greatest impact on child health.

DAY 2

Goal for Drug-Indication Discussion

Dr. Ward

Dr. Ward explained that the goal for drug-indication discussions was for each participating expert to complete a drug review worksheet for each drug in the groups presented below. The drug review worksheets will be compiled and evaluated to inform the drug prioritization process. The final evaluations will subsequently be shared with meeting participants. Dr. Ward noted that, in addition to the meeting presentations, valuable information is provided in *Guidance for BPCA Expert Reviewers in Considering Feasibility, Conditions, and Advisability of Drugs Listing*. Dr. Ward cited other resources that were available to the meeting participants to help them with the prioritization process.

ADHD

Paul P. Wang, M.D., Chair, Society for Developmental-Behavioral Pediatrics, Pfizer Global Research and Development

Dr. Wang reviewed the current knowledge of attention deficit/hyperactivity disorder (ADHD). He first addressed the indication and then addressed the two drugs being considered (guanfacine and clonidine). ADHD is a very common diagnosis and is diagnosed more frequently in the United States than in any other country. It may be a culturally specific diagnosis. The prevalence of ADHD is an order of magnitude higher than other diseases and conditions addressed in this meeting. Dr. Wang noted that guanfacine and clonidine are highly prescribed and highly used in children with ADHD; they are more frequently used in children younger than 12 years of age. ADHD is not an FDA-approved indication for either guanfacine or clonidine; these drugs are, however, approved for the treatment of hypertension in children, 12 years old and older. Dr. Wang suggested two reasons to study guanfacine and clonidine: (1) they are being used for new indications and (2) they are being used in the absence of appropriate information. In addition, because both of these drugs are in the same class, and purportedly have the same mechanism of action, Dr. Wang asked whether it is necessary to study both drugs. He noted that clonidine is used three to five times more frequently than guanfacine.

ADHD is treated primarily with medications. Although there are behavioral interventions, most of the non-medical interventions are generally not covered/reimbursed by health insurance. There are few practitioners of non-medical ADHD interventions. However, clinical studies have shown that treatment of ADHD with drugs alone is as effective as combination therapies. ADHD is most commonly treated with psychostimulants, including methylphenidate (Ritalin), Medidate, dextroamphetamines, mixed salts, and a new medication (Stratera), which is in a different drug class than the psychostimulants. Another new medication (Modafonil) will soon receive FDA approval for treating ADHD.

Dr. Wang said that, although the centrally acting α -adrenergic agonists guanfacine and clonidine are extensively used to treat ADHD, there are a number of gaps in the literature, including:

- Lack of developmental toxicology studies in animals

- Lack of PK data for children
- Formulation issues (tablets versus patches)
- Mixed pediatric populations in clinical studies (for example, children with ADHD only, children with comorbid disorders).

Dr. Wang commented that guanfacine and clonidine have different efficacies in children with ADHD only compared with children with comorbid disorders. The literature does support the efficacy of both drugs. Dr. Wang reviewed several efficacy studies as well as a few meta-analyses, which are limited but supportive. The safety of guanfacine and clonidine has not been well studied in children younger than 12 years of age. Sedation is a known adverse event for these two drugs, and Dr. Wang suggested that their efficacy in ADHD may actually be the adverse effect of sedation. He noted that clonidine is effective for hyperactivity but not attention deficit disorder alone. One study showed that hypertensive children on clonidine perform poorly on math tests. Other safety issues are the potential for cardiac toxicity and rebound hypertension due to variation in sympathetic nervous system activity. Four mortalities have been reported for children taking Ritalin and clonidine in combination.

Guanfacine: *Richard Gorman, M.D., Chair, Section on Clinical Pharmacy and Therapeutics, American Academy of Pediatrics; Dr. Wang; Charles R. Woods, M.D., M.S., Wake Forest University School of Medicine; and Julie Magno Zito, Ph.D., University of Maryland, Baltimore*

Dr. Gorman said that there is a lack of clarity in outcome measures for ADHD treatment, although there are several standard/accepted outcome tests. One study area that has been overlooked is the use of guanfacine and clonidine as first-line treatments in naïve populations. Jeffrey Blumer, M.D., Ph.D., reported that both guanfacine and clonidine have narrow therapeutic indexes and are not particularly safe drugs. He asked whether changes in labeling would result in changes in use of these drugs. Because guanfacine and clonidine are most likely used to treat the effects of psychostimulants, not to treat ADHD per se, these drugs will continue to be used as an adjunct therapy. Susan McCune, M.D., reminded the participants that neither drug is labeled for an adult indication; there is no adult data from which extrapolations can be made. She said that FDA is very interested in studying these drugs as adjunct therapy to psychostimulants because of the overdose potential and the number of deaths associated with their use. Fewer adverse events and deaths have been reported for guanfacine.

Clonidine: *Dr. Wang; Teri Moser Woo, R.N., M.S., C.P.N.P., University of Portland; and Dr. Woods*

Ms. Woo commented that a concern for both guanfacine and clonidine is the low number of studies conducted, and many of the studies had low subject numbers. In general, the study subjects were boys; little is known about the effects of guanfacine and clonidine in girls or minorities. Ms. Woo estimated that about 70,000 children use clonidine and about 20,000 use guanfacine. Dianne Murphy, M.D., described three common uses of clonidine: (1) chronic pain in children and adults, (2) weaning neonates off of benzodiazepines and opioids, and (3) epidural-peripheral nerve block. Jay M. Meythaler, M.D., J.D., noted that clonidine is used to treat spasticity. Dr. Wood said clonidine is also used as a short-term sedative during medical

procedures. Dr. Ward said that guanfacine and/or clonidine typify the dilemma of studying drugs by therapeutic class versus drug-indication pairings. These drugs should be studied as ADHD therapy, not as therapy for hypertension.

Alternative Treatments and Treatment Strategies: Wayne R. Snodgrass, M.D., Ph.D., commented that it is important to know the specific diagnosis (that is, attention deficit disorder or ADHD) when studying clonidine. He said that if clonidine is being used for its sedative effects, there are other sedatives that are much safer to use. Dr. Zito commented that clonidine is most often used in the evenings as a sleep aid. Dr. Snodgrass said that a head-to-head comparison of the two drugs might be informative but may not change the way practitioners practice. Dr. Wang said that no drug has been approved as an at-home sleep aid for children. Sleep in children with ADHD and autism is an area of research interest.

Hypertension

Facilitators: Drs. Taylor-Zapata and Dr. Kavey

Dr. Taylor-Zapata explained that this session was to discuss labetalol, bumetanide, furosemide, hydrochlorothiazide, and spironolactone and whether these drugs should be studied in pediatric populations. She noted that labetalol was recently listed for use in hypertension, whereas other drugs such as ACE inhibitors and calcium channel blockers have not been listed. Dr. Kavey commented that diuretics are generally not an effective treatment for children with primary hypertension. These drugs are frequently used but often not for the labeled indication.

Labetalol: *William Berquist, M.D., Stanford University Medical School, and Michael D. Reed, Pharm.D., Case Western Reserve University*

Dr. Berquist reviewed the clinical use of labetalol and listed the following general information:

- α -/ β -Adrenergic blocker
 - Antianginal
 - Antihypertensive
- Pediatric
 - Not FDA-approved in children
 - Safety and effectiveness for children not established.

Contraindications for labetalol include:

- Bronchial asthma or chronic obstructive pulmonary disease
- Cardiogenic shock
- Conditions associated with severe and prolonged hypotension
- Hypersensitivity to labetalol
- Overt cardiac failure
- Second and third degree atrioventricular block
- Severe sinus bradycardia.

Serious adverse effects include:

- Bronchospasm
- Hepatotoxicity (severe)
- Hyperkalemia
- Ventricular arrhythmia.

Clinical applications include:

- FDA-approved indications
 - Hypertension
 - Hypertension (severe)
 - Hypertensive encephalopathy
- Non-FDA-approved indications
 - Angina pectoris—heart failure (mild to moderate)
 - Angina pectoris—heart failure (severe)
 - Angina pectoris—hypertension
 - Angina pectoris—normal blood pressure.

Dr. Berquist characterized labetalol dosing for:

- Postoperative hypertension
 - Intravenous labetalol was reported effective in the treatment of acute postoperative hypertension in 15 patients (Leslie et al., 1987)
- Hypertensive emergency
 - Repeated intravenous injection
 - Slow continuous infusion.

Dr. Berquist reviewed the studies of labetalol in pediatric populations, noting that most of the information on this drug is from case reports, not randomized clinical trials. There was one cohort retrospective study (Deal et al., *Arch Dis Child* 1992). Dr. Berquist characterized this study as follows:

- Sick Children's Hospital, Toronto
- 454 hypertensive children
 - 110 (24 percent) required emergency treatment
- Group 1 received diazoxide or hydralazine
 - 57 patients were enrolled from 1975 to 1980
 - 13 with complications
 - 4 with serious neurologic injury
- Group 2 received labetalol (1–3 mg/kg/hr intravenously) or nitroprusside
 - 53 patients were enrolled from 1980 to 1985
 - 0 complications.

Dr. Berquist presented clinical details of and causes of hypertension in 110 children treated for accelerated hypertension. He also presented details and comments on antihypertensive drugs used to manage severe hypertension in children 1–17 years old.

Dr. Berquist described labetalol as a dangerous drug that should be used very carefully by pediatricians who know what they are doing. Labetalol is generally not used as a first-line treatment for hypertension; it is more a second-line drug to treat severe hypertension in the intensive care unit. It is an acute intervention that requires close monitoring. Dr. Blumer noted that the contraindications and precautions for labetalol are the same as for other beta-blocking drugs. Dr. Blumer said that the pediatric use of labetalol does not represent a big health issue. Dr. Ward commented that because other, safer drugs are available, labetalol should not be added to the BPCA drug list.

After reviewing the information on labetalol, Dr. Berquist offered the following opinion:

- Effective antihypertensive medication for select pediatric patients
 - Pheo, select hypertensive emergencies where unopposed beta block less desired
- Ambulatory use limited
 - Subspeciality directed use mainly
- Already in use with guidelines, anticipated safety and use in practice
- Dose titrated to accepted endpoints individualized to specific patient
- Accepted guidelines with expert opinion with dosing.

Bumetanide: *Dr. Blumer and Jay M. Meythaler, M.D., J.D., Wayne State University School of Medicine*

Dr. Meythaler provided an overview of bumetanide, listing the following characteristics:

- Indications include
 - Loop diuretic
 - Pharmacology—inhibits sodium reabsorption in the nephron at the thick ascending limb of Henle’s loop
 - Other drugs in the class include furosemide (Lasix) and torsemide (Demadex)
- Contraindications include anuria and oliguria
- Warnings are
 - Volume and electrolyte depletion
 - Hypochloremic metabolic alkalosis
- Precautions are
 - All patients
 - Hypokalemia
 - Ototoxicity
 - Pediatric use section
 - Patent ductus arteriosus and renal calcifications
 - Allergy to sulfonamides
 - Thrombocytopenia
- Adverse events
 - 4.1 percent total in adults, probably in children older than 5 years of age
 - >0.5 percent events
 - Muscle cramps (1.1 percent)
 - Dizziness (1.1 percent)
 - Hypotension (0.8 percent)
 - Headache (0.6 percent)
 - Nausea (0.6 percent)
 - Encephalopathy in patients with preexisting liver disease (0.6 percent)

- 0.5–0.1 percent events
 - Impaired hearing, pruritus
 - Electrocardiographic changes
 - Weakness
 - Hives
- <0.1 percent adverse events
 - Vertigo
 - Chest pain
 - Ear discomfort
 - Fatigue
 - Dehydration
 - Sweating
 - Hyperventilation
 - Dry mouth
- Preterm infants and infants younger than 6 months of age
 - Ototoxicity
 - Renal calcifications
 - Patent ductus arteriosus.
- Abdominal pain
- Arthritic pain
- Musculoskeletal pain
- Rash and vomiting
- Upset stomach
- Renal failure
- Asterixis
- Itching
- Nipple tenderness
- Diarrhea
- Premature ejaculation and difficulty maintaining an erection

Dr. Meythaler further characterized bumetanide:

- Dosing and administration
 - 0.1–0.2 mg/kg every 12 hours
- How supplied
 - 0.5 mg tablets, parenteral, 0.25 mg/ml
- Is formulation appropriate for the target population? No.
 - For parenteral, can be diluted
 - No elixir version
- PK/PD data
 - Marginally, yes, PK/PD data are available, but in small pediatric populations; so not known in all conditions.
 - Little data are available for infants younger than 6 months of age and particularly younger than 1 month of age. The drug has the advantage over furosemide in that bumetanide does not induce an acute rise in plasma renin activity.
 - Plasma half-life of bumetanide in preterm infants is about six times longer than in adults.
 - Half-lives in full-term infants are double the normal adult values.
 - Dosing intervals less than every 12 hours are not recommended. This is less frequent than for furosemide.
- Study population that need to be studied (ages, sex, race/ethnicity, comorbidities)
 - Preterm infants with various conditions and infants younger than 6 months of age.
- Endpoints that need to be studied
 - Dose response curves in preterm infants with various conditions.
- Possible use in intratracheal administration
 - But little advantage over furosemide in this delivery.

Dr. Meythaler asked whether studies are needed to collect data on efficacy of this drug. He answered:

- Marginally yes, but not imperative, for detailed data in preterm infants and infants younger than 6 months of age for renal and hepatic failure preterm infants
- However, there is an adequate substitute with furosemide, and it has significantly more data.

Dr. Meythaler presented some PD data for bumetanide (Marshall et al., *J Clin Pharmacol* 1998;38:994–1002). Areas to be studied include:

- Hypotheses to be tested
 - Serum and urinary excretion dose response curves
 - Long-term side effects such as ototoxicity
- Study population
 - Preterm infants and infants younger than 6 months of age
- Endpoints
 - Dose-response curves for various doses, serum, and excretion.

Dr. Meythaler asked: Would you recommend that this hypothesis be tested in a randomized, controlled clinical trial? His responses were:

- No, parenterally the drug has enough data to know it is effective.
 - The details and advantages of its use over furosemide or torsemide (Demadex) should be evaluated. There does not appear to be much of an advantage of bumetanide over furosemide.
- Bumetanide has not been studied with regard to the beneficial effects it may have on pulmonary function and whether it is superior to furosemide topically, which is an off-label use for both drugs. Topical application is by intratracheal instillation.

Bumetanide safety issues include:

- Long-term ototoxicity, renal calcifications, and patent ductus arteriosus in preterm infants and infants younger than 6 months of age need to be evaluated.
- Study population:
 - Preterm infants and infants younger than 6 months of age.

Furosemide: *Dr. Blumer and Ivor D. Hill, M.B., Ch.B., M.D., Wake Forest University School of Medicine*

Dr. Blumer said that furosemide is labeled as a diuretic; he also said that bumetanide and furosemide should be considered together. There is a wealth of vignette-type information and some PK data, but there are little data on furosemide as an antihypertensive. Although bumetanide is not labeled for hypertension either, it is more potent than furosemide and has an increased safety margin. Furosemide is generally used as diuretic in the secondary treatment of hypertension. Given that diuretics such as bumetanide and furosemide are used as adjunct therapies, Dr. Blumer asked whether their efficacy and safety could be separated from the effects of other drugs. Dr. Blumer suggested that there first be a clarification of the use of the bumetanide and furosemide; there is no need to evaluate these drugs as primary

antihypertensives. Dr. Kavey added there may not be enough pediatric patients to adequately study these drugs, but because there are very little data on their ototoxicity, it would be important to study them. Dr. Ward added that furosemide causes hearing loss in about 3 percent to 5 percent of neonates that receive treatment. Some hearing loss is transient. In addition, there are little data on using furosemide during renal failure. Dr. Meythaler asked whether there were formulary issues regarding the use of bumetanide, furosemide, and torsemide. Alan M. Shapiro, M.D., Ph.D., suggested that there may be difference in use by age. Dr. Ward said that trends in medication usage often reflect clinicians' perceptions of drugs' effects on outcomes.

Dr. Sachs noted that both bumetanide and furosemide are approved to treat edema (not hypertension), but most of the safety data are from intensive care use, not general oral use. Studying the safety of these drugs in children would be challenging because they are never used alone. Diuretics are not effective monotherapy for pediatric hypertension. Abraham Karkowsky, M.D., Ph.D., commented that there are no randomized clinical trials for furosemide in children, nor are there any pediatric indications for bumetanide. Bumetanide is not labeled as an antihypertensive for either children or adults.

Hydrochlorothiazide: *Lynne G. Maxwell, M.D., University of Pennsylvania, and Dr. Reed*

Dr. Reed said that much of what applies for bumetanide and furosemide applies to hydrochlorothiazide, which is a diuretic with distal loop activity. It has some proximal tubule activity and is about half as effective in augmenting sodium load as the loop diuretics. Hydrochlorothiazide is the number one treatment for hypertension in adults. For pediatric populations, hydrochlorothiazide is used in combination therapy with loop diuretics, particularly in children with BPD. Hydrochlorothiazide is also used in intensive care settings, but the intravenous formulation of chlorothiazide is more likely to be used in intensive care units. Hydrochlorothiazide is not labeled for treating hypertension in children. Dr. Reed said that the main issue for diuretics and antihypertensives is defining the best way to treat hypertension in children. He commented that because there are few published studies on thiazide monotherapy for pediatric hypertension, BPCA resources could be put to better use by determining the order of drug therapy for children. Dr. Maxwell noted that, despite the dearth of literature, the hydrochlorothiazide label gives doses for treating hypertension in infants and children. Dr. Simpson acknowledged that the labeling for diuretics and antihypertensives is not consistent, and sometimes the wording from one drug's label is borrowed verbatim from another similar drug. He commented that labeling requirements have changed over the years, and the wording for hydrochlorothiazide was approved in 1986. Dr. Reed explained that children do not respond to diuretics the same way that adults do, but some children do respond to hydrochlorothiazide monotherapy. Dr. Maxwell pointed out that there are no studies of hydrochlorothiazide monotherapy in children.

Dr. Ward commented that hydrochlorothiazide, in combination with spironolactone, is commonly used in children with BPD. This combination therapy is thought to spare the putative calcium wasting that occurs with loop diuretics. Dr. Ward said that there are insufficient data to support this treatment approach, nor are there adequate PK data. Data are needed on the uses of hydrochlorothiazide, but not on its use as an antihypertensive in children. Additional data are

needed on hydrochlorothiazide treatment of obese teenagers with mild hypertension, as well as appropriate dosing for hypertension treatment. Dr. Reed said that a worthwhile study of treating pediatric hypertension would be to determine the appropriate order of drugs to be given. Other possible studies include a pediatric “ALL-HAT” kind of study of antihypertensives and a low-dose hydrochlorothiazide study. Several participants discussed the need for studying PD/PK-dosing relationships.

Spirolactone: *Dr. Berquist and Stephen T. Lawless, M.D., M.B.A., Alfred I DuPont Hospital for Children*

Dr. Berquist reviewed the clinical use of spironolactone and listed the following general information. This drug is a member of the following class(es):

- Aldosterone receptor antagonist
- Antiandrogen
- Cardiovascular agent
- Diuretic, potassium-sparing.

Contraindications include:

- Anuria
- Hyperkalemia
- Hypersensitivity to spironolactone products
- Renal insufficiency, acute.

Serious adverse effects include:

- Agranulocytosis
- Breast cancer; cause and effect not established
- Gastric hemorrhage
- Gastritis
- Hyperkalemia (severe)
- Metabolic acidosis
- Skin ulcer
- Systemic lupus erythematosus.

Non-FDA-approved indications include:

- Acne vulgaris
- Female hirsutism.

FDA-approved indications include:

- Edema, associated with congestive heart failure, liver cirrhosis (with or without ascites), or nephrotic syndrome
- Essential hypertension
- Hypokalemia
- Primary aldosteronism

- Primary aldosteronism; diagnosis.

Dr. Berquist presented data on total study and patient characteristics for spironolactone. He reviewed some of the studies of spironolactone in pediatric populations, noting that most of the information on this drug is from case reports, not randomized clinical trials. The drug is not well studied in pediatric populations. Only one non-randomized controlled trial has been conducted.

Dr. Berquist offered the following opinion and recommendations for spironolactone:

- Rare use for antihypertensive monotherapy
 - Primary hyperaldosteronism
 - Mineral corticoid excess
- Too few patients for monotherapy study
- Safety and clinical monitoring could be extrapolated from adults or pediatric secondary hyperaldosteronism
 - BPD, ascites, congestive heart failure
 - Pediatric correlates exist
 - Urinary potassium, sodium, or serum electrolytes.

Dr. Ward suggested including serum aldosterone levels in pediatric spironolactone studies.

Roselyn E. Epps, M.D., commented that spironolactone has been studied in children with polycystic ovarian syndrome. Although this syndrome is not common, spironolactone therapy in this group might be worth studying. A participant said that the prevalence of polycystic ovarian syndrome may be as much as 10 percent of all women—many times undiagnosed. In this population, spironolactone is used for androgen suppression, not for hypertension. A participant commented on spironolactone PK in adults. Both spironolactone and its sulfur-containing metabolites are thought to be responsible for the drug's action. The drug's half-life in adults is about 1.5 hours, whereas in children, the half-life is about 15 hours. Adverse events include potassium imbalance disorders, hyperkalemia (at least initially), and hypokalemia with long-term use. Only about 4 percent of patients receive spironolactone as a primary treatment. Spironolactone is available only in tablet form. Dr. Ward said that spironolactone is commonly used and generally in a stereotypical fashion. The issues for this drug are how to study it (as primary therapy or as adjunct therapy) and in what pediatric population.

Parasitic Diseases

Amy Klion, M.D., Staff Physician, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, NIH

Dr. Klion provided some background information on parasitic diseases and various treatments for these diseases. She described herself as an adult infectious diseases specialist, not a pediatrician. Dr. Klion clarified that albendazole and mebendazole are antihelminthic drugs, of which there are few. Most antihelminthics are approved for only one or two indications, and they are commonly used for indications for which they are not approved. Dr. Klion noted that there are two issues for albendazole: (1) whether to change the labeling for FDA-approved adult indications of neurocysticercosis and echinococcosis to include children 6 years of age and younger and (2) whether there is a pediatric need to change the indications. With regard to the

first issue, Dr. Klion said that neurocysticercosis and echinococcosis are extremely rare in the United States in children 6 years and younger. It would be almost impossible to study these diseases in the United States. Therefore, there is no reason to change the labeling of these drugs for FDA-approved uses. However, albendazole is a very effective treatment of many non-FDA-approved parasitic diseases. Albendazole is considered to be a first-line treatment for hookworms. Many studies worldwide have shown albendazole to be about twice as effective as mebendazole. Albendazole effectively treats roundworms and strongyloides (nematode parasites). Dr. Klion suggested that there may be a need to study the efficacy of albendazole and mebendazole for treating other, non-FDA-approved diseases. Mebendazole is available in chewable tablets, and albendazole is available in pills only. There are no other formulations, which could challenge the study of these drugs in children 4 years of age and younger. With regard to safety, both drugs are used worldwide in millions of children older than 4 years of age and are considered to be very safe.

Albendazole: *Stanley E. Grogg, D.O., Oklahoma State University, and Dr. Hill*

Dr. Grogg provided an overview of albendazole. Albendazole is an antihelminthic drug used to treat neurocysticercosis (pork tapeworm; *Taenia solium*) and hydatid disease (dog tapeworm; *Echinococcus granulosus*). Dr. Grogg reviewed the life cycle of these two tapeworms in human hosts. Albendazole was first used to treat neurocysticercosis and hydatid disease in humans in 1982 and was made available in the United States in June 1996. Pharmacological mechanisms of action are as follows:

- Neurocysticercosis—via inhibitory effect on tubulin polymerization, which results in the loss of cytoplasmic microtubules
- Hydatid cyst—decreases ATP production and worm becomes lazy and dies.

FDA-labeled indications are neurocysticercosis and hydatid disease. Non-FDA-labeled indications include:

- Ascariasis
- Giardia
- Cutaneous larva migrans (dog, cat hookworm)
- Pinworm (*Enterobius vermicularis*)
- Hookworm (*Ancylostoma duodenale*, *Necator americanus*)
- Visceral larva migrans (toxocariasis).

Contraindications include:

- Documented hypersensitivity
- Hepatic disease
- C-Safety for use during pregnancy has not been established
- Lactation—safety unknown.

Warnings/precautions for pediatrics include:

- Because of CNS inflammatory response, patients must be started on anticonvulsants and high-dose glucocorticoids.

- There is a possibility of increased intracranial pressure as a result of cyst death; observe children for first 24–48 hours for signs.

Adverse events include:

- Headache
- Nausea/vomiting
- Abdominal pain
- Dizziness
- Fever
- Abnormalities in liver function
- Increased intracranial pressure
- Alopecia.

Possible serious reactions include:

- Leukopenia
- Granulocytopenia (rare)
- Pancytopenia (rare)
- Thrombocytopenia (rare)
- Acute renal failure.

Drug interactions include:

- May elevate levels
 - Cimetidine
 - Dexamethasone
 - Praziquantel (Biltricide)
 - Schistosomiasis, tapeworms, and liver flukes
 - Ritonavir
- May decrease levels
 - Carbamazepine (Tegretol).

Pediatric dosing and administration details are as follows:

- Neurocysticercosis
 - 6 years old, body weight less than 60 Kg
 - 15 mg/kg/d PO divided bid for 30 days with meals (max: 800 mg/day)
 - Give three cycles of 28 days on and 14 days off
 - Take with food
 - Monitor complete blood count, liver function tests at baseline and q 2 wks.
 - As adjunctive therapy
 - Start dexamethasone on second or third day of antihelminthic therapy if symptoms of increased intracranial pressure arise
 - Need anticonvulsants
 - To control seizures that result from cysts
- Hydatid disease
 - 2 years old, body weight less than 60 Kg (suggested dosage)
 - 15 mg/day PO divided bid x 8–30 days (max: 800 mg/day)
 - Take with food
 - Monitor complete blood count, liver function tests at baseline and q 2 wks.

Albendazole is supplied in 200 mg tablets (12 for \$23.59; www.drugstore.com). Although it requires a prescription, it is not a controlled substance. The formulation is appropriate for pediatric populations because it can be crushed and chewed.

Dr. Grogg characterized albendazole PK/PD as follows:

- Poorly absorbed from the gastrointestinal tract due to its low aqueous solubility
- Metabolism (albendazole sulphoxide major metabolite): half life 8–12 hours
 - Liver extensively
 - CYP 450
 - 1A inducer
- Excretion
 - Bile primarily
 - Urine minimally.

Dr. Grogg provided a profile of the study population with neurocysticercosis:

- Ages
 - Unlikely in children younger than 2 years
 - Prolonged incubation period of *Taenia solium*
 - Infection can precede symptoms by as many as 5 years
- Sex
 - No sexual predilection
- Race/ethnicity
 - More frequent in Hispanics (prevalence of organism in countries of origin)
- Morbidity (most common parasite infecting nervous system)
 - Typically benign
 - Increased intracranial pressure
 - Hydrocephalus
 - Papilledema
 - Seizures.

Dr. Grogg provided a profile of the study population for hydatid cyst:

- Ages
 - All ages affected; children tend to have higher infection rates because they play with dogs
- Sex
 - Some endemic countries; females are affected more than males because of lifestyle
- Race/ethnicity
 - “Cosmopolitan parasite”
 - No racial predilection
- Morbidity
 - Spontaneous cure is possible
 - Clinical symptoms from pressure on adjacent organs.

Endpoints that need to be studied for neurocysticercosis are:

- After 3–6 months of therapy

- Changes in CT lesions
- Status of seizures
- Eggs in stool.

Endpoints that could be studied for hydatid cyst are:

- Intestinal nematodes after treatment
- Decrease in cyst size
 - Measurement
 - Imaging studies
 - Ultrasound
 - CT
 - MRI.

Dr. Grogg reviewed two efficacy studies. In the first study of efficacy, a 7-year follow-up after albendazole with hydatid disease ($N = 68$) revealed:

- Liver cysts ($N = 59$)
 - 41 percent cures
 - 17 percent marked improvement
 - 24 percent limited improvement
 - 15 percent no change
 - No patient worsened
- Lung cyst ($N = 12$)
 - 72 percent cured
 - 9 percent limited improvement
 - 18 percent no change
 - No patient worsened.

A second study of albendazole efficacy in 1,455 patients with other parasites revealed:

- Enterobiasis, 100 percent
- Ascariasis, 89 percent
- Ancylostomiasis (*Necator americanus*), 88 percent
- Trichuriasis, 70 percent.

Safety issues include:

- Discontinue use if liver function tests increase significantly
 - May resume when levels decrease to pretest values
- Numerous studies indicate few side effects.

Dr. Grogg provided the following comments:

- Neurocysticercosis
 - Alternative drug is praziquantel (Biltricide)
 - More expensive
 - Less effective
- Hydatid cyst

- Alternative drug is mebendazole (Vermox)
 - Less systemic absorption and penetration into hydatid cysts.

Dr. Grogg offered the following recommendations:

- Needs a chewable or suspension formulation
- Further studies would be based on “severity of illness,” not number of cases
 - Neurocysticercosis—fewer than 1,000 new cases per year in the United States
 - Hydatid cyst—100–200 cases annually in United States
- Doubt whether placebo-controlled studies can be conducted
- A priority level of 2 or 3; should be studied, but not a priority
 - Seems to be best drug available for treatment of neurocysticercosis (80 percent improve) and hydatid cyst (70 percent improve)
 - Appears safe.

Dr. Klion commented that the literature for albendazole can be misleading. She noted that the treatment regimens presented by Dr. Grogg were reversed: Echinococcosis is treated in cycles of therapy, whereas the treatment for neurocysticercosis is single therapy. Dr. Klion said that the reported liver toxicities for albendazole involve high-dose, long-term treatment regimens or patients that have echinococcal liver infections. Blood abnormalities may be idiosyncratic. Albendazole has been proven to be very safe and has been used to safely treat thousands of pregnant women. Treatment can occur during lactation. Albendazole is best absorbed when taken with a fatty meal. Dr. Klion reported that albendazole blood levels have never been correlated with efficacy in any of the trials. In concluding, Dr. Klion said that the reported cure rates are correct and may appear to be somewhat low. However, there are no alternative drugs to treat neurocysticercosis and echinococcosis; both of these diseases are fatal. Dr. Klion noted that albendazole is available in a 400-mg tablet, but it is not scored and cannot be easily cut. The indicated dosing is 15 mg/kg body weight.

Mebendazole: *Drs. Gorman and Klion*

Dr. Gorman provided a brief overview of mebendazole. In a subsequent open session, the participants discussed the following issues:

- Mebendazole is available in chewable tablets.
- Pinworms are a trivial health concern in the United States.
- One dose of mebendazole can affect outcomes for up to 1 year.
- Mebendazole is given to pregnant women in Sri Lanka to improve iron loss.
- A powder or liquid formulation would be useful for giving the drug to children younger than 2 years of age.
- Albendazole and mebendazole have about the same efficacy for treating pinworms, but albendazole is better for treating hookworms.
- The standard dose for mebendazole is a 400 mg tablet; absorption rates, however, vary from person to person.
- Clinical tests for stability of mebendazole suspensions are needed.

Pertussis

DeWayne Pursley, M.D., M.P.H., Neonatologist-in-Chief, Beth Israel Deaconess Medical Center, Department of Neonatology-Newborn Medicine, Harvard Medical School

Dr. Pursley provided an overview of pertussis, which he described as not the typical upper respiratory tract infection. He characterized pertussis as follows:

- Description—acute, communicable respiratory tract infection; “whooping cough”
- Microbiology—*Bordetella pertussis* (most)
- Pathogenesis
 - Transmission—inhaled aerosolized droplets
 - Molecular/cellular aspects—poorly understood; biologically active substances
 - Pertussis toxin—virulence factor (systemic).

Pertussis is a primary pediatric problem. Dr. Pursley characterized the epidemiology:

- Transmission—very contagious (50 percent–100 percent secondary attack rate)
- Incidence—11,000 cases in the United States in 2003
 - Increasing—reporting, testing, awareness
 - Cases per 100,000—100 adolescents, 5 adults
 - Peak age—younger than 1 year (>2,000 cases); incomplete vaccination; limited passive immunity
 - Epidemics—every 2–5 years unaltered by vaccination
- Case fatality—0.2 percent in the United States (84 percent of deaths occur in infants younger than 6 months old).

Clinical manifestations include:

- Incubation period—7–10 days
- Clinical illness—three stages:
 - Catarrhal (1–2 weeks)—cough (worsens), coryza
 - Paroxysmal (6–12 weeks)—paroxysmal cough with “whoop”; complications most likely
 - Convalescent (weeks to months); cough subsides.

Atypical presentations include:

- Infants—minimal catarrhal stage; with or without whoop
- Previously vaccinated—milder course
- Older children—vaccine-induced immunity wanes.

Complications in infants can include:

- Apnea—mostly in infants younger than 6 months old (16 percent)
- Pneumonia (primary and secondary)—school-age children, infants (17 percent)
- Posttussive emesis—infants (50 percent)
- Seizures—infants (2 percent)
- Death—infants younger than 6 months (1 percent).

Clinical clues for diagnosis include:

- Case definition: acute cough for longer than 2 weeks with
 - Cough paroxysms
 - Inspiratory whoop
 - Posttussive vomiting
- Laboratory diagnosis
 - Culture (can be difficult after catarrhal stage)
 - PCR (polymerase chain reaction), DFA (direct fluorescent antibody), serology
- Other
 - Lymphocytosis, CXR—nonspecific.

Pertussis prevention measures include:

- Immunization
 - Five doses by age 7
 - Four acellular pertussis-containing vaccines
 - Not 100 percent effective
 - Milder clinical presentation
 - Milder course
 - Effect wanes by early adolescence
 - Newly licensed Tdap vaccine; ages 11–18.

Management/treatment includes:

- Supportive care
 - Infants more likely to require hospitalization
 - Infants may require intensive care unit (16 percent), ventilator (5 percent)
- Antimicrobial therapy
 - Shorten symptom duration
 - Limits spread to household contacts (immunization may not prevent infection).

Primary antimicrobial therapy choices include:

- Erythromycin estolate
 - 14 days; four times per day
 - Well-studied; best studied in young infants
 - Associated with infantile hypertrophic pyloric stenosis; especially in infants younger than 2 weeks of age
 - Not well tolerated
- Azithromycin (and clarithromycin)
 - 5 days; once daily (clarithromycin—twice daily for 7 days)
 - Well studied; not well-studied in young infants
 - May be associated with infantile hypertrophic pyloric stenosis
 - Better tolerated.

Dr. Pursley reviewed a treatment evaluation of azithromycin, clarithromycin, and erythromycin:

- Cochrane meta-analysis
- Ten randomized, quasi-randomized trials

- Short-term (azithromycin x 3 days, clarithromycin x 7 days) versus long-term (erythromycin x 14 days)
- Conclusions
 - Short-term as effective with fewer side effects
 - Both groups—reduced infectivity, same course
- Caveat
 - Only 12 infants in short-term group
 - AAP—erythromycin (life-threatening, inadequately studied).

Alternative antimicrobial therapies for pertussis include:

- Doxycycline, fluoroquinolones
 - Excellent in vitro activity
 - Not recommended for treatment in young children
- Trimethoprim-sulfamethoxazole
 - Variable activity
 - Should not be used in first 6 weeks of life.

Approaches to infection control include:

- Strategies
 - Antimicrobial prophylaxis
 - Recommended for all close contacts
 - Effective if given early
- Contact isolation
 - Until 5 days of therapy completed
- Vaccination
 - Unimmunized or incompletely immunized.

Dr. Pursley offered the following discussion comments, questions, and issues:

- Erythromycin: only FDA-approved treatment
 - Azithromycin does not carry indication for pertussis; would two trials be required?
 - Off-patent written requests issued for azithromycin for *Ureaplasma* (BPD) and *Chlamydia*
- Should prophylaxis of pertussis be studied?
 - Which therapies would have highest priority?
 - How does recent licensure of Tdap influence decision?
 - If azithromycin is given high priority, are there any concerns about issuing a third Written Request?
- How should the potential safety signal of pyloric stenosis be considered?

Azithromycin: *Bernhard L. Weidemann, M.D., Children's National Medical Center; and Theoklis Zauotis, M.D., M.C.S.E., University of Pennsylvania School of Medicine*

Dr. Weiderman reviewed several studies of azithromycin treatment of pertussis, including Aoyama (1996; a study of nasal pharynx eradication) and the Cochrane meta-analysis. It was

noted that immunization rates are lower in developing nations. Dr. Weiderman's conclusion of the studies he reviewed is that the main benefit of azithromycin treatment is to protect other from infection. The PICNIC study, which was not included in the Cochrane meta-analysis, concluded that both erythromycin and azithromycin eradicate *Bordatella pertussis* infections. The main point of treatment is from a public health perspective. Treatment is really prophylaxis. Other issues discussed included:

- Recommendation of Tdap for adults\
- Pyloric stenosis in infants receiving erythromycin treatment
- Challenges of diagnosing *Bordatella pertussis* infections
- Treatment effects on disease course
- Feasibility of studying pertussis infection
- PK/PD of azithromycin in children younger than 6 years of age
- Safety issues
- Better tolerance and compliance with azithromycin compared with erythromycin
- Risk of pyloric stenosis with azithromycin
- Written requests to study azithromycin in
 - Preterm infants as prophylaxis for BPD
 - Mothers infected with *Chlamydia* at time of delivery/prevention of *Chlamydia* conjunctivitis
- Appropriate clinical study endpoints
- Evidence of clinical benefit to patient/efficacy data
- Benefit of treatment to secondary cases in daycare centers/infection prevention
- Adults and adolescents as under- or undiagnosed disease reservoirs
- Clinical benefits of treating adults and adolescents
- Issues of adults refusing vaccination

Influenza

Dr. Gorman

Dr. Gorman provided an overview of influenza, noting that there are three types: A, B, and C. Types A and B are major causes of human disease. Influenza A, which causes pandemics, is characterized by:

- Two surface antigens
 - Hemagglutinin (15 types)
 - Neuraminidase (9 types)
- Antigenic drift—minor antigenic variations
- Antigenic shift—emergence of a new antigen.

Dr. Gorman characterized influenza epidemiology as follows:

- Spread by droplet or direct contact
- Most contagious before symptoms
- Viral shedding for 7 days
- Incubation period is 1–3 days.

Dr. Gorman characterized pediatric influenza epidemiology as follows:

- Attack rate of 10 percent to 40 percent each year
- Hospitalization rate of 1 percent
- Other lower respiratory tract, 0.25 percent to 25 percent
- Children younger than 5 years old suffer increased hospitalization rates
- Neonates suffer from influenza
 - Sepsis-like syndrome
 - Apnea
 - Lower respiratory tract disease
 - None of the vaccines, chemoprophylaxis, or treatments has been studied in neonates or infants younger than 6 months of age.

Dr. Gorman characterized influenza pandemic as follows:

- Influenza A undergoes antigenic shift
- Antigenic shift occurs about every 10 years
- Three pandemics in 20th Century—1918, 1957, and 1968.

Dr. Gorman provided the following reasons to be concerned about H5N1 bird flu:

- No previous human pandemic with H5
- H5N1 pandemic in birds unprecedented
- H5N1 has infected mammals usually not susceptible—tigers, house cats
- H5N1 has become endemic in domestic ducks.

Influenza control measures include:

- Vaccination
- Chemoprophylaxis
- Treatment.

With regard to a targeted vaccination strategy, Dr. Gorman offered the following:

Excessive Hospitalizations	Other Indications
<ul style="list-style-type: none">• Children younger than 5 years old• Hemoglobinopathy• BPD• Asthma• Cystic fibrosis• Malignancy• Diabetes• Chronic renal disease• Congenital heart disease	<ul style="list-style-type: none">• Long-term salicylate therapy• Immunosuppressive disease• Immunosuppressive therapy• HIV infections

Dr. Gorman compared two influenza A antiviral drugs:

<u>Amantadine</u>	<u>Rimantadine</u>
<ul style="list-style-type: none">• Oral administration<ul style="list-style-type: none">– Treatment: yes– Prophylaxis: yes• Ages<ul style="list-style-type: none">– Treatment: 1 year and older– Prophylaxis: 1 year and older	<ul style="list-style-type: none">• Oral administration<ul style="list-style-type: none">– Treatment: yes– Prophylaxis: yes• Ages<ul style="list-style-type: none">– Treatment: 13 years or older– Prophylaxis: 1 year or older

Dr. Gorman compared two influenza A or B antiviral drugs:

<u>Zanamivir</u>	<u>Oseltamivir</u>
<ul style="list-style-type: none">• Inhaled administration<ul style="list-style-type: none">– Treatment: yes– Prophylaxis: no• Ages<ul style="list-style-type: none">– Treatment: 7 years and older– Prophylaxis: not indicated	<ul style="list-style-type: none">• Oral administration<ul style="list-style-type: none">– Treatment: Yes– Prophylaxis: Yes• Ages<ul style="list-style-type: none">– Treatment: 1 year or older– Prophylaxis: 13 years or older

Amantadine: *Drs. Epps, Meythaler, and Pursley*

Dr. Meythaler provided an overview of amantadine. This drug was developed originally as an antiviral agent for influenza. The drug is not recommended as a substitute for influenza vaccine. The dose is generally 5 mg/kg per day for the treatment and prophylaxis of influenza of children. This is an approved use by the FDA.

Dr. Meythaler characterized the bioavailability of amantadine as follows:

- Across studies, the time to Cmax (Tmax) averaged about 2–4 hours.
- Amantadine is predominately renally cleared.
 - Plasma amantadine clearance ranged from 0.2 to 0.3 L/hr/kg after the administration of 5–25 mg intravenous doses of amantadine to 15 healthy volunteers.

Dr. Meythaler characterized the availability of amantadine as follows

- A stable or nearly stable crystalline white powder
- Available in 100 mg tablets, capsules, or in a syrup form (50m/5ml)
- Nine active manufacturers, seven of which produce a syrup/elixir
 - Obviously a large market for the medication.

Dr. Meythaler described the mechanism of amantidine's antiviral action:

- The mechanism of its antiviral action is not clear.
- It appears to mainly prevent the release of infectious viral nucleic acid into the host cell by interfering with the function of the transmembrane domain of the viral M2 protein.
- In certain cases, amantadine is also known to prevent virus assembly during virus replication.
- It does not appear to interfere with the immunogenicity of inactivated influenza A virus vaccine.

- Amantadine inhibits the replication of influenza A virus isolates from each of the subtypes (that is, H1N1, H2N2, and H3N2).
- It has very little or no activity against influenza B virus isolates.
- Rimantadine has fewer CNS effects, does not cross the blood-brain barrier.

Dr. Meythaler provided additional information on amantadine's CNS pharmacology and effects:

- Amantadine enhances dopamine release and inhibits dopamine reuptake.
- Amantadine has anti-NMDA effects.
- Amantadine may act to increase neural growth factors.
- Memantine for Alzheimer's is a dimethyl ester of amantadine.
- Amantadine has been reported to improve alertness and facilitate neurologic recovery in patients with brain dysfunction.
- There have been reports of reduced agitation and improved alertness and function in demented patients treated with amantadine.
- Amantadine is a tricyclic water-soluble amine salt which affects the synthesis, accumulation, release and reuptake of catecholamines in the CNS.
- It is often prescribed as an antiparkinsonian agent, as a treatment for neuroleptic-induced extrapyramidal symptoms, and as an antiviral agent.
- More recently it has been used in other CNS-acquired dementias such as acquired brain injury, multiple sclerosis, and encephalopathies.
- Amantadine causes release of dopamine from central neurons, facilitates its release by nerve impulses, and delays the reuptake of dopamine by neural cells.
 - The drug is rapidly absorbed, but it is not metabolized.
 - It is almost completely excreted by the kidney and can penetrate all cell membranes.
 - Peak plasma concentrations occur 1–4 hours after ingestion.
 - Amantadine is 90 percent excreted unchanged in the urine and the elimination half life is 9.7–14.5 hours.
 - Distribution is through all of the tissues of the body including the CNS.

Amantadine toxicity generally includes CNS-related side effects:

- Acute psychosis, disorientation, nightmares, hallucinations, behavioral disorders (aggressive behavior), CNS depression, dystonia, myoclonus, neuroendocrine effects (syndrome of inappropriate antidiuretic hormone).
- Low doses may have antiepileptic effects, high serum concentrations can cause seizures (Shahar and Brand, *J Pediatrics* 1992;121:819–821).

Additional indications (adults only) for amantadine include:

- Parkinson's disease/syndrome
 - Amantadine is indicated in the treatment of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism.
- Drug-induced extrapyramidal reactions
 - Amantadine is indicated in the treatment of drug-induced extrapyramidal reactions.
- Memantine has similar CNS receptor effects.
 - Possible antiviral effects.

Amantadine off-label uses for adults include:

- Brain injury
- Multiple sclerosis
- Essential tremor
- Chronic hepatitis C
- Hiccups
- Neuroleptic syndrome
- Seizures.

Amantadine off-label uses for children include:

- Alternating hemiplegia
- Brain injury
- Adjunct seizure medication.

Dr. Meythaler offered the following recommendations for further funding:

- The short-term PK of amantadine are well known in children for influenza prophylaxis and studies in adults have been extrapolated to children
 - Amantadine is much more frequently used in traumatically brain injured children than for its indicated use in influenza treatment or prophylaxis.
 - This does not include other off-label CNS pediatric uses.
- The drug is used in CNS disorders for much longer periods of time than the 2 weeks indication for children (influenza).
 - The pharmacology, kinetics, and side effects of long-term use in children have not been established.
 - For example, rapid withdrawal can cause neuroleptic malignant syndrome.
- Traumatic brain injury is the leading cause of disability in children.
 - The effectiveness of this drug in pediatric patients with CNS disorders and the side effects of long-term delivery need to be evaluated as a high priority.
 - The use of this medication for off-label CNS uses in pediatrics is quite high.

Dr. Meythaler offered the following recommendations for further studies:

- Long term trial in pediatric traumatic brain injury patients may be warranted.
 - Adult trials at multiple institutions are currently underway based on a recent smaller trial (Meythaler et al., *J Head Trauma Rehabil* 2002;17:300–313).
 - Trial format similar to the NIH traumatic brain injury clinical trials center's current format.

In a short discussion session, the participants mentioned the following issues and topics:

- Funding from the federal flu initiative to study flu, particularly in children
- Most vulnerable populations—the very young, the very old, people with chronic or existing diseases
- Need to study amantidine safety and efficacy in children younger than 1 year old; amantidine toxicity; amantadine PK data—no data for children younger than 1 year old
- Amantadine and rimantadine not effective against H5N1
- Amantadine resistance due to overuse of the drug
- Amantadine not effective against influenza type B or C

Rimantadine: *Thomas P. Green, M.D., Northwestern University, and Dr. Pursley*

In an open discussion session, the participants mentioned the following issues and topics regarding rimantadine:

- Emerging resistance for both amantidine and rimantadine
- Lack of indication of rimantadine in children younger than 13 years of age
- Need of safe and effective flu drugs for children younger than 1 year of age
- Questionable efficacy of rimantadine in pediatric populations
- Rimantadine toxicity to kidneys and liver; risks outweighing benefits
- Rimantadine safety and efficacy not established
- Lack of rimantadine PK/PD data for children.

Poisoning

Wayne Snodgrass, M.D., Ph.D., Professor, Clinical Pharmacology and Toxicology Unit, Departments of Pediatrics and Pharmacology-Toxicology, University of Texas Medical Branch

Based on his 25 years of experience in dealing with poisonings and overdoses in children, Dr. Snodgrass reviewed a list of agents that are common in poisoning and overdoses in children and described the kinds of treatment/antidotes that best for each. He noted that the numbers of deaths by poisoning are few—fewer than the numbers of deaths caused by injuries in car accidents.

Dr. Snodgrass proposed the following first-tier partial list of poisonings posing greater risk for death/severe permanent sequelae in children (Table 13).

Table 13. First-Tier Poisonings and Antidotes

Drug/Agent	Antidote
Calcium channel blockers	Very high dose insulin plus glucose
+/- Beta blockers	Glucagons
Iron	Deferoxamine
Camphor	No specific antidote; midazolam, lorazepam, phenobarbital for seizures
Clonidine	No specific antidote
Imidazoline eye drops (Visine, etc.)	No specific antidote
Tricyclic antidepressants	High-dosage NaHCO ₃ for cardiac arrhythmias; titrate venous pH up to 7.55; need status of antibody development
Botulism, infant	Need status of antitoxin
Opiates	Naloxone
Lomotil (diphenoxylate plus atropine)	Naloxone
Salicylates	NaHCO ₃ ; KCl; hemodialysis
Glyburide, glipizide, tolbutamide, etc.	Glucose, octreotide
Methanol/ethylene glycol	Fomepizole (Antizole)

Isopropanol	Ethanol; supportive for isopropanol
Cocaine (accidental/infants)	No specific antidote
Air pollution and asthma	Need new planet earth

Dr. Snodgrass proposed the following second-tier partial list of poisonings and antidotes for infants and children (Table 14).

Table 14. Second-Tier Poisonings and Antidotes

Drug/Agent	Antidote
Hydrocarbon pneumonitis	No specific antidote; animal data: less lung toxicity with C9–C12 aliphatic hydrocarbons
Cyanide poisoning	Hydroxocobalamin (available in France, not available in the United States) sodium nitrite/sodium thiosulfate
Organophosphate insecticides	Atropine (primary antidote); pralidoxime (secondary antidote)
Caustics, corrosives, acids, alkalis	No specific antidote
Solvent/inhalant abuse/teenagers	No specific antidote
Digoxin	FAB antibody (Digibind)
Amphetamines/MDMA (Ecstasy)	No specific antidote
Vitamin A	No specific antidote
Amanita mushroom	Sylibinin; need intravenous preparation in the United States
Isoniazid (accidental/infants)	Pyridoxine
Paraquat/diquat	No specific antidote; status of antibody development
Colchicine	No specific antidote; antibody in France, not available in the United States
Lithium	No specific antidote; high dosage NaCl infusion
Ricin	No specific antidote; need antibody
Acetaminophen	modification of FDA label for N-acetylcysteine to provide age-appropriate fluid volumes

Pralidoxime: *Gregory L. Kearns, Pharm.D., Ph.D., University of Missouri-Kansas City; J. Routt Reigart, M.D., Medical University of South Carolina; Dr. Snodgrass*

Dr. Kearns provided an overview of pralidoxime. He began by listing some nerve agent “factoids”:

- Half of terrorist incidents using weapons of mass destruction involve nerve agents
- Tabun, sarin, VX
- Nerve agents are often clear, odorless liquids at room temperature
- Nerve agents are very easy to aerosolize
- Component chemicals for synthesis are easily available

- Methods for synthesis are old and easily acquired
- Delivery systems not sophisticated.

Physical properties of nerve agents include:

- Liquids with varying volatility and persistence
- VX is the least volatile but the most persistent, “oily”; soman is odorless.
- Tabun, sarin, and soman have significant volatility; sarin is the most volatile.
- Absorbed via skin, mucus membranes, lungs, and gastrointestinal system.

Dr. Kearns characterized the toxicity of nerve agents:

- Dermal toxicity: one drop of VX, 1–10 ml of the G agents may be fatal.
- Onset of symptoms may be delayed several hours from exposure to the liquid form, especially VX (up to 18 hours).
- Rapid development of symptoms after exposure is more likely.

VX is extremely lethal: An amount of VX equal in size to one column of the building depicted on the back of a penny would be lethal.

Dr. Kearns summarized nerve agent toxicology:

- Overstimulation of acetylcholine receptors causing cholinergic crisis
- Disrupt function of acetylcholine esterase at muscarinic and nicotinic receptors in autonomic, somatic, and central nervous systems
- Cholinergic crisis—BAG the PUDDLES
 - Bronchoconstriction
 - Apnea
 - Graying/dimming of vision
 - Pupillary constriction (miosis)
 - Urination
 - Diaphoresis
 - Defecation
 - Lacrimation
 - Emesis
 - Seizures
- Signs/symptoms related to dose and route of exposure.

Dr. Kearns characterized the acute and chronic toxic effects of pesticides. Acute exposure is defined as a single dose or multiple doses within a short time (such as 24 hours); acute effects are those that generally occur shortly after acute exposure.

<u>Acute Toxicity</u>	<u>Chronic Toxicity</u>	<u>Target Organ Toxicity</u>
<ul style="list-style-type: none"> • Mortality and morbidity • Neurotoxicity • Immunotoxicity • Dermal toxicity • Reproductive toxicity 	<ul style="list-style-type: none"> • Carcinogenicity • Mutagenicity • Developmental toxicity 	<ul style="list-style-type: none"> • Lungs • Cardiovascular system • Endocrine system • Hematopoietic system • Musculoskeletal system • Liver • Kidneys

Why children are more vulnerable to nerve agent toxicity:

- Smaller mass = larger “mg/kg” exposure

- Airway architecture (dimension) produces difficulty with increased secretion
- Higher respiratory rate and minute volumes increase aerosol exposure
- Lower reserves of fluid and cardiovascular stress responses
- Possibly easier access across blood-brain barrier
- Lower seizure threshold.

Dr. Kearns explained why pralidoxime—not atropine—is an appropriate antidote for oxime poisoning and summarized the toxic mechanism of action of organophosphates. He then provided the following pralidoxime PK data from adults:

- Follows two-compartment model (after intravenous injection)
- $T_{1/2} = 1.4$ hour, $VD = 0.73$ L/kg
- Presumed MEC = 4 mg/L
- Apparent exposure-response data supporting dose strategy targeted toward MEC.

Pralidoxime studies in children include:

- Farrar et al., *J Pediatr* 1990;116:658–661
 - Dosing regimen based on modeling/simulation from adult PK data with “target” MEC of 4.0 mg/L
- Schexnayder et al., *Clin Toxicol* 1998;36:549–555
 - PK validation of previous continuous infusion regimen
- Both represented controlled, open label, treatment trial
- Safety and effect assessed by investigators
- Outcome related to amelioration of symptoms and “atropine sparing” effect of pralidoxime.

Considerations for pediatric labeling include:

- Product labeled for indication in adult organophosphate poisoning
- Preclinical and adult data support pediatric use
- Pediatric treatment trials support safety and efficacy and provide PK data sufficient to guide dosing
- Significance of pediatric labeling
 - Guidance for use in infants and children with organophosphate poisoning
 - Presence of a “therapeutic demand”
 - Presence of a “strategic demand” (national defense initiative for readiness for nerve agent threat)
- Benefit (of wide availability) versus risk (of not labeling based on current data) favors the former
- Feasibility and/or need for additional studies.

In a concluding discussion session, the participants mentioned the following issues and topics regarding pralidoxime and organophosphate poisoning:

- Low, medium, and high risks/toxicities of organophosphate pesticides
- Inhibition of cholinesterase not the mechanism of action for all nerve agents

- Decline of organophosphate poisonings in children for the past years; may not be feasible to study
- Pralidoxime may not be effective with all nerve agents/organophosphates—just acetylcholinesterase inhibitors.
- Pralidoxime has a good safety profile; no reports of adverse events.
- Use of atropine and oxygen as first step in treatment of organophosphate poisonings
- Effects if oxime overdose
- Use of autoinjectors by children

Plans for the Coming Year

Dr. Mattison

Dr. Mattison thanked the participants for their presentations and valuable input to the meeting. He noted that this is roughly the halfway point in the BPCA drug prioritization process. A series of events need to occur between now and the time when BPCA sunsets in 2007 to continue the process, including the identification of studies that improve pediatric therapeutics, ways to change labeling as a minimum standard, completion of feasible studies in real time, gathering of minimum data to have an impact of the process, and improving the quality of information that is shared with reviewers.

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