DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
National Institute of Child Health and Human Development

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Good morning, Mr. Chairman. I am Donald Mattison, Chief of the Obstetric and Pediatric Pharmacology Research Branch at the National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH). We appreciate the opportunity to appear before you and the rest of the Committee to discuss NIH's research activities in relation to implementation of the pediatric drug testing program under the Best Pharmaceuticals for Children Act (BPCA).

The BPCA legislation was enacted in 2002 to address the growing recognition that the great majority of pharmaceutical drugs prescribed for children had never been tested for pediatric use. Health care professionals were forced to depend upon experience and their best judgment in prescribing medications for their pediatric patients. However, without a strong evidentiary base, it becomes difficult for practitioners who work with children of various ages who are at a range of developmental stages to estimate what the correct dose may be. Since children may metabolize or respond to a drug differently from an adult, that drug's effects may be variable – too high a dose for a given child poses risks of toxicity, too low a dose may be ineffective.

Under current law, the NIH is directed to conduct research-related activities in three general categories: identifying and prioritizing those drugs needing study in children, developing new study requests in collaboration with the Food and Drug

Administration (FDA) and other pediatric experts, and supporting studies on priority drugs after manufacturers decline to do so. In most cases, the drugs under consideration for study by the NIH are for off-patent or older medications for which no marketing exclusivity can be granted. In some instances, these medications have been in use for over thirty years, and yet relative dosing, efficacy and safety data have yet to be compiled for children.

This is a challenging area of research. The available data are mostly on adults; some of the conditions these drugs are used to treat are relatively rare; effects on children's growth and development have been largely unrecognized and certainly cannot be studied in adults. In addition, human subjects concerns, with a critical focus on balancing risks versus benefits, are of particular importance in pediatric research. Moreover, long-term follow-up of the possible effects on growth and development can be an important, but costly, aspect of pediatric clinical trials. To conduct these studies and obtain generalizable data, we often need to enroll larger numbers of pediatric patients than have been previously studied.

In order to prioritize the drugs needing study, NICHD has developed an annual cycle of data gathering, expert consultation and critical analysis. The purpose of the process is to distill, from the total number of off-patent drugs (approximately 200) to a manageable number (five to ten) for study in the following year. We look at whether dosing, safety and efficacy data are already available from a reputable source and whether additional data are needed, whether new studies will produce health benefits for some subpopulation of children, the balance between how frequently the condition to be treated may occur and the severity of the condition, and whether there is a need to

reformulate a drug so that children will be able to use it. For example, a drug that only comes in tablet form cannot readily be taken by an infant or by a young child with cerebral palsy.

Together with other NIH Institutes and Centers, the FDA, and other pediatric experts, the NICHD has made significant progress on this front – as required by the BPCA – by developing and publishing an annual list of approved drugs in need of further study in the pediatric population. As of December 2006, 106 total drugs have been discussed in a scientific forum to decide if they should be listed, or whether we need further review of the medical literature or outside consultation. From this group of drugs, approximately 60 drug/indication pairs have been listed as off-patent priority drugs that require further pediatric studies. These annual lists have been provided to the Committee in Table 1.

From each list of prioritized drugs, the FDA, in consultation with the NIH, develops and issues a series of Written Requests to the drugs' manufacturers; to date, all but one has been declined by the manufacturer, and the drugs have been referred to the NIH for study. Table 2 shows the 13 drug studies the NIH is currently funding and the status of each. We could not be conducting this work without the scientific expertise and financial support from the other NIH Institutes and Centers that have significant pediatric research portfolios. BPCA implementation is a major trans-NIH collaboration, as 19 NIH Institutes and Centers are investing more than $25 million annually.

While many of the projects first funded after the enactment of the BPCA are in their final year(s) of funding and results are expected in the next few years, since the enactment of BPCA, we have learned a great deal about the field of pediatric

pharmacology and reach out regularly to the field to better understand the needs of the clinicians who treat children. For example, research findings suggest a need for testing a variety of drugs and other approaches to address the increasing problem of obesity-related hypertension in adolescents (high blood pressure related to weight gain), and improving the health of these young people. We also have organized and invited experts to numerous workshops on the myriad of issues that surround pediatric studies, including formulations for use at different stages of development, the design requirements and ethics of clinical trials in this special population.

Some of what we learned was unexpected. Information on a number of drugs, which we initially thought would require only Phase III or IV clinical trials in children to provide the data we were seeking, proved to be completely inadequate, and we were forced to revise our plans and fund more preliminary studies on safety and efficacy. A number of those studies are now underway.

In summary, significant progress has been made to establish the infrastructure and support for pediatric drug studies that can provide critical information regarding the safe use of these medications in children. We look forward to continuing this important work, and I would be happy to answer any questions you or the other members of the Committee may have.

TABLE 1

2003:

Ampicillin/Sulbactam: treatment of pediatric infections
Azithromycin:

- Prevention of bronchopulmonary dysplasia in infants with Ureaplasma urealyticum
- Prevention and treatment of Chlamydia conjunctivitis and pneumonia

Baclofen: treatment of spasticity in children with cerebral palsy
Bumetanide: treatment of pediatric hypertension
Diazoxide: treatment of hypoglycemia in children
Dobutamine: treatment of hypotension and low cardiac output in children
Dopamine: treatment of hypotension and low cardiac output in children
Furosemide: treatment of pediatric hypertension
Heparin: prevent blood clotting in children
Isofluorane: produce general anesthesia in children
Lindane: treatment of lice and scabies in children
Lithium: treatment of mania in children with bipolar disorder
Lorazepam:

- Treatment of status epilepticus in children
- Provide sedation for children in intensive care being treated with a respirator

Meropenem: treatment of pediatric infections
Metoclopramide: treatment of children with Gastroesophageal reflux
Piperacillin/Tazobactam: treatment of pediatric infections
Promethazine: treatment of nausea and vomiting in children
Rifampin:

- Treatment of Methicillin resistant Staphylococcus aureus endocarditis in children
- Treatment of central nervous system shunt infections in children

Sodium Nitroprusside: produce hypotension in children undergoing surgery to reduce blood loss
Spironolactone: treatment of pediatric hypertension

2004:

Ampicillin: treatment of pediatric infections
Dactinomycin: treatment of pediatric cancer
Ketamine: sedation of children for short procedures
Metolazone: treatment of pediatric hypertension
Vincristine: treatment of pediatric cancer

2005:

Acyclovir: treatment of pediatric infections with herpes
Clonidine:

- Treatment of autism in children
- Treatment of ADHD in children

Cyclosporine: prevention of organ transplant rejection in children
Ethambutol: treatment of children with tuberculosis infections
Flecanide: treatment of cardiac arrhythmias in children
Griseofulvin: treatment of Tinea capitis infections in children
Hydrochlorothiazide: treatment of pediatric hypertension
Hydrocortisone valerate: treatment of inflammatory skin conditions in children
Hydroxychloroquine: treatment of connective tissue disorders in children
Ivermectin: treatment of scabies infection in children
Methadone: treatment of neonates undergoing opioid withdrawal
Sevelamer: treatment of hyperphosphatemia in children with chronic renal failure
Morphine: treatment of pain in pediatric patients

2006:

Albendazole: treatment of children with parasitic infections
Amantidine: treatment of children with influenza
Daunomycin: treatment of children with cancer
Guanfacine: treatment of children with ADHD
Methotrexate: treatment of children with cancer
Mebendazole: treatment of children with parasitic infections
Pralidoxime: treatment of children with organophosphate poisoning
Rimantadine: treatment of children with influenza
Hydroxyurea: treatment of children with sickle cell disease to prevent painful blood sickling crisis
Methylphenidate: characterize safety in this drug used to treat children with ADHD

TABLE 2

The following pediatric drug studies currently are being supported with NIH funding:

- Lorazepam – Phase I, Phase II and Phase III clinical studies to support treatment for status epilepticus (NINDS)

- Lorazepam – Phase I, Phase II and Phase III clinical studies to support sedation of children on respirators in an intensive care unit

- Nitroprusside – Phase I, Phase II and Phase III clinical studies to understand use to reduce blood pressure during surgery to reduce blood loss

- Lithium- Phase I, Phase II and Phase III clinical studies to define treatment of mania in children with bipolar disorder (NIMH)

- Baclofen- Phase I, Phase II and Phase III clinical studies to understand oral treatment of spasticity, most commonly from cerebral palsy

- Vincristine – Phase I, Phase II and Phase III clinical studies to enhance treatment for malignancies in children (NCI)

- Dactinomycin – Phase I, Phase II and Phase III clinical studies to enhance treatment for malignancies in children (NCI)

- Daunomycin – Pharmacokinetics, safety, efficacy of daunomycin to treat childhood cancers and relationship to body weight (NCI)

- Methotrexate - Phase II and Phase III clinical studies to improve treatment outcomes for pediatric patients with high risk acute lymphoblastic leukemia (NCI)

- Ketamine - Preclinical studies to evaluate the scientific and safety concerns about the use as an anesthetic in children

- Hydroxyurea- Preclinical, Phase I, Phase II and Phase III clinical studies to improve treatment of children with sickle cell disease (NHLBI)

- Methylphenidate – Preclinical and clinical evaluation of pharmacokinetics and safety to understand reports of cytogenetic toxicity (NIEHS)

- Morphine – preclinical basic science evaluations of the developmental expression of opioid receptors to better understand management of pain in children of different developmental stages and safety issues in treating pain in neonates