Priority List of Pediatric Therapeutic Needs
Under the Best Pharmaceuticals for Children Act

Background

Title V of Public Law 110-85, the Best Pharmaceuticals for Children Act (BPCA) of 2007, was enacted on September 27, 2007, as part of the Food and Drug Administration (FDA) Amendments Act of 2007.

This legislation, which reauthorizes the BPCA (Section 409I of the Public Health Service Act), extends the provision providing additional patent exclusivity for currently on-patent drugs that are being tested for pediatric use. This legislation also extends and expands the research program at the National Institutes of Health (NIH) established in the earlier law. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) administers the research program through its Obstetric and Pediatric Pharmacology Branch (OPPB), working in cooperation with the other NIH Institutes and Centers (ICs) with significant pediatric research portfolios. The NICHD is responsible for the determination and prioritization of the needs in pediatric therapeutics through the development of a list that will be used to promote further research to address gaps identified through this prioritization process.

Prioritization Process: Methodology

The BPCA prioritization process for determining the future needs in pediatric therapeutics will include the following:

- Level 1: Define boundaries of therapeutics and therapeutic needs
- Level 2: Needs Assessment
  - Gathering data to assist in determining gaps in therapeutic areas and/or drugs, through avenues such as epidemiology studies through database searches and literature summaries
  - Consulting with experts in pediatric research to assist in determining gaps in therapeutic areas and/or drugs. This consultation is done through global outreach and through therapeutic area-specific working groups
  - Consulting with FDA Office of Pediatric Therapeutics, the Pediatric and Maternal Health Division, and with each of the FDA review divisions in the Center for Drug Evaluation and Research (CDER), to determine labeling and study design gaps
- Level 3: Final prioritization at the NICHD to determine the studies to be conducted under the BPCA

Level 1: Defining boundaries of therapeutics and therapeutic needs

- For the purpose of this process, we will use the term “therapeutics” throughout the text to refer to interventions used to treat or improve human diseases.
- For the purpose of this process, the term “interventions” includes drugs and biologics that are specifically targeted at modifying the natural course of a disease.
- For the purpose of this process, we will define therapeutic needs to also include:

- Mode of delivery and delivery systems
- Formulations
- Developmental trajectory—the behavior of a therapeutic within a respective age group
- The spectrum of therapeutic approaches

- To date, the International Classification of Diseases version 9 (ICD-9), has been used as the basis for classification of therapeutic areas. The NICHD is currently evaluating other classification systems.

Level 2a: Needs Assessment: Determining gaps in therapeutic areas and/or drugs from epidemiology studies and literature summaries

- Pharmacoepidemiology research takes advantage of population cohorts to elucidate health services utilization. Under the BPCA, this type of research will be used to evaluate the body of evidence in databases on health services utilization for conditions that bring children into the health care system, and to determine if and how a drug is used in the pediatric population. These data help identify public health problems, identify gaps in pediatric therapeutics, and may provide information on cumulative exposure to a drug that can either add to or preclude the need for a large Phase III clinical trial.
- Literature summaries conducted under the BPCA will include a review of published literature to evaluate the number and quality of randomized controlled trials, case series, and all available information in the literature on needs already identified within a given therapeutic area and/or drug. These summaries will also include a review of the label for information on gaps in treatment including available formulations, and a review of unpublished literature (if possible).

Level 2b: Needs Assessment: Determining gaps in therapeutic areas and/or drugs through consultation with experts in pediatric research

- Consultation with experts in pediatric research occurs in the following manner:
  - **Tier 1: Global Outreach**—Global outreach is necessary for the transparency of the BPCA prioritization process and allows for comprehensive feedback on identified conditions. This outreach also provides a means for additional recommendations for conditions to be considered for study under the BPCA that have not been considered in the past. The global outreach includes experts in pediatric research and clinical care; NIH institute and center representatives; pediatric organizations (including the American Academy of Pediatrics), societies, parent and advocacy groups; and the pharmaceutical industry. Out of the global outreach, a panel of experts in multi-disciplinary areas of pediatric research are developed—and named the *Stakeholders Priority Team*. Global outreach can occur through questionnaires, federal register notices, the BPCA web site, and at the annual scientific prioritization meetings.
  - **Tier 2**: **Therapeutic Area Expert Panels**—The knowledge and experience of experts within a therapeutic category are extremely valuable to our understanding of the condition, the drugs used to treat this condition, and the gaps that exist within the specific pediatric therapeutic area. These groups, which will include NIH institutes and centers liaisons, will provide feedback on available information in the particular

field and will make recommendations to the NICHD on areas that could be considered for study under the BPCA.

- BPCA-related Working Groups (WG) that have been developed over the last five years and/or currently exist include:
    - 2005 Pediatric Hypertension WG
    - 2006 Infectious Diseases WG
    - 2007 Pediatric Asthma WG
    - 2007 Pediatric Formulations WG
    - 2007 Fragile X WG
    - 2008 Pediatric Bio-defense WG
    - 2009 Adolescent Therapeutics WG
    - 2009 Safety of Antipsychotics WG
    - 2009 Cold and Cough Medicines WG

Level 2c: Needs Assessment: Determining labeling/study design gaps through FDA consultation

- FDA consultation—The NICHD works closely with the FDA in determining knowledge gaps in pediatric therapeutics. Consultation with the FDA includes discussion on the best ways to improve pediatric labeling and promote research incentives that will address gaps in pediatric therapeutics.

Level 3a: Determining Priority Areas

- The *BPCA Preliminary List of Needs in Pediatric Therapeutics* has been prepared based on many factors: research conducted under the BPCA since 2002; expert opinion; and emerging public health concerns in pediatric therapeutics.
- Priority categories have been developed by the NICHD. Each year, several therapeutic areas will be selected from the following priority categories:
    - **Category One: Affected Patient Population**
        - Diseases of high prevalence in the pediatric population
        - Diseases with high morbidity and mortality (disease severity)
        - Special Populations, including Neonates and Adolescents
    - **Category Two: Unmet Needs**
        - Diseases with limited availability of treatment alternatives
        - Treatment of rare diseases
    - **Category Three: Scientific Importance**
        - Diseases with public health and global scientific impact
        - Compelling pre-clinical rationale
        - Novel mechanisms of action, trial design, and/or outcome measures
- For each therapeutic area or indication selected, reviews of published literature will be conducted, analyses of databases will be performed (if feasible), and therapeutic area working groups will be developed as determined necessary by the NICHD and FDA.
- Diversity in the types of research that will be funded under the mandate of the BPCA is expected.

Level 3b: Plan for prioritizing interventions within therapeutics areas

- At the BPCA annual meeting, the Stakeholders Priority Team will evaluate the areas identified by the NICHD as priorities for that year.
- Priority scores will be assigned by the stakeholders priority team to the drug, biologic, and/or device based on the following:
  - **Evidence Score**: Level of evidence of available pharmacokinetic, safety, or efficacy data
    - From literature
    - From label
    - From FDA review divisions
  - **Impact Score**: Potential benefit/impact to the pediatric population
    - Relevance of therapeutic intervention to other conditions and/or specialties
    - Impact of research on specific age group, with a focus on neonates and adolescents
    - Global/International impact of research that will benefit the pediatric population
    - Availability of other therapeutic agents for the prioritized indication
    - Severity of the disease(s) for which an intervention is being used
  - **Feasibility Score**: Level of need in the patient population
    - Frequency of drug use in the pediatric population
    - Frequency of the indication(s) for which an intervention is being used
    - Toxicity profile of the drug and/or effects of the drug on growth and development
    - Estimated level of investments needed
    - Ability to perform the trial—i.e., existing infrastructure

Level 3c: Final Prioritization

- Based on the above input, therapeutic areas and subsequent therapeutic interventions considered for final prioritization will be those that provide novel therapeutic opportunities and involve a public health benefit.
- **Prioritization Steering Committee**—the final prioritization will be done by the NIH based on selection criteria that include, but are not limited to, feasibility, relevance to mission of the NIH/BPCA, alignment with core competencies (i.e. infrastructure available), and urgency. This committee includes the NICHD and FDA staff who review and endorse collaborative statements of the therapeutic area panels and the recommendations of the Stakeholders Priority Team. The committee will determine the final direction and priorities of the BPCA program, and are responsible for the dissemination of information on clinical and/or preclinical studies under the BPCA for public knowledge.
- For each priority area that is approved, the NICHD will work with the relevant FDA divisions, through the development of Proposed Pediatric Study Requests (PPSRs) and subsequent written requests, for studies of off-patent drugs that have been prioritized under the BPCA.
- The NICHD will also develop a schema for contacting pharmaceutical companies (New Drug Application holders) to determine if there are existing data for off-patent drugs that are prioritized under the BPCA.

The BPCA scientific prioritization meeting was held from June 30 to July 1, 2008, in Rockville, MD, and a preliminary list of needs in pediatric therapeutics was developed based on input from the Stakeholders Priority Team and other participants who participated in the meeting. In addition, discussions with the FDA as well as discussions with representatives from the European Medicines Agency on drug prioritization and potential collaborations have been taken into account for the development of the final BPCA List. The final list will be available on the BPCA Web site at http://bpca.nichd.nih.gov/index.cfm.

Table 1. Priority List of Needs in Pediatric Therapeutics as of April 17, 2009

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of Study and/or Scientific Needs	Plans and Progress
Infectious Disease				
MRSA Infections	Clindamycin Doxycycline Tetracycline Trimethoprim-Sulfamethoxazole	Optimal therapy and management of skin and soft tissue infections Biomarkers of disease	Pharmacokinetics (PK) and efficacy data	Proposed Pediatric Study Request (PPSR)
Infections	Benzathine Penicillin-G Ampicillin	Streptococcal infections PK and Safety of high dose in very low birth weight neonates	PK studies PK, safety studies	PPSR Review of existing data
Tinea Capitis	Griseofulvin	Safety and efficacy of high dose in children <20kg	PK and safety studies	Review of existing data
Tuberculosis		Formulations	New formulations of TB drugs for children	Pending additional input
Cardiovascular Disease				
Hypertension	Hydrochlorothiazide Beta-blockers ACE-inhibitors	PK, safety, efficacy in <12y and in obese adolescents	Comparative effectiveness studies on dosing and long-term safety;	PPSR
Controlled hypotension Hypotension	Sodium Nitroprusside Therapies for hypotension	PK, safety, efficacy Outcome measures in neonates and children treated for hypotension	PK, short and long-term safety and efficacy trials for controlled hypotension	PK, safety, and efficacy clinical trial under way Developing collaboration with existing NICHD networks Pending additional input

Table 1. (continued)

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of Study and/or Scientific Needs	Plans and Progress
Respiratory Diseases				
Asthma	Asthma therapeutics in young children	Objective measures of lung function and responses to therapy in children <4y	Biomarkers of disease Pharmacogenetic (PG) studies Standardizing outcome measures in research	Collaborations with NHLBI and NIAID asthma networks
	Drug delivery systems	Effectiveness of drug distribution in delivery systems used in children		Pending additional input
	Inpatient Albuterol	PK, safety	Dosing, safety, and efficacy in children in acute care settings	Collaborations with existing NICHD networks
Intensive Care				
Anesthesia/ Sedation	Ketamine Isoflurane Lorazepam	Safety Safety PK, safety, efficacy	Pre-clinical and clinical studies of long-term effects	Pre-clinical studies under way Clinical trial completed; Data under review
CBRNE Research				
Nerve Agent Exposure	Drug delivery systems Scopolamine	Need for Auto-injector Pharmacokinetics	PK modeling studies	Pending additional input
Organophosphate Poisoning	Pralidoxime	Dosing and safety		Under FDA review
Infectious Disease Exposure	Doxycycline Ciprofloxacin	Dosing and safety	PK modeling studies	Pending additional input

Table 1. (continued)

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of Study and/or Scientific Needs	Plans and Progress
Pediatric Cancers				
Neuroblastoma	13-Cis-Retinoic Acid	PK, efficacy and safety	PK and safety studies New formulation	Collaborations with NCI/ Children's Oncology Group (COG) New formulation
Leukemias and Solid Tumors	Methotrexate Vincristine Daunomycin Actinomycin-D	PK, efficacy and safety studies		Collaborations with NCI/ COG. Trials ongoing.
Corticosteroids in Cancer Treatment	Prednisone/Prednisolone Methylprednisolone Dexamethasone	PK, dosing, efficacy and safety		Pending additional input
Cardio toxicity	Dexrazoxane	Prophylaxis of cardio toxicity		At the Foundation for NIH
Psychiatric Disorders				
Depression Smoking Cessation	*Bupropion	Efficacy and safety in teens >12y		At the Foundation for NIH
ADHD	*Methylphenidate	Safety and Toxicity		FDA/NIEHS collaboration for preclinical and clinical studies
Bipolar Disease	Lithium Atypical antipsychotics	PK, safety, efficacy Long-term safety—metabolic derangements	Dosing, long-term safety Long-term safety	PK, safety, and efficacy clinical trial under way 2009 working group under way

Table 1. (continued)

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of Study and/or Scientific Needs	Plans and Progress
Neurological Diseases				
Cerebral Palsy	Baclofen (oral)	PK, safety, efficacy	PK and efficacy New formulation	Clinical trial underway New Formulation
Migraines	*Eletriptan	Safety, efficacy		At the Foundation for NIH
Seizures	*Zonisamide Lorazepam	 PK, efficacy	Dosing and efficacy PK, safety and efficacy	At the Foundation for NIH Comparative effectiveness clinical trial under way
Neonatal Research				
Neonatal BPD/Lung Development	Betamethasone	Dosing, efficacy	Outcome measures	Reviewing existing data
Neonatal Pain	Morphine Methadone	 Opioid withdrawal	Biomarkers of pain	PK, PG, and pharmacodynamic study under way Pending additional input
Neonatal NEC	Meropenem	PK, safety		Clinical trial under way
Adolescent Research				
Over the Counter Drug Use		Health literacy		December 2007symposia http://bpca.nichd.nih.gov
General Therapeutic Needs				2009 working group under way
Hematologic Diseases				
Sickle Cell Anemia	Hydroxyurea	Safety and effectiveness in young children	PK, safety and efficacy (S&E) New formulation	PK, S&E trial completed. Long-term safety follow-up study under way with new formulation.

Table 1. (continued)

Current or Proposed Listed Therapeutic Area	Current or Proposed Listed Drug	Gaps in Knowledge/ Labeling	Type of Study and/or Scientific Needs	Plans and Progress
Diseases with Limited Alternative Therapies or Rare Diseases				
Fragile X		Outcome measures targets for intervention		Co-sponsoring grant for new drug development
Type 1 Diabetes		Immunomodulatory therapies		Collaborations with existing NICHD networks
Dermatologic Diseases				
Atopic Dermatitis	*Hydrocortisone valerate	Effects on growth and HPA axis suppression	Long-term safety data in children < 2 yrs	Pending additional input
Gastrointestinal Diseases				
GE Reflux			Dosing, safety, efficacy in neonates and infants	Pending additional input
Renal Diseases				
Chronic Kidney Failure	Devices used in dialysis			Pending additional input
Rheumatologic Disorders				
Connective Tissue Disorders	Hydroxychloroquine			Pending additional input

Caveats:

Asterisk (*) means that drug is currently on-patent.

Drugs and/or therapeutic areas listed in grey highlight are newly listed for the BPCA 2007 legislation.

Total=33 conditions/therapeutic areas in comprehensive list
Total new drugs or indications listed=16
Total new therapeutic areas listed=5