Overview
BPCA-Sponsored Projects

Best Pharmaceuticals for Children Act

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Overview of the Best Pharmaceuticals for Children Act (BPCA) Program and the Prioritization Process

Overview of the status of BPCA clinical trials

Update on labeling changes
“Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research on microorganisms and animals, clinical trials on humans, and may include the step of obtaining regulatory approval to market the drug”.

Wikipedia.com accessed 11/8/15
# History of Pediatric Drug Development

<table>
<thead>
<tr>
<th>Date</th>
<th>Legislation and Guidelines</th>
<th>Background Information</th>
</tr>
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<tbody>
<tr>
<td>1902</td>
<td>The Biologics Control Act</td>
<td>Enacted following the death of 22 children from tainted anti-toxins</td>
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<td>1938</td>
<td>Federal Food, Drug and Cosmetic (FD&amp;C) Act: Drugs must be safe</td>
<td>Enacted after 100 deaths, many in children, after use of Elixir Sulfanilamide</td>
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<td>1962</td>
<td>Kefauver-Harris Amendments to FD&amp;C Act</td>
<td>Following the thalidomide tragedy in Europe, the amendments required proof of effectiveness data</td>
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<td>1962</td>
<td>FD&amp;C Act Amended</td>
<td>The amendment also stated that drugs not tested in children should not be used in children</td>
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<td>1974</td>
<td>American Academy of Pediatrics (AAP) Committee on Drugs Guidelines</td>
<td>Issued for evaluating drugs for pediatric use</td>
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<td>1977</td>
<td>AAP Ethical Guidelines</td>
<td>Issued for ethical conduct in pediatric studies</td>
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<tr>
<td>1979</td>
<td>Rule</td>
<td>FDA requires sponsors to conduct pediatric clinical trials before including pediatric information in the labeling</td>
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<td>1990</td>
<td>Workshop</td>
<td>Institute of Medicine holds workshop regarding the lack of labeling for pediatric drugs</td>
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<td>1992</td>
<td>Pediatric Labeling Rule proposed</td>
<td>FDA proposes labeling rule and the extrapolation of efficacy from other data</td>
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<td>1994</td>
<td>Final Rule on Pediatric Labeling</td>
<td>Formalizes extrapolation of efficacy. Manufacturers to update labeling if pediatric data existed. However, it allowed a disclaimer to the labeling of drugs not evaluated in children</td>
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<td>1994</td>
<td>Pediatric Plan</td>
<td>To encourage voluntary development of pediatric data</td>
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<td>1997*</td>
<td>Food and Drug Administration Modernization Act (FDAMA)</td>
<td>Creates pediatric exclusivity provision (voluntary); provides 6-months exclusivity incentive</td>
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<td>1998</td>
<td>Pediatric Rule (mandatory)</td>
<td>Products are required to include pediatric assessments if the drug is likely to be used in a “substantial number of pediatric patients” (50,000) or it may provide a “meaningful therapeutic benefit”</td>
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<tr>
<td>2002</td>
<td>Pediatric Rule</td>
<td>Declared invalid by D.C. Federal Court; the rule exceeded FDA’s authority</td>
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<tr>
<td>2002</td>
<td>FDAMA reauthorized as the Best Pharmaceuticals for Children Act (BPCA)</td>
<td>Maintains 6-month exclusivity added to patent life of the active moiety; Creates Office of Pediatric Therapeutics; Mandates pediatric focused safety reviews</td>
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<td>2003</td>
<td>Pediatric Research Equity Act (PREA)</td>
<td>Re-establishes many components of the FDA’s 1998 pediatric rule. Orphan products are exempted</td>
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<td>2007</td>
<td>FDA Amendments Act (FDAAA)</td>
<td>Reauthorizes BPCA and PREA for 5 years; Pediatric review committee (PeRC) formed; Studies submitted will result in labeling. Negative and positive results of pediatric studies will be placed in labeling.</td>
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<tr>
<td>2012</td>
<td>FDA Safety and Innovation Act (FDASIA)</td>
<td>Legislation makes permanent BPCA* and PREA</td>
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What is BPCA?
A Marriage made in Congress

FDA
- The purpose of the legislation was to encourage the pharmaceutical industry to perform pediatric studies to improve labeling for on-patent drug products used in children in exchange for an additional six months patent exclusivity.

NIH
- And for the NIH to sponsor needed studies of important off-patent drug products in cases where the pharmaceutical company (likely a generic manufacturer) would decline to perform the studies.
PRIORITIZED THERAPEUTICS

PRIORITIZATION PROCESS

PUBLIC INPUT ON THERAPEUTIC GAPS

EMERGING SAFETY CONCERNS

National Institutes of Health (NIH)
Processes for BPCA
NIH Processes for BPCA

Prioritization

Medication Use Data Collections

Biomarkers and Outcome Measures Research

Clinical Trials Design

Clinical Trials Performance
BPCA Process Goals

Labeling (dosing, safety, efficacy)

Outcomes (innovative trial designs, training, basic research)

Improved Pediatric Therapeutics

Publications

Eunice Kennedy Shriver
National Institute of Child Health and Human Development
BPCA Prioritization Process

2002: Master List of All Off-Patent Drugs that lack adequate pediatric labeling

Consider for prioritizing:
- Availability of safety/efficacy data
- Are additional data needed?
- Will new studies produce health benefits?
- Reformulation?

Consultation with experts in pediatric practice and research

Develop, prioritize, publish an Annual List of Drugs
Consider for prioritizing:

- Therapeutic gaps
  - Frequency of condition
  - Frequency of med use
- Potential health benefits of research
- Adequacy of necessary infrastructure

Consultation with experts in pediatric practice and research

Develop, prioritize, publish an Annual List of Therapeutic Areas and Specific Needs
Consider for prioritizing:
- A well-defined process
- To identify therapeutic gaps
- To determine feasibility
  - Need for additional data
  - Utilizing Existing data
  - Existing infrastructure

Develop, prioritize, publish a List of Therapeutic Areas and Specific Needs

Regular consultation with experts in pediatric practice and research

2012
BPCA Process for Effecting Label Change

1. Prioritization
2. Written Request/PPSR
3. Clinical Trial
4. Data Submission to FDA
5. Label Change
BPCA Progress to Date

- Thus far, BPCA activities have produced **seven label changes** to date to improve pediatric labeling (dosage, safety, and/or efficacy information).
  - The first label change based on epidemiology work by the NICHD is **Propylthiouracil**.
  - **Pralidoxime** was relabeled in September 2010
  - **Sodium nitroprusside** was relabeled for children in December 2013
  - **Meropenem** was relabeled for intra-abdominal infections in December 2014.
  - We have also had our first device label approved in May 2015, the **Mercy Tape**.
  - **Lisinopril** was relabeled for use in children with renal transplants for the treatment of hypertension in April 2016.
  - **Lorazepam** was relabeled in June 2016.
BPCA Progress to Date

• ~100 drugs/therapeutics and 46 conditions/indications prioritized
• 15 off-patent and 9 on-patent Written Requests received
• 7 Proposed Pediatric Study Requests (PPSRs) submitted to FDA.
• ~30 clinical trials funded to date. Clinical Study Reports (CSRs) for ten of these trials have already been submitted to and reviewed by the FDA for a labeling change.
Status of Clinical Trials
Legacy studies
Nitroprusside

- NIH Priority Area: Intensive Care

- PK, PD, safety and efficacy study of the hypotensive effect of nitroprusside in children requiring blood pressure reduction to reduce blood loss during surgery.

- Studies completed. The results of these trials led to multiple labeling changes for the pediatric use of nitroprusside in December 2013.

- FDA Docket number: FDA-2012-N-0284.
Meropenem

- NIH Priority Area: Neonatal Infections
- Safety, efficacy, PK study of meropenem in neonates with abdominal infections
- Study completed. The results of this trial led a label change for meropenem for intra-abdominal infections in neonates in December 2014.
- FDA Docket number: FDA-2011-N-0918
Lorazepam for Status Epilepticus

- NIH Priority Area: Seizures

- Safety, efficacy, pharmacokinetics/pharmacodynamics (PK/PD) study in children the emergency setting (under an Exception from Informed Consent) comparing lorazepam and diazepam.

- Studies completed. The results of these trials led to a label change in June 2016.

- FDA Docket number: FDA-2015-N-3037
NIH Priority Area: Pediatric Bipolar Disease

PK, Safety, and efficacy study of lithium in children with bipolar illness.

Studies completed. Study results submitted to the FDA in 2010 (for study 1) and November 2015 (for study 2). Final CSR under review.
Hydroxyurea

- NIH Priority Area: Sickle Cell Anemia
- National Heart, Lung, and Blood Institute (NHLBI) study of efficacy, safety, PK of hydroxyurea in young children with sickle cell disease
- Study unblinded January 2010 and Draft CSR submitted to FDA in May 2015. Final data submission to FDA pending.
Lorazepam for Sedation

- NIH Priority Area: Intensive Care
- Safety, efficacy, pharmacokinetics/pharmacodynamics (PK/PD) study in children on mechanical ventilation in the intensive care unit (ICU) comparing lorazepam and midazolam.
- Study completed. Study data to FDA pending.
Baclofen

- NIH Priority Area: Cerebral Palsy
- Safety, PK/PD study of oral baclofen to reduce spasticity in children with cerebral palsy
- Study results submitted to the FDA in 2014. No label change anticipated at this time.
Dopamine

- NIH Priority Area: Neonatal hypotension
- Co-fund with Neonatal Research Network to determine feasibility of larger efficacy/safety trial of dopamine to treat hypotension in neonates.
NIH Priority Area: Pediatric Cancers

Vincristine (VCR): Studies to evaluate neurotoxicity, PK in children (National Cancer Institute [NCI]-Children’s Oncology Group [COG]). Results pending.

Actinomycin-D (Act-D): Studies to evaluate hepatotoxicity/venoocclusive disease (VOD), PK in children (NCI-COG)

- Study 1: data extraction of National Wilms Tumor Study database for toxicity (completed)
- Study 2: catheter-clearing experiments (completed)
- Study 3: PK modeling of published VCR, Act-D data to design prospective PK study (completed)
- Study 4: prospective PK study
- Recruitment completed, data analysis ongoing
NIH Priority Area: Pediatric Cancers

**Methotrexate**: Clinical studies to evaluate neurocognitive outcomes of pediatric patients with high risk acute lymphoblastic leukemia (NCI-COG)
- Relationship of neurocognitive testing to diffusion tensor imaging-magnetic resonance imaging (DTI-MRI)
- Longitudinal and cross-sectional

**Daunomycin**: Disposition and response in relation to body mass index (BMI)

Results from both studies undergoing data analysis.
Isotretinoin: Proposed Pediatric Study Request (PPSR)

- NIH Priority Area: Pediatric Cancers

- Isotretinoin
  - Discussion at Pediatric Subcommittee of the Oncologic Drug Advisory Committee
    - Labeling for neuroblastoma (new indication)
    - Formulation
  - Written Request issued by the FDA, declined, received by the NIH
  - Primary data received from COG
  - Clinical Trials Agreement for formulation in review
  - In 2014, a draft CSR for isotretinoin for use in treating neuroblastoma was submitted. Further analyses pending.
NIH Priority Area: Biodefense Research

FDA Approves Pediatric Use of Chemical Poisoning Treatment

By U.S. Food and Drug Administration
Published: 2010-09-09

The U.S. Food and Drug Administration has approved the pediatric use of Protopam Chloride (pralidoxime chloride), a drug used to treat poisoning by organophosphate pesticides and chemicals (e.g., nerve agents).

“It can be difficult to use IV drugs in children, particularly in emergency situations, so having the new option of IM injection may help health care professionals use this medicine quickly and accurately,” said Dianne Murphy, M.D., director of the FDA’s Office of Pediatric Therapeutics.

Protopam Chloride was approved by the FDA in 1964 to treat various types of pesticide and chemical poisoning in adults. The drug works as an antidote to pesticides and chemicals of the organophosphate class by slowing the attachment of the chemical to nerve endings.
NIH Priority Area: Endocrine Diseases

“The PTU problem came to attention at a Eunice Kennedy Shriver National Institute of Child Health [and Human Development] (NICHD)-sponsored workshop on October 28, 2008. Based on epidemiology and adverse event data presented, it was estimated that the risk of PTU-related liver failure leading to liver transplantation or death was about 1 in 2,000 treated children. Ten-fold more children were estimated to sustain reversible liver damage.”
FDA is notifying healthcare professionals of the risk of serious liver injury, including liver failure and death, with the use of propylthiouracil in adult and pediatric patients.

Reports to FDA’s Adverse Event Reporting System (AERS) suggest there is an increased risk of hepatotoxicity with [propylthiouracil] when compared to methimazole. Although both propylthiouracil and methimazole are indicated for the treatment of hyperthyroidism due to Graves’ disease, healthcare professionals should carefully consider which drug to initiate in a patient recently diagnosed with Graves’ disease. Physicians should closely monitor patients on propylthiouracil therapy for symptoms and signs of liver injury, especially during the first six months after initiation of therapy. Propylthiouracil and methimazole were approved in 1947 and 1950, respectively.

FDA has identified 32 AERS cases (22 adult and 10 pediatric) of serious liver injury associated with propylthiouracil use. Of the adult cases, 12 deaths and 5 liver transplants occurred. Among the pediatric patients, 1 case resulted in death and 6 in liver transplants.
“Physicians should closely monitor patients on propylthiouracil therapy for symptoms and signs of liver injury, especially during the first six months after initiation of therapy. Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of methimazole, and there are no other treatment options available.”
Status of Clinical Trials
Ongoing studies
Infrastructure

- Lessons learned from legacy trials: Need for infrastructure for all aspects of pediatric clinical trials performance
  - Management (site performance)
  - Study design/clinical pharmacology
  - Recruitment
  - Formulations
  - Data analysis
  - Device development/validation
Pediatric Trials Network

- Awarded September 28, 2010
- Duke University
  - [https://www.fbo.gov/index?s=opportunity&mode=form&id=cf49c1b60b546914941b266295b24c84&tab=core&cview=1](https://www.fbo.gov/index?s=opportunity&mode=form&id=cf49c1b60b546914941b266295b24c84&tab=core&cview=1)

**Innovations:**
- Data Access
- Federated IRB
- Master contracts and protocols
- Multi-arm PK/PD and safety studies
- Obesity dosing
- Opportunistic studies
- Training
Lisinopril

- NIH Priority Area: Hypertension
- Open-label, PK and safety study in children 2-17 years with kidney transplant
- Final CSR submitted to FDA in December 2014. **Label change** based on study data in April 2016.
NIH Priority Area: Pediatric Devices

Observational, 2-D and 3-D Mercy TAPE weight estimation device for children ages 2-16 years

Ampicillin

- NIH Priority Area: Neonatal Infections
- Retrospective safety and PK study of doing in neonates to improve label information.
- Final CSR submitted to FDA in December 2014.
Fluconazole

- NIH Priority Area: Neonatal infections
- Randomized, double-blind, PK and safety prophylaxis treatment in preterm infants
- Final CSR submitted to FDA in July 2015. FDA review pending.
Hydroxyurea

- NIH Priority Area: Sickle Cell Anemia

- Open-label, PK/bioequivalence study of liquid hydroxyurea formulation in children 2-17 years with sickle cell anemia.

- Final CSR for PK study submitted to FDA in February 2014. Awaiting final submission of efficacy study (NHLBI Baby HUG study) for final disposition.
Clindamycin (Obesity)

- NIH Priority Area: MRSA infections
- Open-label, PK and safety study in obese children 2-17 years of age to determine dosing.
- Final CSR submitted to FDA in October 2015. Label change under review.
**Acyclovir**

- NIH Priority Area: neonatal infections
- Open-label, PK, safety study in neonates to improve dosing data in this population.
Current Studies

- Pantoprazole: PK and safety in obesity
- Methadone: PK, safety and genetics in children
- Antibiotic safety: randomized safety study evaluating 4 drugs in neonates
- Sildenafil: PK and safety in preterm infants with pulmonary hypertension
- Diuretics: PK, safety, and efficacy in preterm infants
- Caffeine: retrospective safety and dosing analysis in neonates with apnea
- Timolol: PK, safety and efficacy in infants with infantile hemangioma
Current Studies: Opportunistic Study

- NIH Priority Area: All

- Open-label, opportunistic, PK study of understudies drugs in children given as part of standard of care

- Approximately 2000 children enrolled

- Approximately 40 clinical sites including the U.S., Singapore, Israel, U.K, Canada
Additional Data Collections to Inform Clinical Trial Design
NICHD co-funded research with the Prematurity and Respiratory Outcomes Program (PROP)

Data collection of drugs used in the neonatal ICU and following discharge for treatment of bronchopulmonary dysplasia.
Asthma Data Collection

- Collaborative Pediatric Critical Care Network data collection on medication use in children in the pediatric ICU with status asthmaticus.

- Purpose: to determine the use of medications in status asthmaticus, in order to generate hypotheses that could be tested in a clinical trial.
Data collection on the use of asthma and psychotropic medications used in children in the general pediatric setting utilizing electronic health records (eHR).
Outcome Measures to Inform Clinical Trial Design
Clinical and Translational Science Awards (CTSA)

- Need for outcome measures
  - Neonatology
  - Cardiovascular medicine
  - Neurology
Snapshot of BPCA Projects
(18 recommended for funding)

Topic areas: 8 neonatology, 5 neurology, 4 hypertension/hypotension, 3 “other”; >1 topic area possible

1. Duke: Development of a PK algorithm to improve neonatal outcomes
2. UTHSC: Advanced MRI to assess neonatal care and outcome
3. Columbia: Targets and barriers for hydroxyurea use in sickle hemoglobinopathies
4. Utah: Improving management of the neonatal abstinence syndrome
5. U Pitt: Cardiac outcome measures for pediatric muscular dystrophy
6. UNC: Outcome measures for chronic lung disease of prematurity
7. U-CO: Small volume fentanyl PK/PD & PG in neonates
8. UC-Davis: Outcome measures for trials in children with autism
9. Vanderbilt: Wireless home-based tools for studying sleep in autism
10. U-MI: Pediatric Cardiac Intensive Care Data Standards Repository
11. Stanford: Methadone vs. morphine PD/PD in infants after cardiac surgery
12. Indiana: Predictors of vincristine-induced peripheral neuropathy
13. UAB: Nasal potential difference studies utilizing CFTR modulators
14. CWRU: Efficacy outcomes measures in antihypertensive trials in children
15. CWRU: Effect of BMI on exposure-response relationships to lisinopril in children
16. U-Wash: Advancing patient reported outcomes (PROs) in children with cystic fibrosis
17. AECOM: Pediatric hypertension outcome measures
18. Tufts: Improving BPD predictors and outcomes for clinical trials
Methylphenidate and amphetamine do not induce cytogenetic damage in lymphocytes of children with ADHD.

■ RESULTS: Sixty-three subjects enrolled in the study; 47 subjects completed the full 3 months of treatment, 25 in the methylphenidate group and 22 in the amphetamine group. No significant treatment-related increases were observed in any of the three measures of cytogenetic damage in the 47 subjects who completed treatment or the 16 subjects who did not.

■ CONCLUSIONS: Earlier findings of methylphenidate-induced chromosomal changes in children were not replicated in this study. These results add to the accumulating evidence that therapeutic levels of methylphenidate do not induce cytogenetic damage in humans.
NIH-FDA Formulations Platform

- Interagency Agreement with FDA 2010–2011
- Goal: To develop an open-source, technically feasible platform based on chemical structure, to produce orally dissolvable solid dosage forms that are stable at high temperatures/humidity, taste-masked, with good oral absorption, in suitable dosage increments, with minimal excipients
Final Thoughts...
Work in Progress

- New innovative clinical trials under the PTN
- Use of formulations platform to provide open-source information to manufacturers
- Developing new platforms for improvements in areas such as outcome measures, biomarkers research, and clinical pharmacology training
- Synthesis and analysis of all BPCA clinical trials data
Frequently Asked Questions

- Will the Listing Process continue?
  - Yes, the listing process will continue but on a more focused scale.

- How will the prioritization process work with the PTN?
  - Recommendations for prioritized therapeutic areas and drugs will be further prioritized by the PTN for feasibility and other considerations.

- How can I participate in the PTN?
  - If you are interested in participating in pediatric research studies being conducted under the PTN, please visit the [BPCA Web site](#) and the [PTN Web site](#) for additional information.

- Is the PTN the only way clinical trials will be performed?
  - Yes, drug trials will be done through the PTN. However, NICHD will continue to collaborate with other NIH Institutes and Centers and with other government agencies to improve the knowledge in pediatric therapeutics.