Priority List of Needs in Pediatric Therapeutics for 2008–2009 as of September 1, 2009

For many decades, the pediatric medical community, the public health community, and government agencies have recognized multiple gaps in knowledge regarding the use of therapeutics in children. These gaps have resulted in inadequate labeling for pediatric use and in frequent off-label use of prescription drugs in children. Contributing factors to this off-label use of drugs include not only the rarity of some conditions in children, but also the limited patient populations for study, ethical concerns regarding the conduct of clinical trials in children, the lack of accurate information about medication use in children, and the lack of long-term safety data on the medications that are used.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), other federal agencies, and various organizations and industries have taken steps to address the knowledge gaps that exist in pediatric therapeutics. The Best Pharmaceuticals for Children Act (BPCA), originally enacted in January 2002 and reauthorized in September 2007, seeks to improve the level of information about pharmaceuticals used to treat children.

The 2002 BPCA Legislation

The 2002 legislation directed the Secretary of the Department of Health and Human Services (HHS), acting through the Director of the National Institutes of Health (NIH) in consultation with the Commissioner of the Food and Drug Administration (FDA) and experts in pediatric research, to develop and prioritize a list of "off-patent" drugs for which pediatric studies were most urgently needed. The NIH delegated this responsibility to the NICHD.

Since 2002, the NICHD has collaborated with other NIH Institutes and Centers and experts in pediatrics and has sought public comment to identify drugs in need of further study and to prioritize needs in pediatric therapeutics. The NICHD has published updates on this priority list at least annually beginning in 2003.

Under the 2002 BPCA legislation—which required the NIH to consider, for each drug, "whether new pediatric studies concerning the drug may produce health benefits in the pediatric population"—prioritization was based on three major factors:

- Frequency of use in the pediatric population
- Severity of the condition being treated
- Potential for providing a health benefit in the pediatric population.

During the initial years of the BPCA prioritization process (2003–2005), the NICHD identified many individual drugs that required further pharmacokinetic (PK), efficacy, and safety information.

In 2005, based on the input of pediatric experts, an alternative approach began to be discussed that included identification and prioritization of pediatric conditions and therapeutic approaches for those conditions. This condition-based approach makes it easier to identify gaps in scientific knowledge, determine key research agendas in pediatric medicine, evaluate the treatments of

these conditions, and compare the use of both on- and off-patent drugs within a therapeutic class. This approach also would allow the NICHD to obtain focused expertise in specific therapeutic areas to help elucidate the scientific gaps within that specific area.

The "New" BPCA Legislation

Title V of Public Law 110–85, the Best Pharmaceuticals for Children Act of 2007, was enacted on September 27, 2007, as part of the Food and Drug Administration Amendments Act of 2007. This legislation, which reauthorizes the BPCA (Section 409I of the Public Health Service Act), extends the 6-month patent exclusivity provision for currently on-patent drugs being studied for pediatric use. This legislation also extends and expands the research program that the NIH established in the earlier law.

Important changes to the BPCA legislation authorize the NICHD to:

- Focus on a condition-based approach
- Use more flexible funding mechanisms
- Develop and submit to the FDA Proposed Pediatric Study Requests (PPSR)
- Initiate a feasibility study for development of a pediatric formulary
- Increase training of pediatric clinical pharmacologists.

Update on BPCA Conditions/Therapeutic Areas

Throughout 2007 and 2008, the NICHD continued its outreach to pediatric organizations and other NIH Institutes and Centers with the goal of identifying current gaps in scientific knowledge regarding research and treatment of pediatric conditions and, ultimately, determining approved drugs for which future pediatric studies are needed. Minutes of all working group meetings conducted under the BPCA can be found on the BPCA Web site (http://bpca.nichd.nih.gov).

By implementing the provisions of the BPCA, the NICHD strives to improve pediatric therapeutics through scientific advancements and labeling changes that will have an impact on the safe and effective use of drugs in children. This can be accomplished through the following methods:

- Data gathering
  - Use the principles of pharmacoepidemiology research to quantify adverse drug reactions, drug efficacy, and patterns of drug use in large populations to elucidate health services utilization.
  - Bring together multidisciplinary teams to provide input on needs in pediatric therapeutics through outreach to experts in pediatric research in academic institutions, other NIH Institutes and Centers, pediatric organizations, societies, advocacy groups, and industry.

- Submitting PPSR to the FDA
  - The 2007 legislation authorizes the NICHD to develop and submit a PPSR to the FDA for additional studies that are needed to assess the safety and effectiveness of the drug in the pediatric population. (A PPSR is a draft Written Request that describes the elements of the pediatric clinical trials needed to improve pediatric labeling.)

- The submission shall be for drugs that have an approved application under section 505 (j) of the Federal Food, Drug, and Cosmetic Act and have no patent protection or market exclusivity protection for at least one form of the drug.

- Conducting clinical trials
  - Initiate Phase 1, 2, and 3 clinical trials to increase the knowledge of PK, safety, and efficacy of medicines used in children.

- Fostering basic and translational research
  - Support efforts to inform such areas as developmental pharmacology, pharmacogenomics, and pediatric clinical trial design.

The NICHD sponsored the annual BPCA prioritization meeting, held June 30 and July 1, 2008, with stakeholders from the NIH, the FDA, the American Academy of Pediatrics, and other pediatric organizations and societies. The meeting allowed the NICHD to review and discuss the proposed therapeutic areas and present progress from ongoing research. It also offered an opportunity for the medical community to provide input into the future therapeutic areas under the BPCA as mandated by the BPCA 2007 legislation. The next BPCA prioritization meeting will be held on November 18 and 19, 2009.

Below is an updated list of therapeutic areas and drugs that have been prioritized for study since the inception of the BPCA and a summary of the NICHD's progress in these areas.

Priority List of Needs in Pediatric Therapeutics 2008

In accordance with the BPCA legislation, the following list outlines priority needs in pediatric therapeutics for the therapeutic areas listed below.

Table 1. Infectious Disease Priorities

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
Methicillin resistant *Staphylococcus aureus* (MRSA) infections	Clindamycin Doxycycline Tetracycline Trimethoprim-Sulfamethoxazole	Optimal therapy and management of community-acquired skin and soft tissue infections Biomarkers of disease	Pharmacokinetics (PK), safety and efficacy data	Proposed Pediatric Study Request (PPSR)
Infections	Benzathine Penicillin-G	Streptococcal infections	PK studies	PPSR
	Ampicillin	PK and safety of multiple doses in very low birth weight neonates	PK, safety studies	Written Request (WR) received from the FDA
Tinea capitis	Griseofulvin	Safety and efficacy of a high dose in children <20kg	PK and safety studies	WR received from the FDA
Tuberculosis (TB)		Formulations	New formulations of TB drugs for children	Collaborating with the National Institute of Allergy and Infectious Diseases (NIAID)

Caveats:
Asterisk (*) means that drug is currently on patent.
Total = 34 conditions/therapeutic areas in comprehensive list

Back to Top

Table 2. Cardiovascular Disease Priorities

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
Hypertension	Hydrochlorothiazide Beta-blockers Angiotensin-converting enzyme (ACE) inhibitors	PK, safety, efficacy in children younger than 12 years and in obese adolescents	Comparative effectiveness and safety studies using appropriate doses	WR received from the FDA The NICHD is developing a PPSR
Controlled hypotension	Sodium nitroprusside	Dose-response, safety, efficacy	Short- and long-term safety and efficacy trials for controlled hypotension	Short-term dose-response study complete; long-term efficacy/safety study enrolling patients
Hypotension	Therapies for hypotension	Outcome measures in neonates and children treated for hypotension	Outcome measures in neonates and children treated for hypotension	Developing collaboration with existing NIH networks

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Back to Top

Table 3. Respiratory Disease Priorities

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
Asthma	Asthma therapeutics in young children	Objective measures of lung function and responses to therapy in children younger than 4 years	Biomarkers of disease Pharmacogenetic (PG) studies Standardizing outcome measures in research	Collaborating with the National Heart, Lung, and Blood Institute and the NIAID asthma networks to hold a workshop on outcome measures
	Drug delivery systems	Effectiveness of drug distribution in delivery systems used in children		Consulting with experts
	Albuterol	Dose-response, PK, safety, efficacy	Dosing, safety, and efficacy in children in acute care settings	Collaborating with existing NICHD networks

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Back to Top

Table 4. Intensive Care Priorities

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
Anesthesia/ sedation	Ketamine Isoflurane	Safety Safety	Preclinical and clinical studies of long-term effects	Conducting preclinical studies
	Lorazepam	PK/pharmacodynamics (PD), safety, efficacy		Clinical trial completed; data under review

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Back to Top

Table 5. Chemical, Biological, Radiological, Nuclear, Explosive Research Priorities

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
Nerve agent exposure	Drug delivery systems for pralidoxime	Need for autoinjector for pralidoxime		Consulting with experts
Organophosphate poisoning	Pralidoxime	Dosing and safety		Under FDA review
Infectious disease exposure	Doxycycline Ciprofloxacin	Dosing and safety		Consulting with experts

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Back to Top

Table 6. Pediatric Cancer Priorities

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
Neuroblastoma	13-cis-retinoic acid	PK, efficacy, and safety	PK, efficacy and safety studies submitted to FDA New formulation	PPSR submitted to FDA; WR referred to NICHD
Leukemias and solid tumors	Methotrexate Vincristine Daunomycin Actinomycin-D	PK, efficacy, and safety studies		Collaborating with the National Cancer Institute Children's Oncology Group Patient recruitment ongoing
Corticosteroids in cancer treatment	Prednisone/prednisolone Methylprednisolone Dexamethasone	PK, dosing, efficacy, and safety		Consulting with experts
Cardiotoxicity	Dexrazoxane	Prophylaxis of cardiotoxicity		At the Foundation for the NIH[i]

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Back to Top

Table 7. Psychiatric Disorder Priorities

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
Depression, smoking cessation	Bupropion*	Efficacy and safety in children older than 12 years		At the Foundation for the NIH
Attention deficit/hyperactivity disorder	Methylphenidate*	Safety and toxicity		Preclinical and clinical studies are ongoing with the FDA (National Center for Toxicologic Research) and the National Institute of Environmental Health Sciences
Bipolar disease	Lithium	PK, safety, efficacy	Dosing, long-term safety	Conducting PK, safety, and efficacy clinical trial
	Atypical antipsychotics	Long-term safety—metabolic derangements	Long-term safety	Being considered by 2009 working group

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Back to Top

Table 8. Neurological Disease Priorities

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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
Cerebral palsy	Baclofen (oral)	PK, safety, efficacy	PK and efficacy New formulation	Clinical trial underway New formulation in development
Migraines/headache	Eletriptan*	Safety, efficacy		At the Foundation for the NIH; consulting with experts
Seizures	Zonisamide*		Dosing and efficacy	At the Foundation for the NIH; consulting with experts
	Lorazepam	PK, safety, efficacy	PK, safety, and efficacy	PK study complete; study report submitted to the FDA; comparative effectiveness clinical trial under way

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Back to Top

Table 9. Neonatal Research Priorities

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
Neonatal bronchopulmonary dysplasia/lung development	Betamethasone	Dosing, efficacy, safety	Outcome measures	Reviewing existing data
Neonatal pain	Morphine	PK, safety, efficacy	Biomarkers of pain	PK, PG, and PD study ongoing; developing collaborations with existing NIH networks
	Methadone	Opioid withdrawal		Consulting with experts
Neonatal necrotizing enterocolitis	Meropenem	PK, safety		Clinical trial ongoing

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Back to Top

Table 10. Adolescent Research Priorities

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
Over-the-counter drug use		Health literacy		December 2007 symposia http://bpca.nichd.nih.gov
General therapeutic needs				Being considered by 2009 working group

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Back to Top

Table 11. Hematologic Diseases Priorities

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
Sickle cell anemia	Hydroxyurea	Safety and effectiveness in very young children	PK, safety, and efficacy New formulation	PK, safety, and efficacy trial completed; long-term follow-up study under consideration

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Back to Top

Table 12. Diseases with Limited Alternative Therapies or Rare Disease Priorities

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
Fragile X syndrome		Outcome measures and targets for intervention		Cosponsoring grant with the National Institute of Mental Health for new drug development, and a workshop on outcome measures
Type 1 diabetes		Immunomodulatory therapies		Collaborating with existing NICHD networks

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Back to Top

Table 13. Dermatologic Diseases Priorities

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
Atopic dermatitis	Hydrocortisone valerate*	Effects on growth and hypothalamic-pituitary-adrenal (HPA) axis suppression	Long-term safety data in children younger than 2 years	At the Foundation for the NIH; consulting with experts

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Back to Top

Table 14. Gastrointestinal Diseases Priorities

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
Gastroesophageal reflux	Metoclopramide		Dosing, safety, efficacy in neonates and infants	At the Foundation for the NIH; memo to file pending

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Back to Top

Table 15. Renal Diseases Priorities

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
Chronic kidney failure	Devices used in dialysis			Consulting with experts

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Back to Top

Table 16. Rheumatologic Disorder Priorities

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
Connective tissue disorders	Hydroxychloroquine			Consulting with experts

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Back to Top

[i] On-patent drugs are referred to the Foundation for the NIH (FNIH) if the FDA has issued a Written Request, the New Drug Application (NDA) holder has declined to conduct the requested studies, and the FDA determines there is a continuing need for pediatric use information. Subsequently, NICHD may choose to perform the studies.
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