

DRAFT: NOT FOR DISTRIBUTION

TABLE OF CONTENTS

EXECUTIVE SUMMARY	1
BACKGROUND ON PHARMACOLOGY, DRUG RESEARCH, AND THE BRANCH	2
PEDIATRIC PHARMACOLOGY	5
ACTIVITIES OF THE PPRU NETWORK.....	6
ACTIVITIES RELATED TO THE BPCA.....	8
OTHER BRANCH EFFORTS IN PEDIATRIC PHARMACOLOGY	13
OBSTETRIC PHARMACOLOGY	17
ACTIVITIES OF THE OPRU NETWORK	17
OTHER BRANCH EFFORTS IN OBSTETRIC PHARMACOLOGY	20
FUTURE DIRECTIONS FOR THE BRANCH.....	21
PANEL DISCUSSION.....	21
CONTINUE SUPPORT OF INVESTIGATOR-INITIATED RESEARCH TO ADDRESS THE KNOWLEDGE GAPS IN OBSTETRIC AND PEDIATRIC PHARMACOLOGY	23
PROMOTE TRAINING OF NEW INVESTIGATORS IN OBSTETRIC AND PEDIATRIC PHARMACOLOGY	25
INCORPORATE NEW TECHNOLOGY DEVELOPMENTS INTO OBSTETRIC AND PEDIATRIC PHARMACOLOGY	26
FIGURES AND TABLES	FIGURES AND TABLES-1
APPENDIX A: BRANCH PERSONNEL.....	APPENDICES-1
APPENDIX B: BEST PHARMACEUTICALS FOR CHILDREN ACT (BPCA) STUDIES.....	APPENDICES-4
APPENDIX C: BPCA DRUG PRIORITIZATION LIST	APPENDICES-6
APPENDIX D: BRANCH-SUPPORTED MEETINGS, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007.....	APPENDICES-7
APPENDIX E: MEMBERS OF THE EXPERT PANEL	APPENDICES-9
APPENDIX F: BRANCH PUBLICATIONS, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007.....	APPENDICES-10

DRAFT: NOT FOR DISTRIBUTION

EXECUTIVE SUMMARY

Mike Leavitt, current Secretary of the U.S. Department of Health and Human Services (DHHS), explained the underlying motivation for the Obstetric and Pediatric Pharmacology Branch (OPPB), January 19, 2005, when he stated: “When we are alone at night caring for a sick child, we trust [the Department] to ensure that the medicine we give her is effective.”

The OPPB was established in May 2004 within the Center for Research for Mothers and Children (CRMC) of the National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH). The Branch was created to centralize research, clinical trials, and drug development activities for pediatric and obstetric pharmacology within a single organizational entity, in a fashion that complemented the long-standing and highly successful clinical trials work of the NICHD-supported Maternal-Fetal Medicine Unit (MFMU) Network and the Neonatal Research Network (NRN). The Branch combined investigator-initiated research and training with the activities of the Pediatric Pharmacology Research Units (PPRU) Network and those related to the Best Pharmaceuticals for Children Act (BPCA) with efforts within the newly formed Obstetric-Fetal Pharmacology Research Units (OPRU) Network.

The overarching goal of the Branch is to provide a research focus—based on cross fertilization of clinical, translational, and scientific expertise—to promote new research in basic and translational pharmacology with a focus on pregnant women and children. At the same time, the Branch is intended to be reactive to emerging issues by providing mechanisms that allow faster initiation of studies to address critical research questions.

In addition to its role in centralizing pediatric and obstetric pharmacology efforts, the NICHD leadership designed the Branch to:

- Identify, prioritize, and sponsor basic, translational, and clinical research and research strategies to improve understanding of interactions between therapeutics, disease, pregnancy, and development.
- Facilitate training and other educational modalities that enhance pediatric and obstetric pharmacology expertise, as well as skills in reproductive, perinatal, and pediatric epidemiology.

Throughout its first two years, the OPPB initiated a clinical research program to meet the congressional mandates set forth for the BPCA, while building on existing research programs in obstetric and pediatric pharmacology. These activities also helped to identify knowledge gaps in areas of pediatric pharmacology and, subsequently, similar knowledge missing from obstetric pharmacology. Multiple other challenges—including feasibility, ethics, and study design—also had to be dealt with before some of the Branch’s more complex, multi-stage clinical trials could begin.

DRAFT: NOT FOR DISTRIBUTION

Because the Branch is a relatively new entity within the NICHD, its goals and portfolio are still evolving as new areas of need are identified in pediatric and obstetric pharmacology research and training. Nevertheless, the Branch has made significant progress toward achieving many of its initial goals. This report summarizes the productivity of the Branch-supported Networks and grants, as well as the successful implementation of current initiatives.

In addition, this report highlights the Branch's efforts to identify future strategic directions and to implement evolving goals to advance pediatric and obstetric pharmacology. Specifically, the Branch intends to build upon the foundations that the NICHD has fostered in obstetric and pediatric pharmacology since the 1970s through renewed efforts of the PPRU Network, through research conducted by the OPRU Network and BPCA activities, through training opportunities, and through investigator-initiated research. With guidance from an expert panel, which met in July 2007, the OPPB also identified several substantive areas that require increased emphasis, including (but not limited to) investigator-initiated research into therapeutics, an increased emphasis on obstetric pharmacology research, and training grants to develop new obstetric and pediatric pharmacologists. A discussion of these and other key areas for future research is available in the [Future Directions for the Branch](#) section of this report.

BACKGROUND ON PHARMACOLOGY, DRUG RESEARCH, AND THE BRANCH

All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy.

Paracelsus (1494-1541), considered the “father of pharmacology”¹

Pharmacology is the scientific study of drugs and their effects, especially in the treatment of disease. For a drug to be effective, it must be present in the body at an appropriate concentration, meaning it must be properly absorbed, distributed, metabolized, and then eliminated—a process called *pharmacokinetics*. Similarly, an effective drug must be able to reach its appropriate target and produce the desired effect by relying on biochemical and physiological interactions between the drug and the body—a process called *pharmacodynamics*.

Through the study of pharmacokinetics and pharmacodynamics, advances in pharmacology have introduced new opportunities to treat diseases and improve health. These advances have also led to a new field of pharmacology—called *pharmacogenomics*—that relates drug effect to specific genetic patterns. Understanding how genetics contributes to variability in drug response provides a new tool for effectively using therapeutics and offers hope of decreasing the risk for unexpected toxicities.

Developmental aspects of drug disposition and response have largely been excluded from pharmacology research. The changing nature of immature organisms adds complexity to pediatric and obstetric pharmacology research and requires a systems-biology approach to fully

¹ Kearns, G. L., S. M. Abdel-Rahman, et al. (2003). Developmental pharmacology - Drug disposition, action, and therapy in infants and children. *New England Journal of Medicine*, 349(12), 1157-1167.

DRAFT: NOT FOR DISTRIBUTION

understand the inter-relationships of the variables involved. The lack of knowledge in the field has been borne out by medication disasters, such as administration of chloramphenicol to newborns who lacked mature metabolic pathways and developed cardiovascular collapse, or who were exposed *in utero* to teratogens, such as retinoic acid and angiotensin-converting enzyme inhibitors and suffered the resultant anomalies.

Since its establishment, the National Institute of Child Health and Human Development (NICHD) has been the key sponsor of maternal and pediatric research at the National Institutes of Health (NIH). The Pregnancy and Perinatology Branch, in the Center for Developmental Biology and Perinatal Medicine, supports two Networks in related areas: the Maternal-Fetal Medicine Units (MFMU) Network, which was formed in 1986 to focus on clinical questions in maternal-fetal medicine and obstetrics, particularly with respect to the continuing problem of preterm birth; and the Neonatal Research Network (NRN), also formed in 1986, which performs multicenter clinical trials in neonatal medicine in order to reduce infant morbidity and mortality and to promote healthy outcomes.

Because the NICHD had an important stake in the safety and efficacy of drugs used in children, the Institute leadership decided to go beyond its existing commitment and regulations to address gaps in information about the pharmacokinetics, safety, and efficacy of drugs used in pediatric patients. The NICHD established the Pediatric Pharmacology Research Units (PPRU) Network within its Center for Research for Mothers and Children (CRMC) in 1994 to conduct clinical trials and related translational research in pediatric therapeutics. The Network not only sought answers to key questions about pediatric drugs, but it also established and improved the infrastructure for such research, which would facilitate and promote pediatric labeling of drugs. For more information on the Network's activities and progress, see the [Activities of the PPRU Network](#) section of this document.

The PPRU also brought the issue of pediatric pharmacology research to the attention of the pharmaceutical industry. In addition to conducting studies, the PPRU also: provided a locus for pre- and post-marketing clinical trials in children by pairing pediatric clinical pharmacologists with the pharmaceutical industry and contract research organizations; served as an advisory body between the pharmaceutical industry, regulatory agencies, health professionals, and the public on the appropriate use of drugs in children; encouraged and identified areas for research beyond the Network's activities; served as a resource for training health care providers and other professionals; and created opportunities for fellows, medical students, and residents to obtain relevant training. Through the PPRU's more than 10 years of projects, the NICHD helped to establish pediatric pharmacology as a scientific discipline and revolutionized how such studies were conducted.

In 1997, the Food and Drug Administration Modernization Act (FDAMA) permitted the U.S. Food and Drug Administration (FDA) to grant six months of additional market exclusivity to companies that conduct pediatric studies to help encourage the pharmaceutical industry to seek pediatric labeling for its products. At the same time, the FDA adopted an administrative rule to require that holders of New Drug Applications include information on testing in children. The "Pediatric Rule" was struck down in court, but was subsequently enacted by congress as part of the Pediatric Research Equity Act.

DRAFT: NOT FOR DISTRIBUTION

In 2002, the Best Pharmaceuticals for Children Act (BPCA) directed the Secretary of Health and Human Services, working through the Director of the NIH, to establish a program for pediatric drug testing and development. The NIH Director selected the NICHD to implement this new program. For more information on the Act, see the [Activities Related to BPCA](#) section of this report. Once the NICHD received the delegation of authority, it immediately began planning to establish the Obstetric and Pediatric Pharmacology Branch (OPPB).

The Branch was established in 2004 to provide an organizational focus for advancing scientific and medical understanding of safety and effectiveness of drugs used in infants, children, adolescents, and pregnant women. This focus was intended to complement existing activity throughout NICHD as well as build on the historical contributions of the institute in obstetric and pediatric pharmacology. Research topics for the Branch included: research on the nature of growth and development, such as molecular signaling that induces growth and differentiation; development of receptors and transporters and their relationship to genetic polymorphisms, mechanisms of effect (for good or bad), detoxification pathways in the human; and research on homologous pathways in young animals to facilitate extrapolation, all topics in need of dedicated basic research. Analogous areas of clinical focus included assessments of clinical trial feasibility including pharmacoepidemiology; clinical trial designs including observational study methods; and development and validation of biomarkers, non-invasive measures of drug effect and clinical assessment scales. The Branch identified the “systems” approach as the best way to improve the safety and effectiveness of pharmaceuticals, and as a way to promote new research on medications used during pregnancy and in children. A systems-biology approach would allow the field to re-assemble all the component parts into an integrated whole.

The overarching goal of the Branch is to provide a focus for the cross fertilization of clinical, translational, and scientific expertise in pediatric and obstetric pharmacology research. Among the Branch’s early objectives were the following:

- Enable safe and effective treatment of disease during pregnancy, infancy, and childhood, using pharmaceuticals that are appropriately tested within their target populations.
- Provide training that will create specialists who understand the unique qualities of these populations and develop therapies specific to their needs.
- Offer mechanisms that enable research to address emerging issues quickly, effectively, and in manners that are scientifically sound.

Among the Branch’s first activities was the establishment of the Obstetric Pharmacology Research Units (OPRU) Network, with the goal of identifying, characterizing, and studying drugs used during pregnancy. For more information on the Network, see the [Activities of the OPRU Network](#) section of this report.

In 2007, the BPCA was reauthorized with the passage of the FDA Amendments Act (P.L. 110-85), which included language on research related to biologics and pediatric medical devices and expanded the focus of BPCA activities to address a wider range of pediatric therapeutic needs, in addition to pediatric drugs.

DRAFT: NOT FOR DISTRIBUTION

The Branch's method for achieving its goal is to stimulate and fund basic, translational, and clinical research and training in pediatric and obstetric pharmacology, of which BPCA is only one aspect. (Other NIH Institutes and Centers contribute funding to BPCA-specific activities.) Since it was established, the Branch's total funding has ranged from \$29.49 million in fiscal year 2004, to \$37.08 million in fiscal year 2007 (see [Figure 1](#) and [Figure 2](#)). The primary future focus of the Branch will be to continue and expand efforts to enlarge the research portfolio.

The remainder of this document—the OPPB's first report to the National Advisory Child Health and Human Development (NACHHD) Council—highlights the Branch's accomplishments and research highlights in pediatric pharmacology and obstetric pharmacology. The Branch's training efforts in pediatric and obstetric pharmacology and in reproductive, perinatal, and pediatric epidemiology are included in the descriptions of pediatric and obstetric pharmacology.

The final section of the report, [Future Directions for the Branch](#), examines possible future research areas for the Branch and outlines strategies that will enable the OPPB to pursue its goals and mission for the next four years.

PEDIATRIC PHARMACOLOGY

Historically, pediatric pharmacology research has been hampered by a variety of issues, ranging from the absence of a financial incentive for drug companies, to unknown pharmacokinetic and pharmacodynamic differences, to ethical issues of non-therapeutic research and informed consent. As a result, nearly 80 percent of drugs lack data on appropriate dosing, efficacy, and safety for neonates, infants, children, or adolescents. Further, approximately 30 percent of new molecular entities licensed in the United States between 1998 and 2002 did not have a formulation suitable for pediatric use.

The OPPB supports a growing portfolio of efforts intended to address these concerns. The Branch supports projects in diverse areas of pediatric drug development, including animal models to evaluate toxicity, innovative research in the development of novel compounds and devices, research in pharmacoepidemiology, as well as clinical trials. Many of these efforts are conducted through the PPRU Network and through the BPCA. A listing of current PPRU sites and BPCA studies appears in [Figure 4](#) and [Appendix B](#), respectively.

The following sections highlight the Branch's activities related to pediatric pharmacology research.

ACTIVITIES OF THE PPRU NETWORK

Since its establishment, the NICHD has encouraged and supported research in pediatric pharmacology. That support has continued through to the present with research on topics such as pediatric AIDS, and through networks, such as the PPRU Network and the NRN. The PPRU Network, established in 1994, currently includes 13 sites (see [Figure 4](#)) whose overarching goal is to determine how childhood development affects drug disposition, response, and the interplay between drug, development, and disease. As mentioned earlier, the PPRU Network helped not only to bring the issue of pediatric pharmacology research to the attention of industry, but also changed the way pharmacology research is conducted in pediatric populations.

Network researchers perform a variety of studies, including (but not limited to) pharmacokinetic studies (phases 1 and 2 of drug development), pharmacokinetic-pharmacodynamic investigations, studies of trial design, studies of drug metabolism, and pharmacogenetics evaluations. Therapeutic areas studied by the PPRU sites include interventions for common disorders (i.e., allergies, asthma, and upper respiratory infections) and for less common disorders (i.e., cystic fibrosis, severe infections, HIV/AIDS, and sickle-cell anemia).

In addition, although the Network includes studies across all age groups, the unique experience and qualifications of its investigators enables PPRU studies to include children younger than two years of age, including a number of studies in the newborn—an area of pediatric research that has been historically neglected, but is better served now by the PPRU, the NRN and the OPPB-led Neonatal Drug Development Initiative (NNDI); see the [Research in Special Populations](#) section of this document and [Appendix D](#) for more information.

Network accomplishments include the following:

- Total enrollment of patients (1994 through June 2007) = 9,292
- Total studies performed (1997 through June 2007) = 264, including 161 designed/co-designed by an industry sponsor, and 103 designed by investigators
- Journal articles published = 621; this number includes articles on the following topics:
 - o Basic/translational: 27.5 percent
 - o Pharmacokinetics: 38.5 percent
 - o Pharmacodynamics: 1.0 percent
 - o Animals: 9.2 percent
 - o Clinical trials: 23.2 percent
 - o Antibiotic resistance: 0.3 percent
 - o Study design: 0.3 percent
- The Network has contributed to pediatric labeling of 23 drugs.
- The Network has trained 77 pediatric clinical pharmacology fellows, including 52 M.D.s, five Ph.D.s, three M.D./Ph.D.s, 16 Pharm.D.s, and one Ph.D. candidate.

Recent PPRU Network efforts include the following:

- Studying children with *atopic dermatitis* to define a basis for the significant variability in response to antihistamines
- Using new imaging techniques for non-invasive approaches to assess gastric emptying

DRAFT: NOT FOR DISTRIBUTION

- Evaluating early pharmacotherapy for autism using buspirone, guiding the therapies with biomarkers of disease, and measuring responses with positron emission tomography (PET) scan
- Conducting multicenter pharmacokinetic studies of the use of the antifungal medicine, fluconazole, and other antimicrobials in preterm newborns to assess how gestational and postnatal age, kidney function, surgery, and concomitant medications impact drug disposition
- Developing population pharmacokinetic/pharmacodynamic models to assess the effects of polymorphisms in drug-metabolizing enzymes on drug clearance and adverse event profiles, which could allow for personalized dosing and improved patient outcomes
- Developing and evaluating the use of nanotechnology, such as drug dendrimers, which are complexes for targeted drug delivery for treatment of diseases, while taking into account recent findings that indicate drug-dendrimer complexes enter cells more rapidly than do parent drugs
- Developing initiatives to identify and evaluate the determinants of inter-individual differences in response to opioids across the age spectrum to aid development of acute and chronic pain models of disease for neonates and children
- Creating a warehouse of standardized clinical, pharmacogenetic, and pharmacokinetic, and pharmacodynamic data that will allow for simulation modeling, data mining, and trend analysis and will assist in identifying and qualifying safety biomarkers that can be used in designing clinical trials and in monitoring post-marketing safety

When the PPRU was developed in 1994, its main focus was enhancing the infrastructure available for research related to pediatric drug development. Those activities have been highly successful. Such studies focus on the effect and disposition of drugs to treat disease processes and comprise the traditional types of studies that the PPRU Network has conducted. Take the case of CYP2D6—a prime example of a clinically relevant drug-metabolizing enzyme for which genotyping and phenotyping information, resulting from PPRU Network studies, has the potential to improve drug safety and efficacy. CYP2D6 is involved in the biotransformation of more than 40 therapeutic entities, including Selective Serotonin Re-uptake Inhibitors (SSRIs), atomoxetine, risperidone, codeine, and dextromethorphan, which are commonly used in pediatric populations. Considerable variability in *CYP2D6* gene expression and activity results from more than 60 well known genetic polymorphisms.

From a developmental perspective, *in vitro* studies indicate that very limited CYP2D6 activity is present in the fetal liver (at approximately 1 percent of adult values), but that CYP2D6 protein is detectable in all liver samples from newborns. During the first 28 days of life, both CYP2D6 protein and catalytic activity progressively increase to 20 percent of the activity observed in adults. In contrast, *in vivo* results, derived from a PPRU Network longitudinal phenotyping study of more than 100 infants during the first year of life, suggest that the CYP2D6 phenotype is concordant with genotype by two weeks of age (Blake et al. *Clinical Pharmacology and Therapeutics*, 81[4], 510-516). Phenotyping data from older children suggest that CYP2D6 catalytic activity in children is comparable to adults by at least 10 years of age, and probably much earlier.

DRAFT: NOT FOR DISTRIBUTION

Understanding the relationship between *CYP2D6* genotype, phenotype, and drug clearance is as important clinically for pediatrics as it is for adults. Evidence from several sources suggests that drug accumulation and the risk of concentration-dependent toxicities are clearly associated with significant morbidity and mortality in children. *CYP2D6* and possibly developmental or pharmacogenetic factors (or both) could contribute to the increased risk of serious toxicity in this age group.

To ensure that the PPRU Network continues to meet the needs of the pediatric pharmacology research community, the Network is going through a strategic planning process. Consultations with experts in the field suggest that the Network's efforts may be more beneficial if aimed at pediatric therapeutics, which relates diseases or conditions to therapy and includes evaluating the need for treatment. This new emphasis of the PPRU Network is exemplified by a recent study of scalp ringworm disease.

Trichophyton tonsurans is the most common cause of *tinea capitis* in the United States, and its natural history has not yet been determined. Scalp ringworm disease is different in preschoolers and is associated with chronic background colonization and periodic symptomatic disease that improves spontaneously. To learn more about this phenomenon and how it affects treatment, researchers followed 446 children at a single preschool (for children age two years) and collected samples of *T. tonsurans* isolates for genotyping.

In older children, *T. tonsurans* carriage rate is low and symptoms occur at the time of fungal infection; treatment with antifungal drugs is standard practice in such cases. The researchers found that the natural course of the disease in preschoolers was different. The preschoolers had a high *T. tonsurans* background carriage rate. Further, symptoms occurred at any time and were unrelated to acquisition of infection or particular strain types, meaning that treatment with antifungal drugs is unnecessary and ineffective in this population (Abdel-Rahman et al. [2006]. *Pediatrics*, 118, 2365-2373).

Building on the successes of the Network will require critical evaluation of the basic and translational needs in pediatric drug development and represents the first step in an analysis being conducted by OPPB to determine the Network's next investment in pediatric drug research.

ACTIVITIES RELATED TO THE BPCA

In 2002, the NIH Director delegated the NICHD to lead its activities related to the BPCA. The original legislation for BPCA outlined the following tasks: identifying and prioritizing drugs that need study; developing studies in collaboration with experts at the NIH, the FDA, and other organizations; and conducting studies on priority drugs after manufacturers decline to do so.

Since that time, the NICHD (in collaboration with 17 participating Institutes and Centers) has worked closely with the FDA and other organizations to create an authoritative list of off-patent drugs (those without marketing protections or exclusivity) as the first step in the process of prioritizing drugs for study in children.

DRAFT: NOT FOR DISTRIBUTION

Within NIH, the prioritization process involves a number of steps:

- *Identifying an off-patent drug.* Although the process for developing an authoritative listing of off-patent drugs has presented challenges, there has been significant progress. Since 2003, drugs placed on the Priority List have been published in the *Federal Register*. (See [Appendix C](#) for the list.)
- *Determining relevant indications for the drug in pediatric populations.* In prioritizing off-patent drugs for study in pediatric populations, careful attention was given to the identification of relevant diseases and conditions that affect children. The NICHD evaluated data on the use of certain drugs in adults to identify those of potential value to children, resulting in the potential indications or diseases for study in children (note that some of these diseases are unique to children).
- *Reviewing available data about use of drugs in children.* For each drug, the Branch reviewed and evaluated data describing how the drug is used, its pharmacokinetics in children, and its safety and effectiveness to determine the nature of pediatric testing needed. For diseases/conditions in children that did not have comparable diseases/conditions in adults (or the disease or condition does not occur in adults), the branch evaluated the scientific literature to determine if the drug was likely to be beneficial for pediatric populations.

Once these steps are completed, the OPPB begins studies to gather data related to using the drugs in pediatric populations. Some of the studies the Branch is supporting include the following:

- Pre-clinical studies (in animals or cell culture) determine the metabolic pathways and pharmacokinetic and pharmacodynamic properties of a drug. Although pre-clinical studies are required for all drugs approved by the FDA today, many of the drugs prioritized for study under BPCA have long been on the market, so even basic pre-clinical data are missing. For example:
 - Morphine has been available for many years. However, recent clinical studies suggest that newborn infants and especially preterm infants may have unexpected adverse responses, including an increased risk of poor neurologic outcome, when treated with morphine. The Branch is supporting basic science efforts to determine the differences in pain receptors that exist between infants and adults.
 - Similarly, although ketamine has been used for sedation of children for many years, toxicological data obtained from rodent models during the last decade have suggested that anesthetics and sedatives induce central nervous system apoptosis. The NICHD has supported extensive non-human primate studies to assess the effects of this drug on the developing brain, in an animal model similar to a young child. Current data demonstrates that non-human primates do experience windows of vulnerability to ketamine-induced apoptosis and necrosis, one significant difference from observations of rodent models. These windows of vulnerability occur shortly after birth, and sensitivity decreases substantially with increasing age following birth.
- Phase 1 studies are pharmacokinetic and safety studies and may include preliminary efficacy data if patients with the disease of interest are enrolled. All of the prioritized drugs require pharmacokinetic studies in children across developmental stages (e.g., neonate, infant, child, and adolescent). In some instances, the current tablet and capsule formulations are not appropriate; the dosage form may be difficult to swallow, or the correct dose difficult or

DRAFT: NOT FOR DISTRIBUTION

impossible to measure accurately. The development of new formulations for children or for those with specific conditions (e.g., children with cerebral palsy, infants with sickle-cell disease, and young children with neuroblastoma) is also needed.

- Phase 2 studies are small safety and efficacy studies, which employ and refine appropriate dosing as determined by Phase 1 studies. Because efficacy and safety may be dependent on age and developmental status/stage, these studies need to enroll children of various ages/age groups. For example, existing safety and efficacy data for dactinomycin (also known as actinomycin-D) from the National Cancer Institute (NCI) Children’s Oncology Group (COG) are being analyzed to determine the drug’s safety profile—specifically, the relationship of age, diagnosis, and dose of actinomycin-D to incidence of severe hepatic toxicity.
- Phase 3 clinical studies are larger, “pivotal” studies that provide a definitive assessment of the safety and efficacy of a treatment for a given condition. The Branch supports several of these studies, including (but not limited to) the following:
 - o Lorazepam is used to sedate pediatric patients in intensive care units, and to treat severe seizures in children, although it has not been tested in children for either use. The Branch supported studies to assess the dosing and metabolism of this drug in children and is now supporting clinical trials to test safety and efficacy.
 - o Nitroprusside is used to lower blood pressure to decrease the risk of bleeding during surgery. The OPPB sponsored a recently completed clinical trial of nitroprusside dose-response, safety, and efficacy. Results from the trial are expected soon.
 - o Lithium is frequently used to treat bipolar disease. Given this drug’s toxicity, it is possible that the dosage currently used in children, which is based on adult data, is too high. The Branch is currently supporting clinical trials to assess the proper safe and effective dose for children with this condition.
 - o Baclofen was introduced into clinical use more than 30 years ago and is currently used to treat spasticity in children with cerebral palsy. Despite the age of the drug and its frequent use in children, data supporting dosing, efficacy, and safety in children has not been characterized. The Branch, working with experts in pediatric neurology, pediatric pharmacology, pharmacogenomics, and occupational and physical therapy, is conducting the needed studies. In conducting these clinical studies, the Branch has had to develop a liquid formulation of the drug; the only commercially available formulation is a tablet, which difficult for children to consume, especially those with cerebral palsy.
 - o Hydroxyurea has shown great benefit in treating adults with sickle-cell disease, based on studies conducted by the National Heart, Lung, and Blood Institute (NHLBI). The Branch is partnering with NHLBI to evaluate dosing, efficacy, and safety of hydroxyurea in children younger than one year of age. Because the only form of the drug commercially available was a tablet, the NICHD-NHLBI partnership developed a liquid formulation for administering to these very young children.

Progress from BPCA Studies

Research findings for a few specific drugs provide excellent examples of the flexibility of the Branch’s activities under the BPCA and the importance of the studies it supports.

DRAFT: NOT FOR DISTRIBUTION

METHYLPHENIDATE

Methylphenidate—more commonly known as Ritalin®—is widely prescribed to children and adolescents for the treatment of attention deficit/hyperactivity disorder (ADHD). ADHD is the most commonly diagnosed behavioral disorder of childhood, and more than 5 million prescriptions for methylphenidate are written annually in the United States alone. The drug has a long record of beneficial impact on behavior, from reductions in hyperactivity and impulsivity to increases in attention and self control. Despite its benefits and its broad use among a vulnerable population, few studies have explored its long-term safety or effects.

The majority of past reports of the drug's adverse events were consistent with the drug's pharmacological mechanism, namely those related to stimulants, such as decreased appetite and sleeplessness. However, recent research has suggested that adverse events extend to several unanticipated outcomes, including genetic toxicity, sudden cardiac arrest, and issues of growth and pubertal progression.

Researchers from one 2005 study reported a significant increase in genetic damage in its sample of 12 children (ages six to 12 years) diagnosed with ADHD and treated with methylphenidate, with each child acting as his/her own control. The investigators measured the frequency of aberrations in cultured blood lymphocytes of the children before treatment began and after three months of continuous treatment, with doses ranging from 20 mg/day to 54 mg/day (El-Zein et al. [2005]. *Cancer Letters*, 230[2], 284-291). In humans, increases in chromosomal aberrations and micronuclei in cultured blood lymphocytes are associated with an increased risk of cancer.

This study raised important questions about the long-term safety of methylphenidate that experts at the NIH and the FDA took very seriously. The questions were so concerning that experts took the unusual step of asking to visit the researchers' laboratory to discuss the findings and review the data. Since then and with OPPB support, researchers have conducted a number of studies investigating the potential clastogenicity of methylphenidate. The Branch's flexibility under the BPCA enabled these studies to be conducted on a faster timeframe than is usual for federally funded studies. Thus far, the results from these and other studies are reassuring. For instance:

- Suter and colleagues reported no increases in structural or numerical chromosomal aberrations in cultured human blood lymphocytes exposed to methylphenidate at high concentrations. The authors also reported that, when they gave mice a dose of methylphenidate more than 100 times that administered to pediatric patients, the frequency of chromosomal alterations did not significantly increase, not even among bone marrow erythroblasts, a rapidly dividing cell population (Suter et al. [2006]. *Mutation Research-Genetic Toxicology and Environmental Mutagenesis*, 607[2], 153-159).
- In another study, Andreazza and colleagues measured DNA damage in brain and peripheral blood cells of juvenile and adult rats after single and repeated-dose treatments with 1 mg/kg/day, 2 mg/kg/day, or 10 mg/kg/day methylphenidate (1 mg/kg was comparable to a clinical dose of 54 mg in a 30 kg pediatric patient). The technique used permitted the researchers to detect frank strand breaks, lesions, and incomplete repair sites, as well as the frequency of micronuclei in cultured blood lymphocytes. Although the researchers reported no increase in micronucleated lymphocytes for any of the treatment groups, the authors did report increases in DNA damage in cells of the brain and peripheral blood leukocytes. In general, the levels of DNA damage were higher with repeated doses than with high doses

DRAFT: NOT FOR DISTRIBUTION

(Andreazza et al. [2007]. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 31[6], 1282-1288). Although the DNA damage in methylphenidate-treated animals might be cause for concern, the damage might result from cytotoxic rather than genotoxic effects. The lack of a concomitant increase in the frequency of micronucleated lymphocytes indicates that the damage was not converted to chromosome breaks. This finding has yet to be independently replicated.

- One study tried to replicate the results of the research that originally raised the red flags (Walitza et al. [2007]. *Environmental Health Perspectives*, 115[6], 936-940). Researchers conducting this prospective study examined the frequency of micronucleated lymphocytes in cultured blood of pediatric patients (ages five to 17 years) sampled prior to and after methylphenidate treatment for one, three, and six months. Dosages varied from 5 mg/day to 40 mg/day for immediate-release formulations, and 18 mg/day to 54 mg/day for long-acting versions. This study was also larger in size and longer in duration than the previous study. Results failed to show any significant treatment-related increases in frequencies of micronucleated cells in the pediatric patients.

Based on what is now known about the pharmacology and metabolism of methylphenidate (National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction. [2005]. NIH Publication No. 05-4473.), there is little evidence that the drug interacts with DNA by either a direct or indirect mechanism. As a result of Branch-supported activities, there is also a growing body of evidence that methylphenidate does not induce chromosomal alterations in the blood cells of experimental animals or humans treated with the drug.

METHOTREXATE

In the United States, 12,000 new cases of childhood cancer are diagnosed annually. Although, on the positive side, many of those children survive their disease, on the negative side, considerations of long-term drug toxicities are important and unknown. Methotrexate is a mainstay of pediatric leukemia treatment, but causes neurocognitive toxicity, as measured by neurocognitive testing.

The drug is administered intravenously in different ways, including as a high dose with leucovorin rescue, and to the maximum-tolerated dose without leucovorin rescue (called the “Capizzi method”). The Branch is supporting an ongoing clinical study with the NCI COG to determine which of these two regimens causes less neurocognitive damage in children who have with high-risk B-cell and T-cell acute lymphoblastic leukemia without reducing long-term survival.

SODIUM NITROPRUSSIDE

Physicians commonly need to reduce a patient’s blood pressure, such as in the operating room to reduce intra-operative blood loss, and in the intensive care unit. Clinicians have used sodium nitroprusside as a hypotensive agent for many years, but the drug lacks pediatric labeling for dosing, safety, and efficacy.

The Branch is sponsoring two clinical trials in children who are receiving sodium nitroprusside as part of routine clinical care. The goal of Study 1 is to determine the nitroprusside dose-response relationship. This randomized, blinded study of four dose levels of nitroprusside for

DRAFT: NOT FOR DISTRIBUTION

children ages birth to 17 years, who are undergoing operative procedures requiring blood pressure reduction, recently completed enrollment (n=203) following two years of recruitment. The goal of Study 2 is to determine if tachyphylaxis (loss of sensitivity to the blood-pressure lowering effect) occurs in children who receive sodium nitroprusside during long-term continuous infusions in the intensive care unit.

Challenges involved in performing these studies include time constraints related to consent, allowing time for the infusion preparation, and issues of anesthesiologists' access to surgical patients.

OTHER BRANCH EFFORTS IN PEDIATRIC PHARMACOLOGY

In addition to its studies conducted through the PPRU Network and related to the BPCA, the OPPB also supports efforts in the following areas.

Toxicity Research

The OPPB supports a number of grants that use animal models to evaluate and understand various aspects of toxicity in a developing organism. For instance, using infant rat and pregnant guinea pig models, one investigator is studying how the developing brain is vulnerable to potential neurotoxic actions of drugs during synaptogenesis (a brain growth spurt), which occurs at different times in different species. The hypothesis is that the drug suppressed neuronal activity to lower-than-normal physiological degrees, thereby disrupting synaptogenesis, which causes immature neurons to receive an internal signal for apoptosis or programmed cell death. This process is a concern because an increase in cell death in a developing brain may have consequences across the lifespan. Another investigator is evaluating the potential toxicity of stimulants on dopamine axons in the non-human primate model.

Novel Research

The OPPB has awarded numerous Small Business Innovative Research (SBIR) awards for researchers to conduct novel research in the area of pediatric pharmacology drug development. One investigator is working to synthesize a novel low-molecular-weight compound that can be used to treat Respiratory Syncytial Virus (RSV) infection in children. RSV infection alone results in more than 126,000 hospitalizations and 500 deaths in infants and young children annually. Currently, ribavirin is the only FDA-approved agent for treating RSV, and its efficacy in young children with the virus is questionable. The drug is also difficult to administer and costly. The investigator's plan is to complete key *in vitro* studies in the cotton rat model to determine activity, and then develop *in vivo* studies for potential clinical use.

Other investigators were funded to conduct other novel research, such as: using nanotechnology to develop a device that will deliver a controlled amount of subcutaneous insulin to patients; developing the technology to miniaturize a biocompatible device; developing hybrid drugs that can be used in the future for the treatment of ADHD; and conducting stereospecific studies to assess the regulation of transporter genes in the disposition of psychostimulants.

Research in Special Populations

The Branch has several initiatives that focus on the neonatal population, which is certainly a therapeutic “orphan”; only a small fraction of drugs used in this population are approved for use, leaving large gaps in dosing, safety, and efficacy information. One investigator is developing a tool for early detection of nephrotoxicity in newborns treated with aminoglycoside (AG). The current tools, including serum-concentration monitoring and urinalysis, are neither sensitive nor specific to AG toxicity. The investigator is using state-of-the-art proteomics (tools that separate and identify differentially expressed proteins as candidate markers of toxicity) approaches for the characterization of normal and AG-treatment induced urine changes in newborns.

In addition to safety and efficacy studies, pharmacokinetic studies are also rare in the neonatal population. The Branch is funding a researcher who will be conducting a pharmacokinetic study to determine the proper dose of azithromycin for treating preterm neonates infected with *Ureaplasma urealyticum*—a bacterium believed to be involved in the development of chronic lung disease in neonates.

Epidemiology Research

The Branch has an interest in how epidemiological research can augment clinical research, in addition to how it might identify gaps in fields of interest to help direct future clinical research directions. For instance, using a hospital database, one investigator is conducting a multisite, retrospective, cohort study to understand clinical outcomes and adverse events related to treatment with oseltamivir in children who are hospitalized with influenza infection. This research is both timely and innovative because administering oseltamivir to hospitalized children has not been investigated, even though the burden of illness is high and the global implications related to a potential pandemic are considerable. Additionally, recent reports suggest that an unusual form of central nervous system toxicity is present in preadolescent children treated with oseltamivir; this research may help to understand this phenomenon.

Other Branch epidemiological research has developed databases that describe health services utilization among children and the medications associated with their interactions with the health system. For example, recent research evaluated use of psychotherapeutic medications among Medicaid-insured preschoolers (two years to four years of age) using data from seven different state Medicaid programs. Among these children, more than 2 percent received a psychotherapeutic medication on one or two occasions. This usage of psychotherapeutic medications is double that reported in an earlier analysis of Medicaid data. Increased use also suggests, given the lack of knowledge of the effects of these drugs on the developing brain, the need for more detailed understanding of appropriate use, dosing, safety, and efficacy in young children.

Another example of pharmacoepidemiological research conducted by the Branch explores the use of asthma medications among children who have the diagnosis of asthma. Asthma is one of the most common chronic conditions in children; it is the third leading cause of hospital admission for children and often impacts throughout the lifespan of the individual. Current asthma treatment and prevention guidelines emphasize the need for controller medications among children with asthma, yet in the study, fewer than 60 percent of the children with a diagnosis of asthma were treated with controller medications. This finding is consistent with

DRAFT: NOT FOR DISTRIBUTION

other observations suggesting that children with asthma may be receiving suboptimal care. These types of data also emphasize the need for the Branch to work closely with other groups to improve pediatric therapeutics.

In addition, the OPPB has also collaborated with contractors RTI International and Westat to construct more precise estimates of the frequency of conditions affecting children in the United States, and the frequency of use of certain medications in U.S. children. This activity was an essential, arduous, and expensive process, given the daunting complexities of choosing datasets, setting useful parameters, and resolving methodological problems. These data were gathered both in response to the requirements of the BPCA, and to better inform the development of the drug prioritization list. The Branch is now working to translate these findings and databases into resources interested pediatric researchers can use. The OPPB's current approach contemplates developing both training sessions for potential users, as well as appropriate public-use datasets.

Training

One of the Branch's key mandates is to promote and promulgate the fields of pediatric and obstetric pharmacology. Within the PPRU Network, support for such training comes in the form of the Mentored Scientist/Clinical Investigator Development Award (MSCIDA) mechanism (U10). This small research grant is given to a young investigator so that he/she can study pediatric pharmacology and learn about pediatric drug development.

Each year, the PPRU sites can nominate one young investigator for consideration for this award. The applications are reviewed and the award given to the most deserving applicant. This innovative mechanism helps young investigators get additional support for focused training in pharmacology. To date, the MSCIDA has supported seven pediatric clinical pharmacology fellows, six M.D.s, and one M.D./Ph.D.

Collaborations

The Branch has played a leadership role in several collaborative efforts within the federal government by assembling experts in pediatric health and ethics from the United States, Europe, and Canada:

- In 2004, the Branch sponsored an NDDI meeting with representatives from industry, academia, the FDA, and the NIH. Thus far, the outcome of this ongoing Initiative has been a summary published as a special supplement of *Pediatrics* and more detailed descriptions of research needs published in *Clinical Therapeutics*. The Branch also intends to follow-up on the Initiative to:
 - o Perform clinical studies based on the templates developed by the Working Groups (e.g., pain, bronchopulmonary dysplasia, and neonatal seizures).
 - o Determine the feasibility of studying specific drugs in low-birth-weight infants based on current use by indication in neonatal intensive care units across the United States.
 - o Develop novel study designs that take into account the small number of patients who are available, ethical limitations, standard practices, and feasibility issues.
 - o Create initiatives to address the knowledge gaps, which will be identified at an upcoming meeting of the Working Groups for this Initiative.

DRAFT: NOT FOR DISTRIBUTION

- Also in 2004, the Branch (in collaboration with FDA) sponsored a meeting on the use of animal models to understand developmental differences in safety and efficacy of drugs. For a complete list of Branch-supported meetings and conferences, see [Appendix D](#).
- In December 2005, the NICHD conducted a Pediatric Formulation Initiative with representatives from the government, industry, and academia to explore a range of issues and challenges related to creating pediatric drug formulations. The effort sought to identify issues and discuss the many barriers that block access of children and infants to important drugs. This initiative is ongoing.
- In January 2006, the Branch supported a follow-up workshop, *Emergency Research in Children: Ethical, Regulatory, and Clinical Challenges*, to identify issues and concerns related to the conduct of research involving children under the Emergency Exception from Informed Consent (EFIC) statute allowed under FDA and DHHS regulations. Invited participants included investigators, ethicists, and Institutional Review Board members.
- The January 2006 meeting led to a subsequent meeting, held in September 2006, with federal representatives from the NIH, FDA, the Health Resources and Services Administration (HRSA), the DHHS Office of Human Research Protections, investigators, and ethicists. The purpose of the meeting was to discuss the investigators' approach to EFIC in the Branch's lorazepam–status epilepticus study. This study, approved by the FDA, is the first to be conducted in pediatric patients under EFIC requirements.
- In March 2006, the Branch convened a meeting of international leaders in pediatric pharmacology research to determine how to successfully establish a global consortium for addressing important issues in clinical pharmacology, therapeutics, and toxicology relevant to the health of children. Groups currently engaged in international pediatrics research, teaching, and clinical activities are essential for developing such a global consortium on pediatric pharmacology. Engaging these international organizations is critical for potential infrastructure assistance and to benefit from lessons learned in international pediatrics.
- The Branch has collaborated with the Canadian Institute of Health Research and the NICHD Division of Epidemiology, Statistics and Prevention Research (DESPR) to offer Summer Institutes in Obstetric Pharmacology and in Reproductive, Perinatal, and Pediatric Epidemiology during the summers of 2005, 2006, and 2007. The Branch, DESPR, and the Canadian Institute are now planning the fourth set of Summer Institutes for 2008. These sessions have been extremely useful in addressing the lack of training and investigator-initiated research in both areas.

DRAFT: NOT FOR DISTRIBUTION

OBSTETRIC PHARMACOLOGY

Pharmacoepidemiological surveys indicate that nearly two-thirds of all pregnant women take at least four drugs during pregnancy and labor, and that medication use frequently continues during breastfeeding. Because the use of these drugs is largely based on an empiric approach, rather than on a scientific basis, and because much of the use does not take into account the profound physiologic changes characteristic of pregnancy, the lack of appropriate testing of drugs in populations of pregnant women is a significant concern.

A key issue of drug tests in this population is accounting for the physiological changes during pregnancy that influence pharmacokinetics and pharmacodynamics. For example: the gastric emptying time and intestinal transit time are increased during pregnancy, which could affect the gastrointestinal absorption of drugs; glomerular filtration rate and renal plasma flow increase from the sixth week of pregnancy to delivery, meaning an increase in the renal excretion of some drugs, such as beta-lactam antibiotics and lithium.

Further complications arise because the physiological changes characteristic of a normal pregnancy may be different in a pregnancy complicated by various conditions and disease states. So, just as information about pregnant women cannot be extrapolated from non-pregnant women, information on the disposition and effects of drugs in abnormal pregnancies cannot be extrapolated from data on normal pregnancies. Effects of the pathologic abnormalities associated with the disposition and action of drugs in abnormal pregnancies is an even less-studied aspect of obstetric pharmacology.

In determining the types of pharmacology research that should be conducted in obstetrics, the field needs to consider that pregnant women have a significantly different set of complexities compared to other populations, and that, because of these complexities, pregnant women should be studied separately from other populations. Obstetric pharmacology needs large studies of pregnant women that have sufficient statistical power to answer important questions. Studies should also focus on issues specific to pregnant women, such as pregnancy-specific conditions (i.e., preeclampsia) and medications given during labor, to really make progress in understanding dosing, effectiveness, and safety.

ACTIVITIES OF THE OPRU NETWORK

Throughout its history, NICHD has fostered research in pregnancy. Current intramural and extramural activities are reflected in training and research supported by the Branch, by DESPR, and through the MFMU Network. The OPRU Network, created in 2004, aims to enhance and focus efforts related to obstetric pharmacology (see [Figure 5](#) for a map of sites).

The structure of the OPRU Network differs from most other NICHD-supported efforts in that it mandates pairing a clinical Principal Investigator (PI) with a basic science co-PI to facilitate the translational nature of the work. The Network seeks to identify, characterize, and study those

DRAFT: NOT FOR DISTRIBUTION

drugs that are of therapeutic value during pregnancy, and whose clinical pharmacology (both pharmacokinetics and pharmacodynamics) is altered by the normal and abnormal pregnant states.

Based on the data needs related to this population, key goals of the OPRU Network are to:

- Serve as a resource for pharmacologic studies of drug disposition and effect during normal and abnormal pregnancies.
- Conduct multisite cooperative clinical studies that advance the knowledge of pharmacokinetics and pharmacodynamics of drugs used during pregnancy.
- Conduct pharmacogenetic studies of the effects of pregnancy on drug delivery and action on the mother as well as on the developing fetus.
- Perform studies of placental transfer of drugs.
- Facilitate translational research so that clinical materials can be utilized for basic research studies.
- Enhance the exchange of information among basic scientists, neonatologists, and obstetricians.
- Serve as a resource for training health care providers in the field of obstetric pharmacology.

The following institutions were selected during the initial funding cycle of the OPRU Network:

- University of Washington
- Georgetown University
- University of Texas Medical Branch at Galveston
- University of Pittsburgh

Initial efforts of the Network focused on creating a collaborative environment by implementing a systems-biology approach in obstetrical pharmacology to provide pharmacokinetic and pharmacodynamic information currently lacking for obstetric therapeutics, as well as a more detailed understanding of disease-pregnancy-therapeutics interactions. Pregnancy is a perfect example of systems biology in action in that three entities function together in a complicated maternal-fetal-placental unit. Because systems biology attempts to understand and evaluate the coordinated system of transporters, channels, receptors, and enzymes acting together as gatekeepers to endogenous and foreign molecules, and to unite biological fields instead of approaching each one separately, the OPRU Network has developed its protocols and scientific interests to take full advantage of the systems-biology approach. These efforts include a study of the oral hypoglycemic glyburide, which is used to treat gestational diabetes, and the drug thought to be active in preventing prematurity, 17-alpha hydroxyprogesterone caproate.

Additionally, each Network site has identified up to 10 drugs that are frequently used during pregnancy (a total of approximately 30 drugs) for which basic pharmacokinetic and pharmacodynamic studies are now being performed. These studies are conducted using a generic set of pharmacology protocols, called “opportunistic protocols,” and each OPRU site is responsible for developing assays and standard operating procedures for these studies. When completed, each of these studies will contribute important information to guide therapy during pregnancy. One clever aspect of these studies is that the researchers study pregnant women who require one of the 30 drugs as standard treatment for her own health; thus, the required informed consent focuses primarily on risks and inconvenience associated with blood sampling, rather

DRAFT: NOT FOR DISTRIBUTION

than on the non-therapeutic use of the drug. These opportunistic protocols allow each site to play to its own strengths and unique patient populations. For example, one university has a large transplant service and has enrolled many women treated with immune modulators. There is also efficiency to this process because each site is responsible for studying approximately eight drugs, but can cross enroll subjects from their site into studies from the other sites.

Since the Network was established, its researchers have conducted a considerable amount of basic, translational, and clinical research, including studies in non-human primates and other experimental animal models to better understand the changes common during pregnancy that impact pharmacokinetics and pharmacodynamics. In 2005, as a result of this basic research, researchers developed a second clinical protocol and Investigational New Drug application for 17-alpha hydroxyprogesterone caproate.

At the time this report to the NACHHD Council was written, researchers from the OPRU Network had authored 19 publications and 20 abstracts.

Current Protocol Summaries

The OPRU Network currently supports the following protocols:

- Glyburide. Although gestational diabetes remains a difficult metabolic condition to treat, effective management is required to prevent adverse pregnancy outcomes. At present, little is known about pharmacokinetics and pharmacodynamics of oral hypoglycemics used during pregnancy. The Network's research efforts have clarified pharmacokinetics and pharmacodynamics of these drugs in human and non-human pregnancies and have demonstrated placental transport and metabolism, as well as metabolism by other organs. The data collected allow researchers to describe systems-biology models of pregnancy, gestational diabetes, and therapeutic approaches—all major advances in understanding.
- 17-Alpha Hydroxyprogesterone Caproate. Despite efforts and attention on many levels, rates of preterm birth in the United States continue to increase. Recent data suggest that caproate may, in select groups, decrease the risk of preterm birth; however, researchers know little to nothing about the pharmacokinetics and potential mechanisms of action of this drug. Network investigations are providing needed information on metabolism, pharmacokinetics, pharmacodynamics, and mechanisms in humans and non-human primates, and for pregnant and non-pregnant states. This data will be shared with the FDA as it considers the strength of evidence and mechanistic information concerning the potential utility of this drug. The researchers will also use these data to create a systems-biology model, which will provide a mechanistic base for further investigations of preterm birth.
- Opportunistic studies. As explained earlier, the OPRU Network performs these types of studies as preliminary evaluations before identifying drug-condition studies, which may later get full or systems approaches for evaluation.

OTHER BRANCH EFFORTS IN OBSTETRIC PHARMACOLOGY

In addition to its studies conducted through the OPRU Network, the OPPB also supports efforts in the following areas.

Animal Research

The OPPB has funded research to evaluate the functions and nuances of the complex systems-biology model of mother-fetus-placenta. One investigator is using imaging to understand the cellular and metabolic derangements that occur during inflammatory processes, and that lead to brain injury during fetal development. The hypothesis is that endotoxin-induced intrauterine inflammation activates microglial cells in the fetal brain; this activation progresses to nerve-cell and white-matter injury, called periventricular leukomalacia. The theory is that, if the activation can be decreased or turned off, the degree and magnitude injury will subsequently decrease. The investigator is using PET scans to assess microglial response in the rabbit model, using PET tracer PK11195. The researcher believes that using neuroimaging to assess inflammatory processes could aid the future development of novel therapies.

Another researcher is evaluating the effects on the fetus of SSRI treatment in the mother during pregnancy. One theory suggests that a fetus exposed to SSRIs will have excess serotonergic activity and, consequently, will show signs of serotonergic withdrawal after the drug is discontinued or after the fetus delivered. The study is using the baboon model to quantify and compare the fetal metabolism of two SSRIs with the fetal and maternal metabolic enzyme activity of the drugs. The study will also examine changes in parameters of autonomic regulation to assess fetal effects.

Novel Research

The Branch continues in its mission to advance the science in the field of obstetric drug development. One innovative award seeks to determine fetal pharmacotherapy through transplacental drug delivery strategies. The Branch also supports an investigator who is exploring the association between prenatal exposure to prescription drugs and teratogenicity and chronic diseases of the offspring later in life. Using linked administrative databases, the researcher will assess the associations of maternal use of SSRIs on congenital lung and heart malformations. Using epidemiological data to evaluate potential toxicities is innovative in the field of obstetrics—especially because most safety studies in pregnant women have several limitations, such as recall bias of drug exposure and a sample size often too small to detect rare adverse events.

Training

Currently, the Branch offers Institutional Training Grants (T32) through its Predoctoral Training Program in Reproductive, Perinatal, and Pediatric Epidemiology. These grants establish a new predoctoral program that will train outstanding candidates in the discipline of epidemiology and will mentor them in team research that integrates basic, clinical, and population sciences. This program will prepare the students to be both teachers and independent researchers.

DRAFT: NOT FOR DISTRIBUTION

After three rounds of review, the Branch selected four sites for the program: Emory University, the University of Washington, Boston University, and the University of Pittsburgh. Although the program's initial focus was reproductive, perinatal, and pediatric epidemiology, the Branch intends to expand the program to include pharmacoepidemiology and health services impacts, as well as pre- and postdoctoral training.

In addition, since July 2005, the Branch has co-sponsored the annual Summer Institutes in Maternal-Fetal Pharmacology and in Reproductive, Perinatal, and Pediatric Epidemiology, held in conjunction with the Canadian Institutes of Health Research and DESPR to help increase the infrastructure in obstetric pharmacology and epidemiology.

FUTURE DIRECTIONS FOR THE BRANCH

The OPPB's activities are guided by a strategic planning process, which focuses on critical research issues in obstetric and pediatric therapeutics, tempered with the Congressional mandate for BPCA and subsequent legislation. In accordance with the NICHD's process for increasing accountability and transparency in strategic planning for its Branches, the OPPB sought expertise and feedback on its future directions from a panel of experts in the fields of obstetrics, gynecology, drug development, microbiology, birth defects, pharmacokinetics, and pediatrics. The panel, which met in July 2007, also included members of the NACHHD Council, public representatives, and patient advocates (see [Appendix E](#) for a list of expert panel members).

The meeting provided the Branch with an opportunity to review its activities, progress, challenges, and areas of need and to lay out goals in obstetric and pediatric pharmacology for the future. Meeting participants discussed the Branch's activities and goals within the framework of three overarching questions:

- Given its mission, what are the most important scientific opportunities that the Branch should try to pursue during the next four years?
- Given its mission, what are the most important public health issues that the Branch needs to address during the next four years?
- What areas deserve less emphasis because progress has been made or will continue without further stimulation from the Branch or from the NICHD?

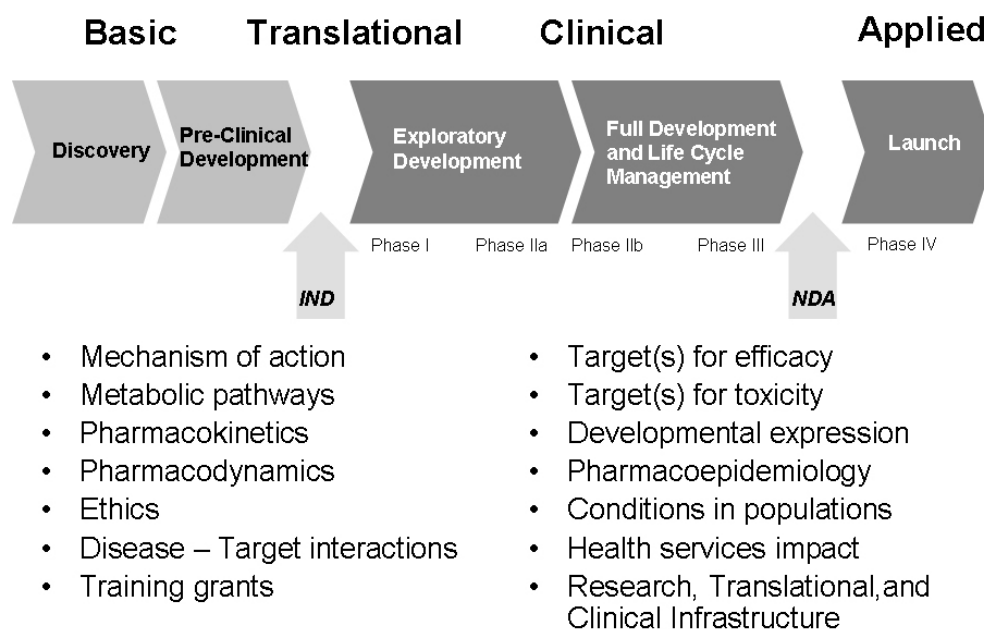
The first section of this report provides a summary of the expert panel discussion; the following sections describe goals for the Branch for the next four years.

PANEL DISCUSSION

The panel began with a discussion of the Branch's research from the perspective of the drug-development pipeline (see Figure below). Much of the Branch's research has focused on the clinical and applied side of the process, including research using mature products to better understand use, safety, and efficacy during pregnancy and in children. Overall research at NIH,

however, focuses on basic and translational activities. The panel encouraged the Branch to transition some of its research and training activity in the direction of more basic and translational research. From the perspective of 21st century biomedical science, such research would provide the foundation for future product development, while also clearly emphasizing the respective roles of NIH and industry in drug development.

Figure A: Drug Development Pipeline



An important issue now facing the Branch is how to build on the foundation it has created since 2004, and on previous work done in the NICHD on obstetric and pediatric drug development. The panel emphasized the need to integrate obstetric and pediatric pharmacology by enhancing the focus on pharmacoepidemiological research initiatives. The panel also noted that the opportunity to encourage and support basic and mechanistic research related to pediatric and obstetric pharmacology represents a critical need. By integrating the Branch’s portfolio more thoroughly—the PPRU Network, the OPRU Network, the BPCA activities, and the investigator-initiated efforts—the Branch will make more progress toward achieving its goals.

The panel noted a need to identify knowledge gaps in relevant diseases and respective treatments in pediatric and obstetric pharmacology. Such a review is necessary to assure the best allocation of available resources. In addition, the participants discussed the successes and challenges associated with existing efforts to identify new ways to promote collaborations and partnerships, and how to use existing mechanisms for developing innovative approaches for conducting research and training.

DRAFT: NOT FOR DISTRIBUTION

Using input from the panel, the Branch identified three key goals for advancing knowledge in obstetric and pediatric pharmacology:

- Continue support of investigator-initiated research to address the knowledge gaps in obstetric and pediatric pharmacology
- Promote training of new investigators in obstetric and pediatric pharmacology
- Incorporate new technology developments into obstetric and pediatric pharmacology

The remainder of this report outlines possible activities for the Branch within these key areas of research.

CONTINUE SUPPORT OF INVESTIGATOR-INITIATED RESEARCH TO ADDRESS THE KNOWLEDGE GAPS IN OBSTETRIC AND PEDIATRIC PHARMACOLOGY

Although knowledge gaps exist in both pediatric and obstetric pharmacology, the gaps in obstetric therapeutics are substantial and deserve more emphasis than they have received in the past. For example, the current guidelines for treating anthrax do not consider pregnancy and the current dosing recommendations might be ineffective in pregnant women. Similarly, despite progress made, specifically through the efforts of the PPRU Network, challenges also remain in pediatric pharmacology. For example, the current assumptions and tools used to study many drugs used in children are ineffective in determining safety and efficacy.

During the next four years, the Branch plans to expand its portfolio of investigator-initiated grant research with a focus on the following areas.

Study Design and Outcome Measures

The Branch will consider these activities:

- Continue to promote research that highlights the differences in pharmacokinetics and pharmacodynamics, as well as toxicity and adverse events in children and pregnant women. These areas of interest must include the characterization of disease processes and the influence of development on disease processes.
- Encourage innovative research to improve the tools and methodology available for analyzing therapeutic outcomes after treatment during pregnancy and in children, including analysis of drug safety. Identifying important pediatric and obstetric diseases and focusing the Branch's resources using an approach that matches the tools available with the medical need are vital to accomplishing this goal.
- Create initiatives to encourage research on developing relevant therapeutic measurement tools for use in pregnancy and childhood. Many drug trials fail, not because they are ineffective, but because the evaluations of efficacy are inappropriate for pregnancy or children.
- Continue studies in animal models and efforts to determine what role these model systems play in extrapolation to human studies, particularly in the area of a developmental pharmacology.

DRAFT: NOT FOR DISTRIBUTION

- Diversify the Branch portfolio to devote more funds to obstetric pharmacological research to help balance current funding proportions, emphasizing studies across the course of pregnancy, labor, and breastfeeding.
- Consider creating a bio-bank as an important, inexpensive, and economical approach to acquiring samples for pharmacology research, beginning with a repository for OPPB trials to collect samples for pharmacokinetic, pharmacodynamic, and pharmacogenomic analyses.
- Shift the focus of the PPRU Network from clinical trials to cross-disciplinary research. This type of research is critical for advancing drug development in pediatrics and fosters the Network's collaboration with industry, the FDA, and practitioners. The OPRU Network will also continue its cross-disciplinary approach for addressing therapeutic concerns unique to pregnancy.
- Create integrated teams of investigators, with overlapping and complementary expertise, to strengthen the focus on research collaboration, cross fertilization of knowledge, information exchange, and hypothesis generation.
- Increase efforts in obstetric and pediatric pharmacoepidemiology. This field is largely undeveloped and unaddressed, but has the potential to answer many of the questions related to these populations. For example:
 - o The common off-label use of drugs represents a significant public health concern and clinical dilemma, but an equally untapped research resource. Large pharmacoepidemiology databases, both existing and new, could be used to quantify off-label use and, more importantly, study its effects.
 - o Pharmacoepidemiological analysis of drug use and its unique consequences in children and during pregnancy could be appropriately structured to help evaluate efficacy and safety. The Branch plans to fund research to enhance understanding of how these data resources can contribute to knowledge of therapeutics.
- Foster research to enhance safety evaluations and pharmacokinetic research of drugs in obstetrics and pediatrics. Many drugs studies lack pharmacokinetic data, while others relied on flawed study designs to obtain their data. Collecting this data is a challenge given the small number of patients available for study in pediatrics and obstetrics. However, linking innovative epidemiological approaches to clinical trials will aid in evaluating drug safety and efficacy from across-disciplinary perspective.

Partnerships and Collaborations

The Branch will consider these activities:

- Continue and expand partnerships with experts in multiple specialties of pediatric therapeutics to develop and implement clinical trials. With the very recent reauthorization of the BPCA, the NIH is taking a more proactive role in the development of proposed pediatric study requests, so enhancing these collaborations will be critical. The Branch will also seek to expand linkages with cooperating NIH Institutes and Centers in the pediatric arena and to include appropriate obstetric collaborations.
- Partner with agencies whose activities are treatment related. Because Branch-supported research will impact treatment, collaborations with organizations such as the Agency for Healthcare Research and Quality (AHRQ), which recently spent \$13 million on the Centers for Education and Research Therapeutics to conduct research and provide education that will advance the optimal use of drugs, medical devices, and biological products, are vital. The

DRAFT: NOT FOR DISTRIBUTION

AHRQ is creating a network of 100 million participants to link data resources for studying drug safety. By partnering with AHRQ, the OPPB could enhance the focus on obstetric and pediatric populations.

- Refine and expand partnerships with the FDA. Such efforts will help to identify study design and labeling opportunities and will make industry participation in obstetric and pediatric therapeutic research more attractive.
- Enhance partnerships that the Branch has already developed with the American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists (ACOG), relevant research societies, and clinical pharmacology societies.
- Consider partnerships to foster therapeutics in pediatrics and obstetrics, perhaps providing funding options, such as a supplement to Clinical and Translational Science Awards, or limited competition research funding consistent with Institutional Awards.

Other Priority Areas

In an effort to increase staffing and to develop the infrastructure needed to support research, the Branch will consider the following activities:

- Maintain Branch statisticians. Using these resources for multi-center studies could be more economical than funding individual statisticians or data coordinating centers.
- Create a bio-bank collected from funded studies within the Branch and in other Centers. This resource would be helpful to investigators interested in pharmacological studies.
- Consider opportunities in new arenas outside of traditional research studies, specifically in the area of ethics. For example:
 - o The panel also suggested forming an oversight committee that would review the Branch's activities and make specific suggestions on how to share resources or develop new opportunities based on currently funded research.
 - o The panel noted that OPPB research has already encountered and would continue to encounter situations, which, if fully analyzed, can contribute to understanding research ethics involved in studies during pregnancy and childhood. The panel strongly endorsed the concept of adding an ethical, legal, and social component to the Branch.
- Disseminate the information coming from this cross-disciplinary, basic, translational, and clinical research through partnerships and collaborations.

PROMOTE TRAINING OF NEW INVESTIGATORS IN OBSTETRIC AND PEDIATRIC PHARMACOLOGY

Because the fields of pediatric and obstetric pharmacology have been relatively invisible until recently, a dearth of trained specialists exists that can best be addressed through formal training programs in obstetric and pediatric clinical pharmacology. The panel indicated that the Branch should assist in the development of these training activities. The Branch indicated its interest in exploring links with clinical pharmacology training programs supported by the National Institute of General Medical Sciences. In addition, training programs should address the emerging areas of obstetric and pediatric pharmacoepidemiology. In developing training programs, the OPPB could also leverage resources; the investment is important because a solid two- to three-year

DRAFT: NOT FOR DISTRIBUTION

training grant can give a researcher a career. These training opportunities may also contribute to development of resources needed to do larger studies.

Panel members noted increasing challenges related to becoming salaried on K and T tracks. Although the creative resources at the NIH have been revolutionary, science careers are not being sought out by as many young investigators as in the past. The panel added that the Branch might consider allowing a provision for administrative supplements to existing grants as a bridge between training funding and a salaried research grant.

The Branch will also consider expanding its training portfolio in the following ways:

- Place a greater focus on balancing pediatric and obstetric research by increasing the portfolio of research in obstetrical therapeutics
- Encourage translational research, including a strategic principle that would require connections and collaborations among fields. The Branch could also stress the importance of cross-disciplinary training for those who apply for its grants and training programs.
- Develop programs to train existing obstetricians and pediatricians in new fields of biomedical and clinical science, such as pharmacogenomics, metabolomics, informatics, and systems biology.
- Partner with organizations, such as the AAP, ACOG, and the Association of Professors of Gynecology and Obstetrics to develop resident training programs.
- Include more K awards, including the Mentored Clinical Scientist Development Award (K08), the Mentored Patient-Oriented Research Career Development Award (K23), and the Institutional Mentored Clinical Scientist Development Award (K12), in the Branch portfolio.
- Track awardees' career progress to better evaluate efforts to increase training and specialists to ensure that Branch funds are being used effectively.

INCORPORATE NEW TECHNOLOGY DEVELOPMENTS INTO OBSTETRIC AND PEDIATRIC PHARMACOLOGY

The expert panel discussed the challenges of refocusing the Branch's efforts on the discovery of new molecules for consideration in obstetric and pediatric therapeutics, recognizing that with the increasing information from genomics, proteomics, metabolomics, systems biology, and informatics, researchers would be better able to design needed drug research approaches. Informing the OPPB's efforts with information from these new fields enables the Branch to embrace 21st century medical science.

To better utilize new technology developments and to encourage novel research, the Branch will consider the following activities:

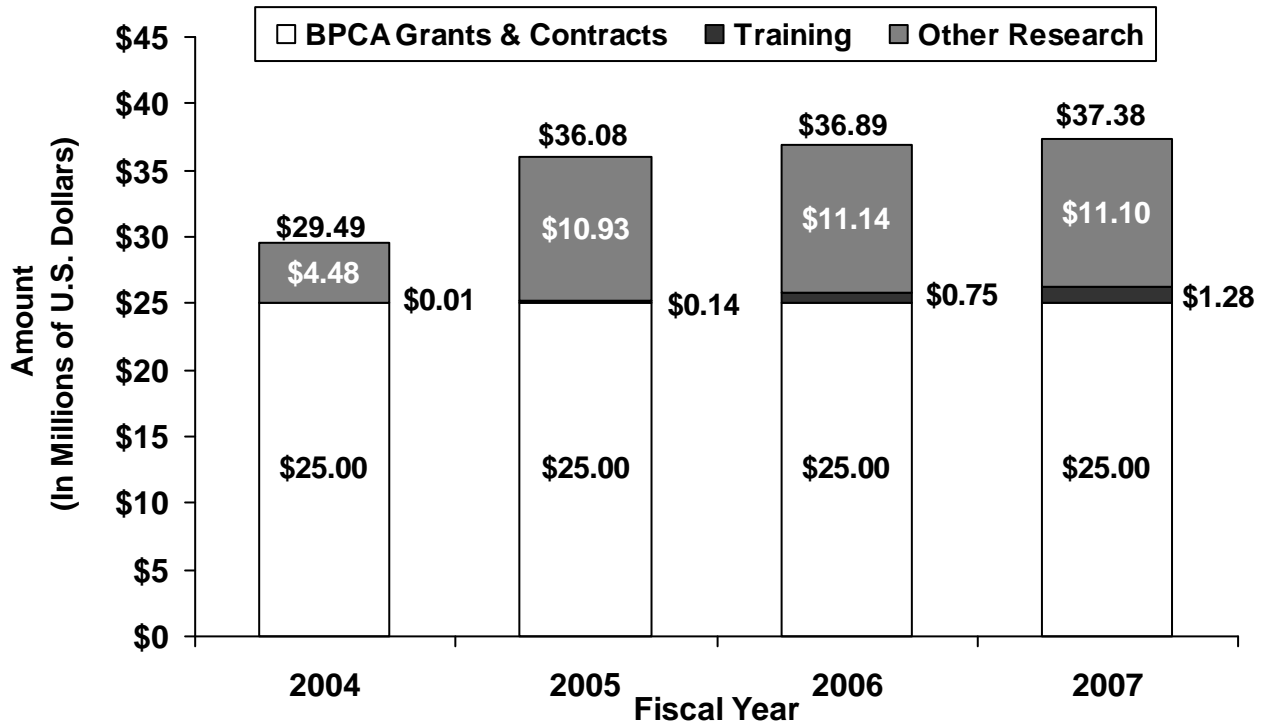
- Stimulate and explore innovative research designed to enhance drug discovery for obstetric and pediatric populations. Research priorities will include (but are not limited to):
 - o Determining the numbers of children and women with a given condition
 - o Identifying whether established therapies in that drug class exist for obstetric and pediatric populations
 - o Creating novel methods of drug development specific for obstetrics and/or pediatrics

DRAFT: NOT FOR DISTRIBUTION

- Establish criteria to mark and follow progress, such as noting project accomplishments that change the paradigm of current thinking or fill gaps in a much needed area of research or clinical care. Areas of interest include (but are not limited to):
 - o Pharmacogenomics in pregnancy and across development
 - o Research practice-related findings in obstetric and pediatric therapeutics
 - o Analysis of current disease drug treatment guidelines to determine if existing recommendations have an appropriate evidence base for obstetrics or pediatrics
- Apply the latest techniques of laboratory-based and translational science, including pharmacogenetics, to the Branch's pediatric and obstetric pharmacology research activities.
- Strengthen application of genetic and biomarkers to patient care and build upon existing knowledge in this area.
- Include translational research, specifically the effects of the environment, reproductive toxicants, nutrition, and weight on drug metabolism, in OPPB efforts to embrace the vision of contemporary biomedical science. Other areas of interest include (but are not limited to):
 - o Studies of drug use during breastfeeding
 - o Evaluation of treatment effects on mother and fetus of drugs intended for fetal benefit
 - o Development of new methodologies to determine the safety and efficacy of drugs used in obstetrics and pediatrics
- Create Program Announcements to address the dearth of informatics in pediatric and obstetric pharmacology.
- Encourage innovation in pediatric and obstetric therapeutics, with a continued focus on disease and patient oriented approaches.

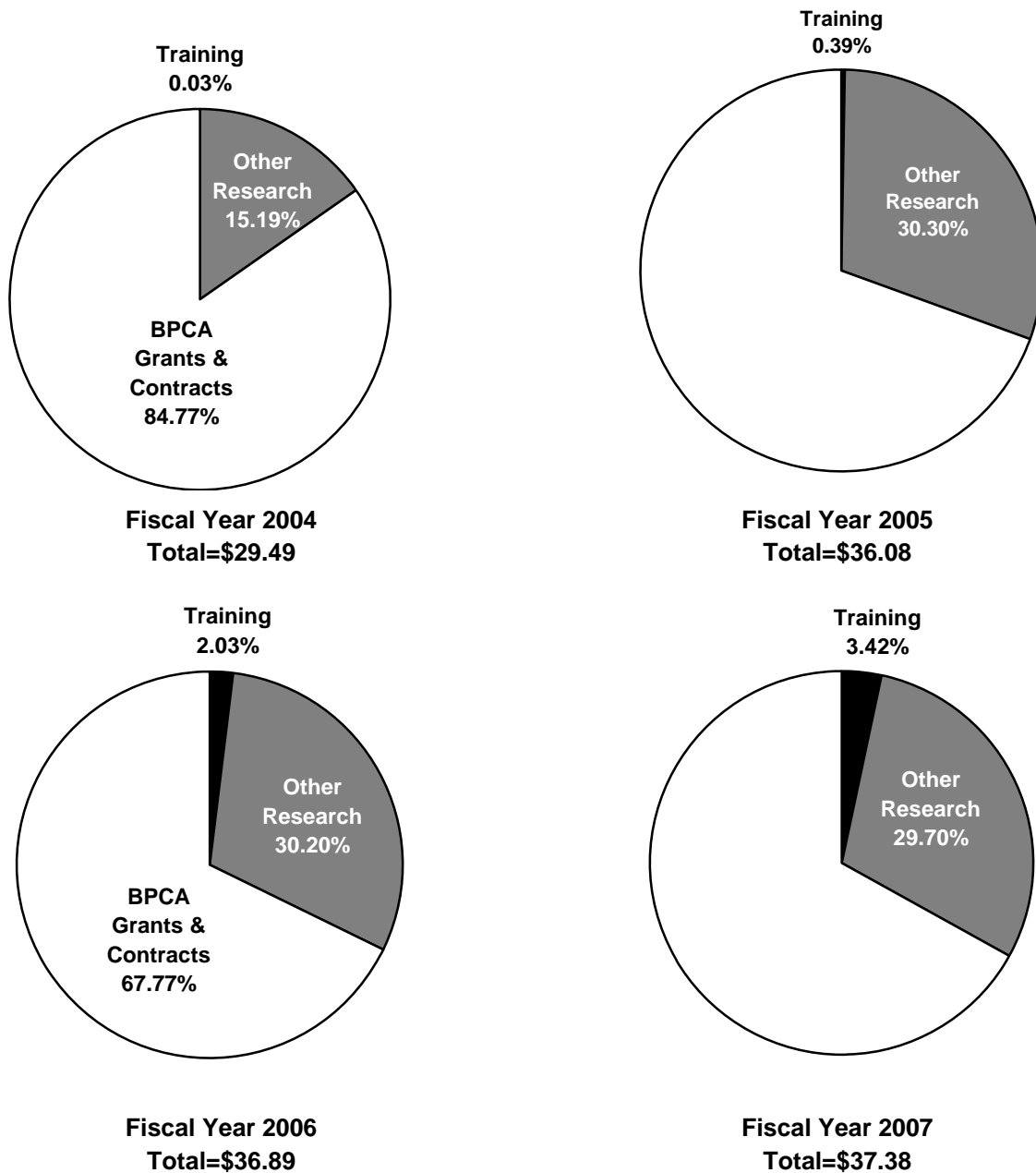
FIGURES AND TABLES

FIGURE 1: BRANCH FUNDING BY TYPE, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007



Note: “Other Research” and “Training” funds support competitive proposals, which fall within the referral guidelines of the Branch. Included in the “Other Research” category are the two Branch-supported Networks (PPRU and OPRU). The “BPCA Grants & Contracts” are utilized to support competitively awarded preclinical and clinical research proposals requested by Congress in the Best Pharmaceuticals for Children Act (BPCA) and its reauthorization.

FIGURE 2: PROPORTION OF BRANCH FUNDING BY TYPE, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007



Note: All amounts in millions of U.S. dollars. “Other Research” and “Training” funds support competitive proposals, which fall within the referral guidelines of the Branch. Included in the “Other Research” category are the two Branch-supported Networks (PPRU and OPRU). The “BPCA Grants & Contracts” are utilized to support competitively awarded preclinical and clinical research proposals requested by Congress in the Best Pharmaceuticals for Children Act (BPCA) and its reauthorization.

FIGURE 4: PEDIATRIC PHARMACOLOGY RESEARCH UNITS (PPRU) NETWORK SITES

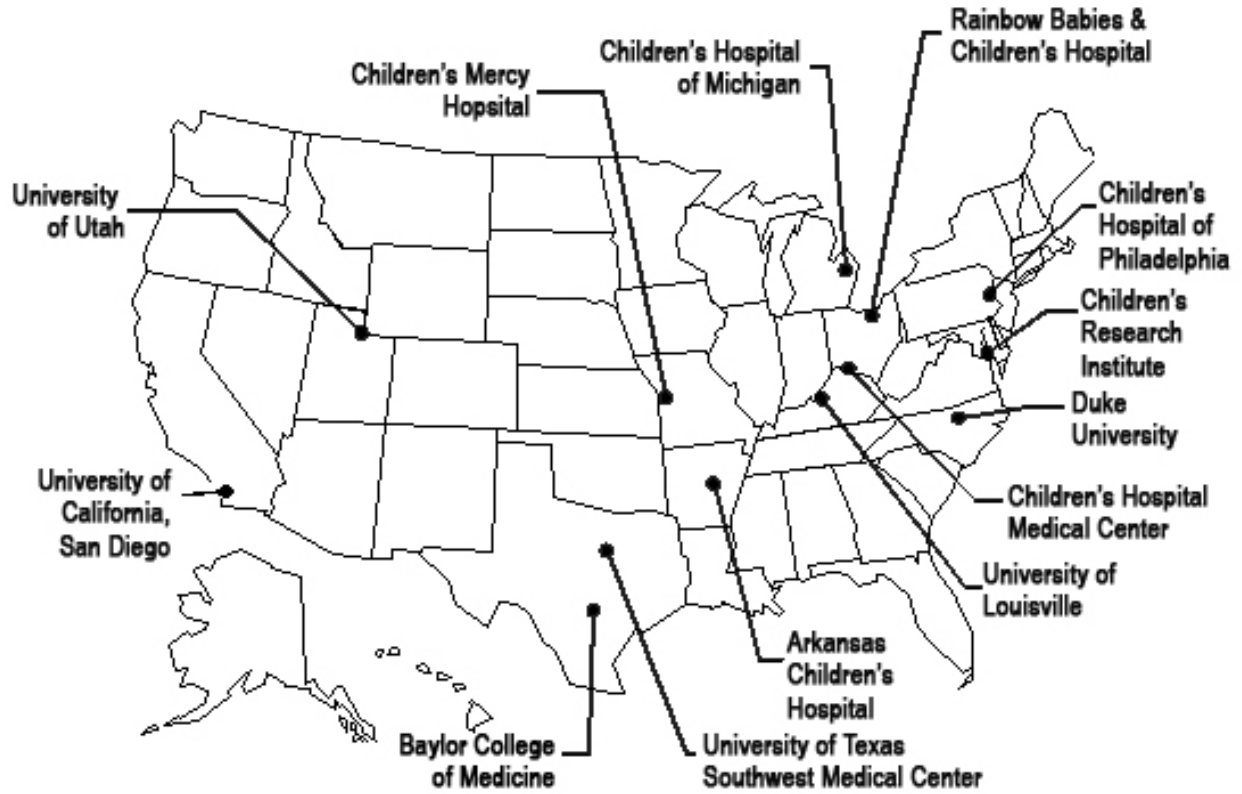
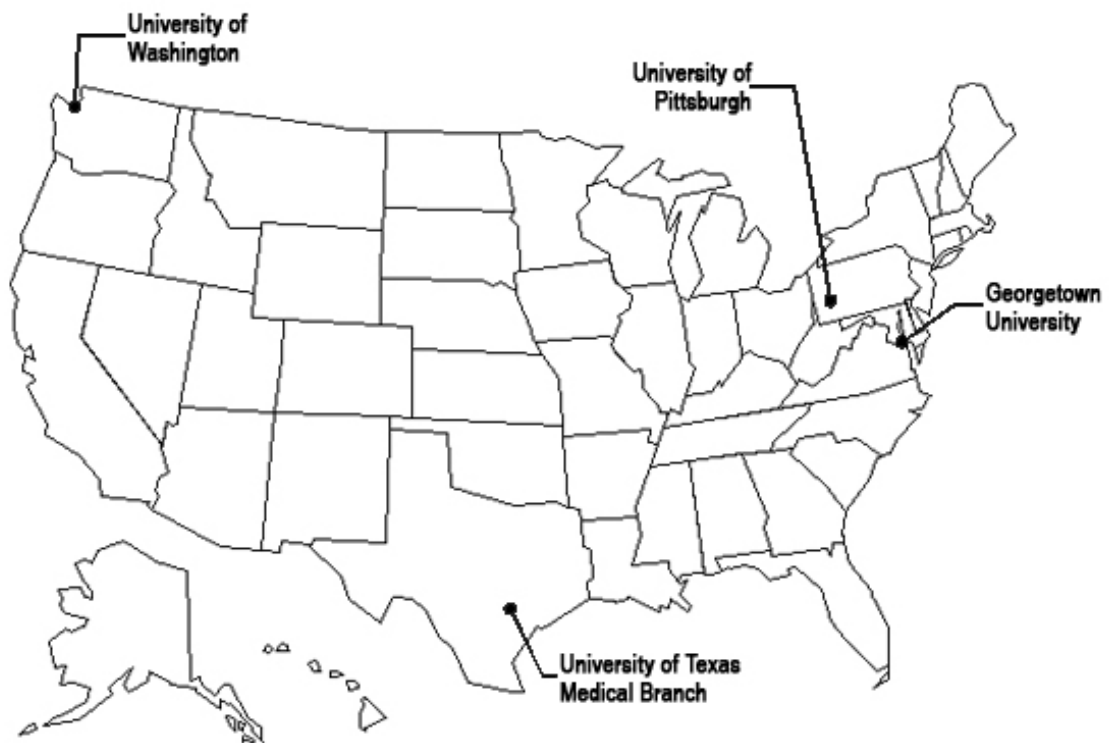


FIGURE 5: OBSTETRIC PHARMACOLOGY RESEARCH UNITS (OPRU) NETWORK SITES



DRAFT: NOT FOR DISTRIBUTION

APPENDIX A: BRANCH PERSONNEL

George P. Giacoia, M.D., is project director of the PPRU Network at the NICHD. His research interest is in the area of neonatal and pediatric pharmacology. He is a fellow of the American Academy of Pediatrics (AAP) and has served as the NIH Liaison to the AAP Committee on Drugs since July 1999. Dr. Giacoia completed a residency in pediatrics and a fellowship in neonatology at the Johns Hopkins University residency program. He received additional training in pediatric pharmacology at Buffalo Children's Hospital. Dr. Giacoia is board certified in pediatrics and neonatal-perinatal medicine. He is the author of approximately 160 articles, book chapters, and abstracts. He has been a reviewer for several journals, including *Pediatrics*, *Journal of Pediatrics*, *Developmental Pharmacology*, *Clinical Pediatrics*, *Obstetrics and Gynecology*, and the *American Journal of Obstetric and Gynecology*. Previous appointments include clinical professor of pediatrics at Georgetown University, professor of pediatrics at the University of Oklahoma, and Director of Neonatology at the Buffalo Children's Hospital.

Jan Leahey is currently the program coordinator for the OPPB at the NICHD. She oversees all administrative activities for the Branch including the budget, contracts, and staffing. Previously, Ms. Leahey served as the executive secretary of the National Children's Study Federal Advisory Committee. Ms. Leahey received her bachelor's degree from the University of Maryland. She has worked in different places in DHHS, including the Office of the Assistant Secretary of Health and Human Services and the Health Resources and Services Administration (HRSA). Ms. Leahey worked in the area of government contracts for more than 10 years, and during the 1990s was designated as a DHHS Contracting Officer. Prior to working in the OPPB, Ms. Leahey was a contracting officer for the NICHD.

Donald R. Mattison, M.D., Captain, USPHS, was appointed senior advisor to the NICHD Director and to the director of the CRMC in 2002 and became Chief of the OPPB in 2004. He provides oversight on obstetric and pediatric pharmacology programs within NICHD. As USPHS Captain, he has been deployed on various missions to provide medical and public health support. In 2005, he was awarded the PHS Achievement Medal for his role in the National Children's Study. Dr. Mattison has held numerous academic, clinical, and research appointments, including medical director of the March of Dimes, dean of the Graduate School of Public Health at the University of Pittsburgh, and professor of obstetrics and gynecology and interdisciplinary toxicology at the University of Arkansas for Medical Sciences. He was elected as a fellow of the American Association for the Advancement of Science in 1997, a fellow of the New York Academy of Medicine in 1999, a member of the Institute of Medicine in 2000; he also received a Distinguished Alumni Award from Augsburg College in 2005. He is the author of more than 200 peer-reviewed articles. Dr. Mattison earned a B.A. (chemistry and mathematics) from Augsburg College in Minneapolis, Minnesota; an M.S. (chemistry) from the Massachusetts Institute of Technology; and an M.D. from the College of Physicians and Surgeons, Columbia University. He did his clinical training in obstetrics and gynecology at the Sloane Hospital for Women in the Columbia-Presbyterian Medical Center in New York. He did his training in pharmacology and toxicology at the NIH.

DRAFT: NOT FOR DISTRIBUTION

David Siegel M.D., F.A.A.P., is a board-certified pediatrician from the New York metropolitan area. After earning his bachelor's degree in biological sciences from the State University of New York at Stony Brook, he attended medical school at New York Medical College and completed his pediatric residency at the Montefiore Hospital of the Albert Einstein School of Medicine. He has had a multi-faceted career, spanning 30 years as a clinician, educator, and administrator in academic and community-based settings. As a clinician he worked in the outpatient, emergency, and inpatient settings. As an educator/administrator he became an ambulatory attending physician at the Children's National Medical Center immediately following completion of his residency program; he then had a major role in the development and management of a new pediatric residency program at INOVA Fairfax Hospital for Children, as the associate residency director, and was the inpatient director at Connecticut Children's Hospital. Following the events of September 11, 2001, while working in the emergency department at the Children's National Medical Center, he initiated and managed the development of a pediatric preparedness training program, which dealt with the medical consequences of weapons of mass destruction, conducted through a grant from HRSA. Dr. Siegel joined NICHD in October 2007 and, in addition to his functions as a medical officer, will be the Institute's program director for Chemical, Biological, Radiological/Nuclear, and Explosive Incidents.

Perdita Taylor-Zapata, M.D., is a board-certified pediatrician from the Washington D.C. area. She graduated from Howard University Medical School in 1994 and completed her pediatric residency training at the Children's National Medical Center in Washington, DC. After residency, she started working at the NIH as a clinic physician in the Pediatric HIV Working Group of the National Cancer Institute (NCI), where she spent seven years taking care of the outpatient and inpatient medical needs of the HIV-positive pediatric patients enrolled in phase I/II clinical treatment trials. She was also involved in medical research, writing parts of clinical protocols and conducting retrospective and prospective research projects. As her career developed while at NCI, she became interested in the use, side effects, and toxicity profiles of medications used in children; in 2004, she published a paper in *Pediatrics* on lipodystrophy in HIV-infected children. Dr. Taylor-Zapata joined the OPPB in August 2004. She is now a medical officer working with a team of experts responsible for the implementation of BPCA activities.

Anne Zajicek, M.D., is a board-certified pediatrician and pediatric clinical pharmacologist. After earning her bachelor's degree in pharmacy from Duquesne University in 1982, Dr. Zajicek went on to obtain her doctorate in pharmacy from the State University of New York at Buffalo in 1985. Dr. Zajicek then completed a postdoctoral fellowship in the Department of Pharmaceutics of St. Jude Children's Research Hospital in 1987. From 1987 to 1991, she was an assistant professor at the University of Colorado School of Pharmacy and a clinical pharmacist at National Jewish Hospital and Research Center. In 1991, she entered medical school at the University of Pittsburgh. In 1998, she completed a pediatrics residency at the Children's Hospital of Pittsburgh. Dr. Zajicek continued her training as a pediatric clinical pharmacology fellow at Stanford University, and she later joined the Food and Drug Administration in the Office of Clinical Pharmacology and Biopharmaceutics. In August 2003, she joined the NICHD as a pediatric medical officer and is currently the project officer for the BPCA Coordinating Center, for the BPCA-sponsored study of pharmacokinetics and pharmacodynamics of sodium

DRAFT: NOT FOR DISTRIBUTION

nitroprusside in pediatric subjects, and for multiple BPCA-sponsored pediatric oncology studies. Dr. Zajicek is also the program officer for the OPRU Network.

DRAFT: NOT FOR DISTRIBUTION

**APPENDIX B: BEST PHARMACEUTICALS
FOR CHILDREN ACT (BPCA) STUDIES**

STUDIES CONDUCTED THROUGH CONTRACTS/GRANTS FROM THE NICHD

Site	Drug/Indication	Study Type
Washington University, St. Louis	Baclofen for treatment of spasticity in children with cerebral palsy	Chart review, Phase I Pharmacokinetics and Pharmacodynamics study Phase II and III dosing, safety, and efficacy studies
Case Western Reserve University	Lithium for the treatment of pediatric mania	Phase I—Pharmacokinetics study; Phase II—8-week, randomized, placebo-controlled, double-blind study
Children's National Medical Center	Lorazepam for the treatment for status epilepticus	Phase I—Pharmacokinetics study
Case Western Reserve University	Lorazepam for the sedation of children on respirators in an intensive care unit	Randomized double-blind active comparator
Duke University and Stanford University	Nitroprusside for the control of blood pressure	Randomized double-blind parallel group
Duke University	Meropenem for intra-abdominal infections in neonates	Phase I and II—Pharmacokinetics and safety study

CROSS-DEPARTMENT AND CROSS-NIH STUDIES

Drug(s)	Details	Organization	Study Type
Ketamine	Evaluate the scientific and safety concerns about the use as an anesthetic in children; initiated September 2004	National Center for Toxicological Research, U.S. Food and Drug Administration (FDA)	Preclinical toxicology studies in primates
Vincristine and Dactinomycin	Evaluate safety and efficacy of treatment for malignancies in children; initiated September 2004	National Cancer Institute (NCI) Children's Oncology Group	Data collection and pharmacokinetic studies
Hydroxyurea	Determine the safety and efficacy of hydroxyurea in children with sickle cell disease (SCD); initiated July 2005	National Heart, Lung, and Blood Institute	Phase III clinical trial
Methotrexate	Evaluate methotrexate-related neurotoxicity; initiated August 2005	NCI Children's Oncology Group	Randomized 2x2 factorial design
Methylphenidate	Evaluate genetic toxicity in mice and monkeys to enable the conduct of a safety assessment in humans; initiated August 2005	National Center for Toxicological Research, FDA	Pre-clinical studies in mice and monkeys

DRAFT: NOT FOR DISTRIBUTION

Drug(s)	Details	Organization	Study Type
Methylphenidate and Adderal®	Evaluate the effects on specific chromosomal damage endpoints in lymphocytes of children diagnosed with Attention Deficit/Hyperactivity Disorder (ADHD); initiated August 2005	National Institute of Environmental Health Sciences (Through Duke University)	Longitudinal observational study of pediatric ADHD patients
Daunomycin	Determine pharmacokinetics in children; initiated September 2005	NCI Children's Oncology Group	Pharmacokinetic studies

(Reference: <http://bpca.nichd.nih.gov/clinical/studies/index.cfm>)

DRAFT: NOT FOR DISTRIBUTION

APPENDIX C: BPCA DRUG PRIORITIZATION LIST

Drugs which have been placed on the lists and published in the *Federal Register* since the implementation of BPCA. Once the drug is selected for consideration for study in children, the Branch works with FDA and the pharmacoepidemiology database to determine feasibility of the potential clinical study. In some instances, it has not been possible to reach agreement among pediatric experts about endpoints for the studies. In other instances, the FDA has suggested that drugs are being developed that seem to offer substantial benefit over the drug originally considered for study. Finally, in some instances, concerns about toxicity suggested the need to develop animal studies before the human studies were designed.

2003	
<ul style="list-style-type: none">• Ampicillin/Sulbactam• Azithromycin• Baclofen• Bumetanide• Diazoxide• Dobutamine• Dopamine• Furosemide• Heparin• Isoflurane	<ul style="list-style-type: none">• Lindane• Lithium• Lorazepam• Meropenem• Metoclopramide• Piperacillin/Tazobactam• Promethazine• Rifampin• Sodium nitroprusside• Spironolactone
2004	
<ul style="list-style-type: none">• Ampicillin• Bupropion• Dactinomycin• Ketamine	<ul style="list-style-type: none">• Metolazone• Morphine• Vincristine
2005	
<ul style="list-style-type: none">• Acyclovir• Clonidine• Cyclosporine• Dexrazoxane• Eletriptan• Ethambutol• Flecainide• Griseofulvin• Hydrochlorothiazide	<ul style="list-style-type: none">• Hydrocortisone valerate• Hydroxychloroquine• Hydroxyurea• Ivermectin• Methadone• Methylphenidate• Sevelamer• Zonisamide
2006	
<ul style="list-style-type: none">• Albendazole• Amantidine• Bumetanide• Clonidine• Daunomycin	<ul style="list-style-type: none">• Furosemide guanfacine• Methotrexate• Mebendazole• Pralidoxime• Rimantadine

DRAFT: NOT FOR DISTRIBUTION

APPENDIX D: BRANCH-SUPPORTED MEETINGS, FISCAL YEAR 2004 THROUGH FISCAL YEAR 2007

- *Efficacy vs. Safety: Study Design Issues*; Rockville, Maryland; February 20, 2004
- *Newborn Drug Development Initiative Meeting*; Baltimore, Maryland; March 29-30, 2004
- *Preclinical Models and Pediatrics Workshop*; Rockville, Maryland; October 28, 2004
- *Consent Issues in Pediatric Clinical Trials*; Rockville, Maryland; November 9, 2004
- *Neuroprotective Agents Conference*; Monterey, California; November 14–19, 2004
- *Improving Pediatric Therapeutics through the BPCA*; Washington, D.C.; May 16, 2005
- *Pediatric Hypertension Workshop (Part I)*; Rockville, Maryland; June 17, 2005
- *Conditions in Children Report Review*; Rockville, Maryland; September 20, 2005
- *Medication in Children Report Review*; Rockville, Maryland; September 28, 2005
- *Meeting on Parental Permission*; Rockville, Maryland; November 4, 2005
- *BPCA Drug List Prioritization Annual Meeting*; Bethesda, Maryland; November 8-9, 2005
- *Pediatric Formulation Initiative Working Meeting*; Bethesda, Maryland; December 6-7, 2005
- *Emergency Research in Children: Ethical, Regulatory, and Clinical Challenges*; Bethesda, Maryland; January 12-13, 2006
- *Global Consortium on Pediatric Pharmacology Meeting* (held in conjunction with the American Society of Clinical Pharmacology and Therapeutics); Baltimore, Maryland; March 6, 2006
- *Society for Gynecologic Investigation Mini-Symposium*; Toronto, Ontario, Canada; March 23, 2006
- *Pediatric Hypertension Workshop (Part 2)*; Bethesda, Maryland; April 7, 2006
- *2nd Annual Summer Institute in Maternal-Fetal Pharmacology*; Denver, Colorado; July 23-29, 2006
- *Meeting on the Waiver of Informed Consent—Community Involvement*; Bethesda, Maryland; September 20, 2006
- *BPCA Drug List Prioritization Annual Meeting*; Bethesda, Maryland; December 5-6, 2006
- *OPRU/PPRU Networks Meeting*; Rockville, Maryland; July 19-20, 2007
- *3rd Annual Maternal-Fetal Summer Institute and 3rd Annual Reproductive and Perinatal Epidemiology Institute*; Montreal Quebec, Canada; July 29-August 4, 2007
- *Methylphenidate Scientific Discussion Meeting*; Rockville, Maryland; September 24, 2007
- *Pediatric Infectious Diseases Meeting: Methicillin Resistant Staph Aureus*; Bethesda, Maryland; November 28-29, 2007

DRAFT: NOT FOR DISTRIBUTION

- *Meeting on Adolescent Health Literacy and use of Over-the-Counter Medications*, Bethesda, Maryland; December 6-7, 2007

DRAFT: NOT FOR DISTRIBUTION

APPENDIX E: MEMBERS OF THE EXPERT PANEL

Sandra Carson, M.D.
Division of Reproductive Endocrinology
and Infertility
Department of Obstetrics and Gynecology
Women and Infant Hospital of Rhode Island
Providence, RI

George Daston, Ph.D.
Miami Valley Laboratories
Procter & Gamble Inc.
Cincinnati, OH

Dave Flockhart, M.D., Ph.D.
Chief, Division of Clinical Pharmacology
Indiana University
Indianapolis, IN

Richard Gorman, M.D.
Chair, Section on Clinical Pharmacology
American Academy of Pediatrics

Michael Katz, M.D.
Senior Vice President for Research and
Global Programs
March of Dimes Foundation
White Plains, NY

Sam Maldonado, M.D., M.P.H.
Vice President, Pediatric Drug Development
Johnson & Johnson Pharmaceutical
Research and Development
Raritan, NJ

Brian Strom, M.D., M.P.H.
Associate Vice Dean
School of Medicine
University of Pennsylvania
Philadelphia, PA

Stan Szeffler, M.D.
Helen Wohlberg and Herman Lambert Chair
in Pharmacokinetics; Co-Director, Weinberg
Clinical Research Unit; Director, Pediatric
Clinical Trials Center
National Jewish Medical and Research
Center
Denver, CO

Richard Weinshilboum, M.D.
Professor, Molecular Pharmacology
Mayo Clinic College of Medicine
Rochester, MN

DRAFT: NOT FOR DISTRIBUTION

**APPENDIX F: BRANCH PUBLICATIONS, FISCAL YEAR 2004
THROUGH FISCAL YEAR 2007**

(Branch staff names appear in **bold** below.)

- Attardi, B.J., Zeleznik, A., Simhan, H., Chiao, J.P., **Mattison, D.R.**, & Caritis, S.N. (2007). Comparison of progesterone and glucocorticoid receptor binding and stimulation of gene expression by progesterone, 17-alpha hydroxyprogesterone caproate, and related progestins. *Am J Obstet Gynecol*, 197, e591-597.
- Berlin, C.M., LaKind, J.S., Fenton, S.E., Wang, R.Y., Bates, M.N., Brent, R.L., Condon, M., Crase, B.L., Dourson, M.L., Ettinger, A.S., Foos, B., Furst, P., **Giacoa, G.P.**, Goldstein, D.A., Haynes, S.G., Hench, K.D., Kacew, S., Koren, G., Lawrence, R.A., Mason, A., McDiarmid, M.A., Moy, G., Needham, L.L., Paul, I.M., Pugh, L.C., Qian, Z., Salamone, L., Selevan, S.G., Sonawane, B., Tarzian, A.J., Rose Tully, M., & Uhl, K. (2005). Conclusions and recommendations of the expert panel: technical workshop on human milk surveillance and biomonitoring for environmental chemicals in the United States. *J Toxicol Environ Health A*, 68, 1825-1831.
- Frattarelli, D.A., Reed, M.D., **Giacoa, G.P.**, & Aranda, J.V. (2004). Antifungals in systemic neonatal candidiasis. *Drugs*, 64, 949-968.
- Giacoa, G.P.**, Birenbaum, D.L., Sachs, H.C., & **Mattison, D.R.** (2006). The newborn drug development initiative. *Pediatrics*, 117, S1-S8.
- Giacoa, G.P.**, & **Mattison, D.R.** (2005). Newborns and drug studies: The NICHD/FDA newborn drug development initiative. *Clin Ther*, 27, 796-813.
- Giacoa, G.P.**, & **Mattison, D.R.** (2006). Selected proceedings of the NICHD/FDA newborn drug development initiative: Part II. *Clin Ther*, 28, 1337-1341.
- Giacoa, G.P.**, **Taylor-Zapata, P.**, & **Mattison, D.** (2007). Need for appropriate formulations for children: The National Institute of Child Health and Human Development Pediatric Formulations Initiative, Part 1. *International Journal of Pharmaceutical Compounding*, 11(1), 5-8.
- Giacoa, G.P.**, **Taylor-Zapata, P.**, & **Mattison, D.** (2007). Need for appropriate formulations for children: The National Institute of Child Health and Human Development Pediatric Formulations Initiative, Part 2. *International Journal of Pharmaceutical Compounding*, 11(3), 220-221.
- Jacobson-Kram, D., **Mattison, D.**, Shelby, M., Slikker, W., Tice, R., & Witt, K. (2007). Methylphenidate and chromosome damage. *Cancer Lett*, Dec 3, [Epub ahead of print].
- Koren, G., Kramer, M., & **Mattison, D.** (2007). The Summer Institutes in Maternal-Fetal Pharmacology: Building critical mass in a neglected area. *J Obstet Gynaecol Can*, 29, 544-545.
- Mattison, D.**, & **Zajicek, A.** (2006). Gaps in knowledge in treating pregnant women. *Gend Med*, 3: 169-182.

DRAFT: NOT FOR DISTRIBUTION

- McClure, E.M., Goldenberg, R.L., Brandes, N., Darmstadt, G.L., Wright, L.L., Armbruster, D., Biggar, R., Carpenter, J., Free, M.J., **Mattison, D.**, Mathai, M., Moss, N., Mullany, L.C., Schrag, S., Tielsch, J., Tolosa, J., Wall, S.N., Schuchat, A., & Smine, A. (2007). The use of chlorhexidine to reduce maternal and neonatal mortality and morbidity in low-resource settings. *Int J Gynaecol Obstet*, *97*, 89-94.
- Simhan, H.N., Chiao, J.P., **Mattison, D.R.**, & Caritis, S.N. (2007). Human decidual cell Toll-like receptor signaling in response to endotoxin: The effect of progestins. *Am J Obstet Gynecol*, *Oct 11*, [Epub ahead of print].
- Slikker, W., Jr., Young, J.F., Corley, R.A., Dorman, D.C., Conolly, R.B., Knudsen, T.B., Erstad, B.L., Luecke, R.H., Faustman, E.M., Timchalk, C., & **Mattison, D.R.** (2005). Improving predictive modeling in pediatric drug development: Pharmacokinetics, pharmacodynamics, and mechanistic modeling. *Ann N Y Acad Sci*, *1053*, 505-518.
- Taylor-Zapata, P.**, & **Mattison, D.R.** (2007). Making progress for how medicines are used in children. *Arch Pediatr Adolesc Med*, *161*, 916; author reply, 916-917.
- Ward, R.M., Benitz, W.E., Benjamin, D.K., Jr., Blackmon, L., **Giacioia, G.P.**, Hudak, M., Lasky, T., Rodriguez, W., & Selen, A. (2006). Criteria supporting the study of drugs in the newborn. *Clin Ther*, *28*, 1385-1398.
- Zajicek, A.**, & **Giacioia, G.P.** (2007). Obstetric clinical pharmacology: Coming of age. *Clin Pharmacol Ther*, *81*, 481-482.
- Zhang, S., Mada, S.R., **Mattison, D.**, Caritis, S., & Venkataramanan, R. (2007). Development and validation of a high-performance liquid chromatography-mass spectrometric assay for the determination of 17alpha-hydroxyprogesterone caproate (17-OHPC) in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*, *856*, 141-147.
- Zito, J.M., Safer, D.J., Valluri, S., Gardner, J.F., Korelitz, J.J., & **Mattison, D.R.** (2007). Psychotherapeutic medication prevalence in Medicaid-insured preschoolers. *J Child Adolesc Psychopharmacol*, *17*, 195-203.