

NICHD Global Consortium on Pediatric Pharmacology Meeting
March 6, 2006
Hyatt Regency Baltimore
Baltimore, MD

This meeting was sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS).

The rationale for the meeting was as follows:

Since the last discussion about 4 years ago, much has changed internationally in pediatric pharmacology, including legislation and research activity. These changes and upcoming international meetings provide an opportunity to reexamine the potential benefit of creating a global consortium on pediatric pharmacology.

The goals of the meeting were to discuss:

- The benefit of creating a global consortium in pediatric pharmacology
 - Global collaboration in developed countries
 - Global collaboration in developing countries
- The next steps in this conversation
 - Meeting in Stockholm, Sweden (European Society of Developmental Perinatal and Paediatric Pharmacology [ESDP])
 - Meeting in Shanghai, China (International Union of Basic and Clinical Pharmacology [IUPHAR] Satellite Meeting).

Welcome

Donald R. Mattison, M.D., Chief, OPPB, NICHD, NIH, DHHS; and Stuart MacLeod, M.D., Ph.D., FRCPC, Executive Director, Child and Family Research Institute, British Columbia Children's Hospital

Dr. Mattison welcomed the participants and noted that this meeting provides an opportunity to reassess potential international collaboration. This meeting is fortuitous in that it precedes the upcoming meetings in Sweden and China, and it allows participants from Europe and Asia to describe current activities in their respective countries. Discussions of strategies for enhancing pediatric pharmacology allow information sharing and help identify potential collaborations. Dr. Mattison cited a recent collaboration between Canada and the United States, which evolved from discussion between Michael Kramer, M.D., Scientific Director of the Human Development and Child and Youth Health Research Institute, Canadian Institute for Health Research, and NICHD staff. A joint Canadian-U.S. course in obstetric pharmacology was developed and implemented in 2005. Dr. Mattison hopes this course is the first in a number of long-standing and successful joint pediatric pharmacology activities. Dr. Mattison credited Gideon Koren, M.D., for his efforts in developing and implementing the course. Subsequent discussions have focused on a joint Canadian-U.S. solicitation for obstetric and pediatric pharmacology activities. Dr. Mattison

explained that he would be listening to the meeting presentations and discussions with the hope of discovering new potential collaborations between NICHD and its international partners.

Dr. MacLeod thanked the participants for attending the meeting and noted the broad representation of people interested in pediatric clinical pharmacology and the international aspects thereof. This meeting evolved about a year ago from a meeting in Vancouver, British Columbia, of Canadian pediatric clinical pharmacologists from the 17 academic medical centers with interests in better drug therapy for children. Dr. Mattison, Terence Stephenson, M.D., from the United Kingdom, and Hidefumi Nakamura, M.D., Ph.D., and others who attended the Vancouver meeting believed that it was time to reexplore the opportunities in international pediatric pharmacology. International pediatric pharmacology experts have met twice to initiate a global movement in pediatric pharmacology, but tangible results have yet to be produced. Because of the evolution of a highly organized group in Europe, the development of connections with IUPHAR (for example, the upcoming Shanghai satellite meeting), and the interest of the International Pediatric Association, pediatric clinical pharmacology experts are moving closer to the reality of a global consortium. Dr. MacLeod urged the meeting participants to produce tangible recommendations for international pediatric clinical pharmacology.

Introduction

George P. Giacoia, M.D., Program Scientist for the Pediatric Pharmacology Research Unit Network, NICHD, NIH, DHHS

Dr. Giacoia explained that a Global Consortium on Pediatric Pharmacology (GCPP) was conceptualized during a joint meeting of ESDP and the Pediatric Pharmacology Research Unit (PPRU) Network in Liège, Belgium, in 2002. Dr. Giacoia listed the overall vision and overall objective for a GCPP:

- The overall vision is to improve drug therapy for the pediatric age group worldwide.
- The overall objective is to create a global network of physicians, scientists, and other stakeholders that will work toward improving drug therapy for infants, children, and youths through research and education.

The following recommendations for a GCPP were made at the Liège meeting in 2002:

- Avoid duplication and work with other organizations (for example, World Health Organization [WHO], government regulatory agencies, and funding agencies)
- Identify list of important drugs
- Give top priority to the needs of children in developing countries
- Recruit and work with experienced individuals in developing countries to guide prioritization of problem areas
- Start with PPRU units and expand to other networks
- Consortium should develop focused training programs, visiting professorships, NIH conferences to link people from developing countries with existing knowledge and technology
- Need for identification and interaction with key stake holders in developing countries
- Top issue identified: availability of specific drugs and appropriate formulations of drugs currently use in pediatrics.

Dr. Giacoia explained that—because of more experience, problems, and resolutions—a GCPP should now be reconsidered. He listed the following legislative changes:

- Best Pharmaceuticals for Children Act (BPCA)—in effect since 2002
- European Parliament resolution on Medicinal Products for Pediatric Use
- Medicines Investigation for the Children of Europe (MICE)—pending final passage.

Role of the International Pediatric Association

Jane G. Schaller, M.D., Executive Director, International Pediatric Association; Visiting Professor of Pediatrics, University of British Columbia

Dr. Schaller characterized the International Pediatric Association (IPA):

- Founded in Europe in 1910
- First international congress held in Paris in 1912
- Original purpose: sharing friendship and knowledge among pediatricians
- 23 subsequent congresses held on all continents
- Next congresses: Athens 2007, Johannesburg 2010.

Since its founding and the present, IPA has changed:

- Members cover the globe—national, regional, and specialty societies
- Evolution from meetings to action
- Current areas of action include
 - Child health in Africa
 - Childhood tuberculosis
 - Children’s environmental health
 - Essential medicines for children
 - Child health in humanitarian emergency
 - Universal immunization
 - Newborn survival and health
 - Nutrition
 - Adolescent health
 - Quality of care
 - HIV/AIDS
 - Teaching and training.

Current IPA working relationships include:

- WHO
- United Nations Children’s Fund (UNICEF)
- Global Alliance for Vaccines and Immunization
- Partnership for Maternal Newborn and Child Health
- Alliance for Prevention of Obesity and Chronic Disease
- Stop TB.

Dr. Schaller characterized IPA’s issues with and program goals for the WHO Essential Medicines for Children List:

- Issues
 - The list provides standards for the developing world but is not child friendly.
 - No consensus exists concerning definitions of essential medicines for children:
 - Integrated Management of Childhood Illness list of essential medicines is too limited.
 - Pediatric formularies from rich countries are too extensive.
 - Unique developmental stages of children are accorded insufficient attention.
 - Many drugs are not formulated for infants and children.
 - Many drugs are not tested in infants and children.
 - Many drugs are not available for children at country level.
- Program goals
 - Define essential medicines for children at global and regional levels.
 - Review WHO treatment guidelines for children.
 - Review WHO Essential Medicines List for suitability for children.
 - Define needed changes and advocate for their adoption.
 - Develop a global drug list and formulary for children.
 - Work for availability of essential medicines at country level.
 - Establish continuing monitoring and updating system.

IPA's recommendations for the WHO Essential Medicines for Children include:

- Establish IPA program committee of experts representing global community
- Work with partners such as WHO, UNICEF, the previously mentioned partners, and others to address issues
- Explore working relationships with
 - Pediatric Pharmacology Global Consortium
 - NICHD PPRU Network.

Updates and Summary of Current Activities

ESDP 2006 Meeting in Stockholm

Johannes N. van den Anker, M.D., Ph.D., President-Elect, ESDP; Professor, Department of Pediatrics, Children's National Medical Center

Dr. van den Anker presented the agenda for the upcoming ESDP meeting in Stockholm, Sweden:

Thursday, June 15

- Symposium 1: Neonatal Therapy—Something Old, Something New
 - Clinical trials of surfactants: Henry Halliday (Belfast, Northern Ireland)
 - New applications of therapy with inhaled nitric oxide (NO): Claes Frostell (Stockholm, Sweden)
 - Pharmacological treatment of neonatal encephalopathies: Stéphane Marret (Rouen, France)
 - Perinatal strategies: Henrik Hagberg (Gothenburg, Sweden)
 - Oral presentations
- Symposium 2: Paediatric Medicines—What Is Happening in Europe?
 - European regulation: Daniel Brasseur (Brussels, Belgium)

- Predictive value of juvenile animal studies: Paul Baldrick (North Yorkshire, United Kingdom)
- Dose finding studies in children: Stephanie Läer (Düsseldorf, Germany)
- What industry-driven paediatric research on off-patent and patent-protected drugs will be stimulated by the European Directive?: Klaus Rose (Basel, Switzerland)
- The European Perspective of Antibiotics Resistance—the Need of New Strategies: Otto Cars (Stockholm, Sweden)
- General Assembly.

Friday, June 16

- Symposium 3: Paediatric Pharmacoepidemiology
 - Advantages and possibilities in using register-based prescription data—the Finnish experience: Heli Malm (Helsinki, Finland)
 - Building an international antiepileptic drugs and pregnancy register when national databases are insufficient (EURAP): Torbjörn Tomson (Stockholm, Sweden)
 - Epidemiology of psychotropic drugs in Italy: Maurizio Bonati (Milan, Italy)
 - Epidemiology of psychotropic drugs in United Kingdom: Ian Wong (London, United Kingdom)
 - Doping in teenagers: Christian Möller (Gothenburg, Sweden)
 - Oral presentations
 - Oral poster presentations
 - “News room”: Meeting with the press
 - Congress Dinner at Junibacken.

Saturday, June 17

- Symposium 4: Immunotherapy for Paediatric Rheumatic Disorders
 - Overview of new immunotherapeutic principles: Ann-Marie Prieur (Paris, France)
 - Anti-TNF therapy (eterncept) for juvenile rheumatic disorders: Daniel Lovell (Cincinnati, United States)
 - Anti-IL2R (daclizumab)—an experimental therapy for chronic uveitis complicating juvenile idiopathic arthritis: Anders Fasth (Gothenburg, Sweden)
 - New biologics for paediatric rheumatic diseases: Patricia Woo (London, United Kingdom)
 - Oral poster presentations
- Symposium 5: Pregnancy and the Developing Foetus
 - Foetal analgesia and stress responses at invasive interventions: Jan Deprest (Leuven, Belgium)
 - How to introduce new drug treatment in pregnant women?: Risto Kaaja (Helsinki, Finland)
 - Treatment of urea cycle defects: Mendel Tuchman (Washington, DC, United States)
 - Plenary lecture
 - Closing Ceremony.

ESDP Activities

Imti Choonara, M.D., MRCP, Secretary-General of ESDP; Professor, Academic Division of Child Health, Derbyshire Children's Hospital, University of Nottingham

Dr. Choonara characterized ESDP:

- Founded in 1988
- Congress held every 2 years
- Largest international pediatric pharmacology meeting
- Lectures
- Free communications
- IUPHAR affiliation?

Dr. Choonara characterized the ESDP membership:

- 63 members
- 48 in Europe
- Corresponding members
- 10 in North America
- 3 in Israel
- 2 in Australasia.

Paediatric Perinatal Drug Therapy (PPDT) is the official journal of ESDP and the Neonatal and Paediatric Pharmacists Group. The journal was founded in 1997 and has an editorial board and independent publisher. PPDT editorial board members are from eight countries (France, Australia, Germany, Canada, Italy, New Zealand, United Kingdom, and United States). Researchers need to submit papers for publication in the journal to be eligible for editorial board membership.

Paediatric Clinical Trials annual workshops were held in Derby, United Kingdom, in 2003 and 2005 and in Canada in 2004. The 2006 workshop will be held in Toronto, Canada, on September 28–29. The workshops are conducted jointly by PPDT and the Association of Clinical Research Professionals. Dr. Choonara characterized the Paediatric Clinical Trials Register:

- Only one pediatric register
- Web site: www.dec-net.org
- 195 trials on register
- Participating countries include Italy, France, Spain, and the United Kingdom
- Will expand to other European countries
- Eventually worldwide?

A Paediatric Clinical Trials network is being established in the United Kingdom; the coordinating center will be located in Liverpool. Training and collaboration activities of the network include the following:

- Training in the United Kingdom
 - Pediatric clinical pharmacology
 - Approved subspecialty of pediatrics in United Kingdom
 - 1st trainee completed

- 3 other trainees
- Training in Europe
 - 14 pediatric clinical pharmacology
 - 14 trainees
 - Finland, France, United Kingdom
- Collaboration efforts among
 - Derby
 - Milan
 - Rotterdam
 - Paris
 - London, Ontario.

Dr. Choonara urged the meeting participants and other pediatric clinical pharmacology experts to create a worldwide Paediatric Clinical Trials Register, join ESDP, support PPDT, and do research together.

Pediatric Research in France: Network of Clinical Investigation Centers

Evelyne Jacqz-Aigrain, M.D., Ph.D., Professor, Department of Paediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, Paris

Dr. Jacqz-Aigrain described the pediatric research collaborations in France:

- Research structures—Institut National de la Santé et de la Recherche Médicale (INSERM), Délégation à la Recherche Clinique, Agence Nationale de la Recherche
- Hospitals—Paris, Lyon
 - Pediatric Pharmacology departments (three)
- Universities
- Pharmaceutical industries and Les Entreprises du Médicament
- Agencies—Agence Française de Sécurité Sanitaire des Produits de Santé, European Agency for the Evaluation of Medicinal Products (EMA).
- Aim of federating the existing competences in pediatric clinical research.

The focus of Dr. Jacqz-Aigrain’s presentation was the French Network of Pediatric Clinical Investigation Centers (CIC.P). From 2000, pediatric departments dedicated to clinical research were created and financed by both INSERM and hospitals. The pediatric departments were integrated into teaching hospitals. The objectives of the CIC.P network are to:

- Optimize drug evaluation in children by combining the existing strengths in pediatric medicine, clinical pharmacology, data management, and biostatistical analysis
- Stimulate clinical research in children, including research in physiology, physiopathology, pharmacology, and therapeutics, including translational research
- Increase teaching and training.

The network of clinical investigation centers in France includes:

- 25 clinical investigation centers
 - 8 CIC.P—Pediatric network
 - Cardiovascular network

- Gastroenterology network
- Endocrinology network
- Neurosciences network.

Dr. Jacqz-Aigrain described the 2005 French pediatric population as follows:

Cumulative pediatric activities in hospitals connected to the network in 2005

Number of pediatric beds	1,843
Number of daycare beds	192
Number of hospitalized patients	241,433
Number of pediatric consultations	482,543

Dr. Jacqz-Aigrain characterized the multidisciplinary team dedicated to pediatrics:

- Protocols in all age groups (neonates to pregnant women)
- Team trained in clinical evaluation—nurses, lab technicians, and medical doctors
- Team of high technicity—trained to techniques central in both medical care and evaluation
- Pain scores in pediatric patients
- Management of central catheter, suprapubic tube
- Microdialysis, calorimetry, impedancemetry
- Pharmacokinetics (PK).

Dr. Jacqz-Aigrain presented a chart showing the collaborating research structures among INSERM research departments, CIC.P, clinical departments, medicotechnical departments, CRB 2004, CIC EC 2003, URC, and CIB 2004. Translational research includes:

- Leptin and lipo-atrophic diabetes (C. Levy-Marchal)
 - Metabolic effects of leptin in lipo-atrophic diabetes (three bar graphs)—sensitivity to insulin, liver volume, triglycerides
- Pathophysiology, prevention, and treatment of neonatal ischemic brain lesions (P. Gressens)
 - Animal model—excitotoxic-induced brain lesions in the newborn rabbit
 - Screening of 250 pharmacological agents protective effects against melatonin
 - Clinical research—impact of melatonin on brain lesions in premature babies
- Pharmacogenetics and adverse drug reactions (E. Jacqz-Aigrain).

CIC.P network 2005 activities include:

- 136 protocols
 - 60 percent drug evaluation
 - 40 percent physiology-pathology
 - 28 percent single center
 - 41 percent multicenter—national
 - 29 percent multicenter—international.

Dr. Jacqz-Aigrain characterized CIC.P collaborations:

- At the national level
 - Specialized networks
- At the European level

- Medical networks: Penta—Task Force in Europe for Drug Development for Young (TEDDY)
- Infrastructure networks through the European Clinical Resources Infrastructures Network
- Future European EMEA network
- European Network for Drug Investigation in Children (ENDIC) and members of ESDP.

Pediatric Pharmacology: Australia, Regional, and Global 2006

Noel E. Cranswick, Med.Sc. M.B.B.S., FRACP, Director, Australian Paediatric Pharmacology Research Unit, Murdoch Children's Research Institute and the Royal Children's Hospital; Associate Professor, University of Melbourne, Parkville, Australia

Dr. Cranswick was not present for this multimedia presentation. The presentation topics included:

- Local developments in Melbourne
- National developments in Australia
- Regional developments in Southeast Asia
 - Indonesia
 - India
- WHO initiatives.

Local developments in Melbourne include:

- Dedicated clinical trials facility
 - 9 subject inpatient treatment area
 - 3 outpatient rooms
- Over the last 5 years
 - 40 pediatric clinical drug trials
 - Majority industry sponsored.

The Web site for the Melbourne clinical trials facility is <http://www.appru.com>. Photographs of the clinical trials facility were presented, showing that it is a modern facility that is uniquely situated.

National developments in Australia include:

- Australian Health Ministers' Advisory Council (AHMAC)—Working Party
 - Assessment and registration process of medicines for pediatric use—status report of the pediatric pharmaceuticals working group; 2006
 - Government has yet to respond
 - No proposed legislation at present
 - Report can be found at <http://www.health.wa.gov.au/publications/AHMACPaediatricPharmaceuticalsWorkingGroupInterimReport.pdf>.
- AHMAC—proposed Australian national formulary
 - Aims
 - Independent
 - Authoritative
 - National

- Use current best evidence
- Congruent with national treatment guidelines and drug labels (product information)
- Widely accessible (including electronic)
- Regularly and reliably updated.

Regional developments in Southeast Asia include:

- Indonesia—appropriate use of medicine in children
 - Partially WHO funded
 - Based in Jakarta
 - Run by single opinion leader—Dr. Purnamawati S. Pujiarto (pediatric gastroenterologist)
 - Focused on appropriate use of medicines in children
 - Addressing local (Indonesian) issues
 - Using multimedia approach including radio and newspapers to reach public
- India—new textbook for local use (India) titled *Drug Therapy in Paediatrics*
 - By Dr. C.M. Kamaal, Department of Pharmacology, J. N. Medical College, Amu, Aligarh
 - Single author
 - Mostly local advisory board
 - Dr. Cranswick served as chief of the advisory board for this textbook.

WHO-funded developments for the Essential Medicines List for Children include:

- Initial analysis of the current list through pediatric clinical pharmacology in Melbourne
- Interim report January 2006 (complete)
- Final report due May 2006
- Focused on current list and availability of formulations for children
- Need to look at what is missing separately.

Japan

Hidefumi Nakamura, M.D., Ph.D., Director, Division of Clinical Research and Office of Drug Evaluation, National Children's Medical Center, National Center for Child Health and Development, Tokyo

Dr. Nakamura characterized the Japanese Society of Developmental Pharmacology and Therapeutics (JSDPT):

- Activity started as a Symposium on Developmental Pharmacology in 1974
- About 300 registered members
 - Fewer active members
 - Mostly pediatricians, some pharmacists
 - Very few “clinical pharmacologists” involved
 - Recently, more attendants from industries
- Affiliated with Japan Pediatric Society (JPS) but not with the Japanese Society of Clinical Pharmacology and Therapeutics.

The 31st annual meeting of the JSDPT was held in 2004 and included the Japanese Society of Pediatric Pharmacology and Therapeutics. The second joint meeting of these two societies will be held in 2006.

Dr. Nakamura explained the current Japanese situation with off-label use of drugs in children:

- Off-label use is common.
- A survey of package inserts for commonly prescribed drugs in children (Onishi, Morita, et al., 2000) found that
 - Only 15.8 percent had a pediatric dosage
 - 33.3 percent did not have pediatric dosage but had no negative comments on pediatric use
 - 38.5 percent said, “Safety has not been established in children.”

JPS considers facilitation of clinical trials and solution of off-label use as a mission. The JPS Committee on Drugs drafted an action plan to fulfill JPS’s mission. Under the action plan, JPS:

- Will reevaluate the priority list and further categorize the off-label drugs and then work on possible solutions for each category
- Seek possible solution for the use of chemicals and unauthorized formulations
- Seek for stronger support system
- Work on strengthening infrastructure of pediatric clinical trials
 - Positively engage in the Ministry of Health, Labor and Welfare (MHLW) supported investigator-initiated registration-directed clinical trials
 - Discuss with JPMA [Japan Pharmaceutical Manufacturers Association?] and regulatory authorities
- Work on establishing legal/regulatory framework to facilitate clinical trials
- Involve actively in postmarket surveillance.

Two groups of pediatric specialists are involved in addressing pediatric off-label drug use:

- JPS Committee on Drugs
- Grant-supported activity and research task force on the solution of off-label use in children
 - Started in 1998
 - Representatives from all the 20 societies of pediatric subspecialties are actively involved.

Dr. Nakamura presented a chart titled “New MHLW project to solve off-label use starting 2005.”

The chart depicted the role and relationships of the National Center for Child Health and Development (NCCHD) in the process of solving off-label pediatric drug use. The project aims to evaluate 100 drugs in 5 years. The MHLW Committee on Unlicensed Drugs will:

- Evaluate essential drugs that are approved in major countries but do not exist in Japan
 - Drugs whose approval is strongly requested by physicians and patient groups
- Recommend either manufacturer-sponsored or investigator-initiated (registration-directed) clinical trials (similar to a U.S. Food and Drug Administration [FDA] written request).

Dr. Nakamura explained that the Center for Clinical Trials of the Japan Medical Association supports investigator-initiated, registration-directed clinical trials for drug approval and is funded by grants from MHLW. Three pediatric projects have started and one more pediatric project is under preparation. NCCHD will play a key role in the pediatric clinical trials.

Dr. Nakamura presented a chart titled “Revision of the Pharmaceutical Affairs Law” that compared activities before and after enactment of the law in July 2003. Investigator-initiated clinical trials (not registration-directed) had not been well funded by the government until recently. Japanese Good Clinical Practice (GCP) guidelines have not been required, resulting in poor processes and poor quality control. The concept of the International Conference on Harmonization (ICH) GCP guidance is not necessarily well understood by pediatricians.

Dr. Nakamura characterized investigator-initiated clinical research (not registration-directed):

- 13 MHLW grant-supported multicenter clinical research initiated since 2002
 - Better quality control possible
 - Also support salary for physicians, research nurses, and pharmacists
 - Clinical trial networks being developed in some areas (for example, neonatology, nephrology, endocrinology, hematology/oncology)
- New MHLW grant for clinical research infrastructure starting in 2006
- Plan to set up a Center for Clinical Research inside NCCHD.

Canada

Gideon Koren, M.D., FRCPC, Director, Motherrisk Program; Hospital for Sick Children, University of Toronto

Dr. Koren described some of the issues of the role of pediatric pharmacology. He said that pediatric pharmacology clinical trials should not be the focus. Instead, the focus should be on training and education. Dr. Koren commented that the ability to train pediatric pharmacology should be developed in developing countries. He explained that there are 15–20 subfields within pediatric pharmacology. A full 2-year program may not be necessary for all training. Training and education can be tailored to an individual’s needs, as necessary.

Dr. Koren noted some of the pediatric pharmacology activities in Canada. The Division of Clinical Pharmacology/Toxicology at the Hospital for Sick Children, Toronto was established in 1978 by Dr. MacLeod. Faculty consists of 4 full-time doctors (M.D.s—all graduates of the program) and 15 cross-appointees (7 previous fellows).

There is ongoing clinical and translational research in:

- Ontogeny of drug transport
- Maternal-fetal toxicology
- Drugs in breast milk
- Drug errors in children
- PK/pharmacodynamics (PD) in children (pain, cardiovascular, toxicology).

Clinical programs include:

- Motherrisk Program
- DART [Developmental And Reproductive Toxicology?] clinic
- Poison control center
- Consultation program.

With regard to education, the only accredited pediatric clinical pharmacology program—Royal College—trains about 6–10 postdoctoral students each year (from 36 countries). Canadian pediatric pharmacology programs are at:

- University of British Columbia
 - Dr. MacLeod, R. Peterson, Bruce Carlton
 - Focus—adverse drug reactions, drug safety, pharmacoeconomics
- University of Western Ontario
 - M. Rieder, D. Matsui, D. Knoppert, G. Koren
 - Focus—immunopharmacology, compliance-utilization, perinatal pharmacology
- University of Toronto
 - S. Ito, G. Koren, M. Thompson, I. Nulman
 - Focus—drug safety, drug transport, maternal-fetal pharmacology.

United States: PPRU Network

Michael D. Reed, Pharm.D., Professor, Department of Pediatrics, Case Western Reserve University School of Medicine

Dr. Reed discussed the PPRU Network. The subtitle of his presentation was “Where have we been, and where are we going?” He described the network as “the road well traveled.” The network originated from the vision of Sumner J. Yaffe, M.D. Dr. Reed characterized the therapeutic orphan:

- Incentive to develop drugs and drug dosing guidelines for infants and children is small
- About 70 percent of *Physicians’ Desk Reference* entries have
 - No dosing information for pediatric patients
 - Explicit statements that the safety and efficacy in children has not been determined
 - Restrictions on age at 18, 12, 6, or 2 years
- Most patients are pharmacologically mature by age 12
- Very few therapeutic indications are unique to infants and children
- Absolute quantities of drugs required by infants and children are small
- On an actuarial basis, humans spend about 16 years as children and about 60–80 years as adults.

Dr. Reed characterized the evolution of the PPRU Network:

- Molded by external events (for example, Food and Drug Administration Modernization Act [FDAMA], BPCA)
- Reactive
- Opportunistic
- Labeling mandate a mixed blessing.

Benchmarks of pediatric drug development include:

- 1977—American Academy of Pediatrics statement concerning the need to conduct trials in children
- 1979—FDA requires trials in children parallel to adult process
- 1994—FDA requires sponsors to update label; introduces “extrapolations”

- 1997—Congress passes FDAMA/Exclusivity Provision—“Incentives” (voluntary)
- 1998—FDA publishes Pediatric Rule (mandatory)
- 2002—Congress passes BPCA
 - Renewed exclusivity
 - Provides process for off-patent drug development
 - Public posting of results
 - Reporting of all adverse events for 1 year after exclusivity granted
- 2003—Congress passes Pediatric Research Equity Act (PREA)
 - Requires the study of drugs and biologics for pediatric population except in defined situations
 - Creates Pediatric Advisory Committee.

The PPRU Network was established by NIH in 1993 and was funded to provide experienced centers with seed money to maintain a research infrastructure to attract industry-funded clinical trials. The PPRU Network conducts studies on the PK and PD of drugs in children and serves as an advisory body to the pharmaceutical industry, regulatory agencies, health professionals, and the public on appropriate use of drugs in children.

Each PPRU unit includes:

- A principal investigator experienced in clinical trials
- A team of pharmacologists and clinical investigators representing all subspecialties of pediatrics
- Other clinical trials specialists such as a nurse coordinator and a data coordinator
- A core analytical and biomedical laboratory for sample analysis and computer modeling of drug disposition.

The PPRU Network has continued to evolve:

- 1994–1998 proof of concept
 - Labeling studies (Section 111 FDAMA)
 - Ontogeny studies (DMEs)
 - Single PPRU studies allowed
- 1998–2004 expansion translational research
 - Working groups
 - Strategic plan of 2003
 - BPCA—beginning involvement of PPRU
 - Single PPRU studies not allowed unless approved by Network Steering Committee [correct?]
 - Supplemental funding (2002–2004).

Dr. Reed described the reengineering of the PPRU Network:

- Redefinition of PPRU studies
- Elimination of Phase III sponsored studies without majority PPRU participation
- Investigator-initiated studies (IIS) must be part of an overall integrated and synergetic PPRU research agenda
 - Local IIS studies should be pilots of future network studies

- Local studies may be requested as part of a predefined network research plan.

The current PPRU organizational structure is as follows:

- PPRU Network Advisory Board [correct? Slide unclear]
 - PPRU Network Steering Committee [correct?]
 - PK/PD
 - Working groups
 - Physiologic PK/PD
 - Trial simulation 1
 - Translational basic research
 - Working groups
 - Pharmacogenomics
 - Proteomics
 - Animal, *in vitro* studies
 - Clinical trials
 - Working groups
 - Study design
 - Biostatistics
 - BPCA-related issues.

The PPRU Network's goals for the PK/PD core include:

- Developmental PK—define drug disposition based on developmental and physiologic based process
- Physiology-based developmental model
- Drug data integration
- PK/PD disease modeling
- Clinical trials simulation and population PK analysis.

The short-term goals for developmental PK include:

- Characterization of renal function/drug elimination (birth to adolescents) with a unified model that incorporates GA and PNA
- Inositol PK in infants defines ontogeny/activity of transporters (reabsorption)
- Neonatal morphine PK and UGT ontogeny
- Characterization of hepatic metabolism
- Ontogeny (midazolam and study linked to pharmacogenomic data).

Intermediate and long-term goal for physiologic-based PK/PD developmental models include:

- Capitalize on “in silico” modeling
- Develop animal model for azithromycin performed in parallel with BPCA study to describe disposition in tissues and interstitium
- Codeine central nervous penetration and systemic and brain metabolism
- Tissue drug concentrations for PK/PD modeling.

The data collection and assimilation goals for the PPRU pediatric PK/PD knowledgebase include:

- Constructing a searchable network-based database repository for PK/PD and outcome data generated by PPRU and possibly others
- Providing data mining and exploitation tools to facilitate PK/PD, Pop-PK, and clinical trial simulation analysis across the PPRU Network
- Creating a public access library of pediatric PK to serve as the foundation for and promote modeling and simulation (“in silico”)
- Supporting a variety of data streams/input.

PPRU Translational Research Working Group activities include:

- Lorazepam sedation to facilitate mechanical ventilation (efficacy, safety, and toxicology)
- Codeine central nervous system penetration and systemic and brain metabolism
- Areas of interest include obesity, diabetes, inflammation, pain, and sedation.

Dr. Reed characterized the relationship between the PPRU Network and BPCA:

- Response to *Federal Register* notices
- Review of FDA guidelines for industry for drug studies by indication
- Respond to requests for proposals
- Develop paradigm for necessary ancillary research studies
- Proposals based on major research issues, not solely on individual principal investigators’ interests
- Proposals vary with drug/indication.

Boston University Center for International Health and Development

Mark Mirochnick, M.D., Director of Neonatology, Department of Pediatrics, Boston University School of Medicine

Dr. Mirochnick reviewed activities at the Boston University Center for International Health and Development. The center is involved with the following programs:

- Pharmaceutical Policy Program
 - WHO Collaborating Center in Pharmaceutical Policy
 - Projects to develop pharmaceutical delivery systems for HIV and Primary Care in Central Asia
- Lesotho Country Program
- Ghana Country Program
- Zambia Country Program.

The center’s pediatric projects include the following:

- Amoxicillin Penicillin Pneumonia International Study (APPIS I)—demonstrated that an oral amoxicillin is as effective as injectable penicillin for severe pneumonia in hospitalized children (APPIS trial, *Lancet*, 2004)
- APPIS II—three community-based follow-up studies:
 - Delineate safety and efficacy of home care with oral amoxicillin versus hospital care with injectable ampicillin for severe pneumonia in Pakistani children
 - Compare effectiveness and feasibility of using community health workers to classify and treat children presenting with malaria and pneumonia

- Assess the safety of outpatient treatment of severe pneumonia with oral amoxicillin in children in five countries
- LUNESP study—evaluate the feasibility and efficacy of training Zambian traditional birth attendants in rural areas in modified neonatal resuscitation and provision of single dose nevirapine for prevention of HIV transmission and standby oral antibiotics for neonatal sepsis.

Boston University international pediatric HIV projects have been implemented in Africa, Asia, and South America. The projects have been sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), NICHD, the Centers for Disease Control and Prevention, UNICEF, the U.S. Agency for International Development, and WHO. Project activities include:

- Clinical trials
 - Participated in eight pharmacokinetic projects and three phase III trials of antiretrovirals in infants and pregnant women
- Operational research
 - The Zambia Exclusive Breastfeeding Study
 - LUNESP study
- Implementation training
 - Center of Excellence in Pediatric HIV Care and Treatment, University Teaching Hospital, Lusaka, Zambia
 - Training of local clinicians in pediatric and perinatal HIV diagnosis and treatment in Ethiopia, Cameroon and Uganda.

NIH International Studies

Danuta Krotoski, Ph.D., Acting Associate Director, Prevention Research and International Programs, NICHD, NIH, DHHS

Dr. Krotoski described NIH's activities in pediatric pharmacology:

- 12 of 27 institutes/centers (ICs) support training or research in pediatric pharmacology
- Most is domestic with exception of HIV/AIDS
- Dramatic increase in international funding during doubling of the budget (1998–2004)
- Increase in international research funding enhanced by HIV/AIDS epidemic
- Opportunities to build on already established NIH networks and programs
- What are the opportunities for support in middle- and low-income countries?

Dr. Krotoski summarized NIH support for pediatric pharmacology as follows:

- Training
 - Career development awards
 - Individual 36
 - Program 4
 - Training grants 9
- Research
 - Grants 35
 - Cooperative agreements 43
 - Clinical research center 8.

Dr. Krotoski presented a graph depicting increasing NIH international research expenditures for fiscal years 1994–2003 for visiting program, direct foreign research awards, foreign components of domestic awards, and training grants. Dr. Krotoski also presented a world map showing locations of NICHD extramural international activities.

NIH programs that could be expanded to include pediatric pharmacology research include:

- Global Network for Women’s and Children’s Health
- U.S./India bilateral programs
- NICHD and NIAID Pediatric Clinical Trials
- International Clinical, Operational and Health Services Research Training Award.

Dr. Krotoski characterized the Global Network for Mothers and Children:

- Unique private-/public-sector collaboration to build public health research capacity in maternal and child health in developing countries
- Focuses on important sustainable perinatal public health problems
- Broad-based capacity and infrastructure building: scientific, technical, clinical, institutional, and field
- 10 sites in Asia, Africa, and Latin America
- Cofunded with the Bill and Melinda Gates Foundation, and other NIH ICs.

Dr. Krotoski presented a world map showing locations of the Global Network for Mothers and Children. She then characterized U.S./India bilateral programs:

- Established to promote collaboration between the United States and India
- India has strong pharma and is developing platforms for clinical trials
- JWG collaborative projects (PAR HD 196)
- Joint workshops
- Scientific exchange.

Dr. Krotoski characterized the U.S./India Program on Maternal and Child Health and Human Development Research (MCHDR):

- Partner is Indian Council for Medical Research/Ministry of Family Health and Welfare
- Supports research collaboration in all areas of maternal and child health
- Five MCHDR-sponsored workshops to stimulate collaborative research
 - Nutrition and children’s health
 - Low birth weight
 - Factors associated with acute lower respiratory tract infections in India
 - Risk factors for maternal morbidity and mortality in India
 - Risk factors for pediatric morbidity and mortality in India.

Dr. Krotoski characterized NICHD International AIDS Trials:

- Designed to identify effective treatment and prophylaxis for maternal and pediatric HIV
- Latin American and the Caribbean
 - Brazil—Post-Exposure Prophylaxis of Infant “PEPI” trial

- NICHD Network collaborates with Pediatric AIDS Clinical Trials Group in development and conduct of clinical trials
- 1 site in Bahamas, 5 in Brazil: Rio de Janeiro (2 sites); San Paulo; Ribeirao Preto; Belo Horizonte
- NICHD International Site Development Initiative
- Sub-Saharan Africa
- Southeast Asia—India and Thailand.

The International Clinical, Operational, and Health Services Research and Training Award supports training to develop and extend core research support capabilities that are necessary for long-term sustainability of the research capacity in the institutions in the low- and middle-income countries (Brazil, China, Haiti, Russia, Uganda, and Zimbabwe). These core research capabilities include:

- Expertise in ethics and compliance issues
- Protection for human subjects, animal welfare
- Fiscal management, budgeting, program and grants administration
- Grant and report writing, preparation of scientific manuscripts
- Technology transfer and management of intellectual property
- Information technologies, data management, and Internet connectivity.

Challenges to the pediatric pharmacology research in developing countries include:

- Identifying partners
- Ensuring that partners have all assurances
- Compliance with U.S. and foreign institutional review boards and integration of differing cultural norms regarding informed consent
- Compliance with U.S. and foreign “FDA” regulations and availability of common formulations
- Clarifying financial and administrative reporting procedures for foreign sites, U.S. universities, and NIH staff
- Technology transfer and intellectual property
- Capacity building and sustainability of research
- Development of strategic partnerships.

Developing Countries: Updates and Summary of Current Activities

Kalle Hoppu, M.D., International Union of Basic and Clinical Pharmacology (IUPHAR); Chairman of the Sub-Committee for Paediatric Clinical Pharmacology, Hospital for Children and Adolescents; Director, Poison Information Centre, Helsinki University Central Hospital, Finland

Dr. Hoppu described his roles and affiliations as a pediatric clinical pharmacologist. He is:

- Consultant to the WHO Department of Child and Adolescent Health and Development from 1989 to present
 - Pediatric clinical trials performed in Brazil, Ethiopia, Guatemala, Pakistan, and Vietnam
 - Meeting to Explore Simplified Antimicrobial Regimens for the Treatment of Neonatal Sepsis, Geneva, 2002

- UNICEF/WHO Technical Consultation: Improving Access to Appropriate Paediatric ARV Formulations, Geneva, 2004
- Member of the Eastern European Committee of the European Association of Poison Centres and Clinical Toxicologists, 2004
- Chairman, Sub-Committee for Paediatric Clinical Pharmacology, IUPHAR, Division of Pharmacology, 2004–2008.

Dr. Hoppu noted that in developing countries, the most pertinent health issue for children of the developing world is not medicines. Medicines are, however, important for case management of:

- Anti-malarial treatment
- Antiretroviral treatment
- Antibiotic treatment of pneumonia and neonatal sepsis.

Pediatric initiatives in the developed world can have effects on children elsewhere:

- In the worst case, the current initiatives could increase exploitation of the children of the developing countries.
- In the best possible case, the initiatives could also be of enormous benefit for the children of the developing world.
- Development of a formulation suitable for newborns not requiring cold-chain transport and storage would be of enormous benefit in for the children in the developing world.

The following advocacy activities would have an impact on the health of children in the developing world:

- Keeping (reinstall) children on the political agenda of international health
- Getting the need for expertise in pediatric pharmacology recognized by governments, international agencies, and nongovernment organizations.
- Incorporating global benefit into activities in the developed world.

Charge to Work Groups: Framework, Objectives, and Goals

Moderator: Dr. Giacoia

Dr. Giacoia characterized the approaches for the work groups:

- Developed countries
 - Discuss overall framework
 - Identify two to four priorities on the basis of significance, feasibility, and greatest chance of success
 - Initially consider separately issues of developed and developing countries
 - Highlight issues and opportunities
 - Determine feasibility of developing a GCPP
- Developing countries
 - Discuss overall framework
 - Identify two to four priorities on the basis of significance, feasibility, and greatest chance of success
 - Identify who is currently involved in the area or how to obtain information on projects and programs

- Describe how interactions and partnerships with groups, organizations, associations, and institutions could be established
- Identify role of the GCPP and define its “niche”
- Could a pilot program or add-in be performed with available funding from other projects or with resources available?

According to Dr. Giacoia, some common issues in developed countries (Europe, United States, Canada, and Japan) include:

- List of essential off-patent drugs
- Pediatric formulations
- Clinical trials to study off-patent drugs
- Adverse drug reactions
- Irrational use of drugs
- Ethical concerns
- Need for pediatric pharmacology expertise in the design of pediatric drug trials.

Dr. Giacoia characterized the global market in developed countries:

- European Union
 - Current 2005 100 million children
 - Projected 2015 150 million children
- United States
 - Current 2005 79 million children
 - Projected 2015 100 million children

He noted that only 17 of 71 drugs in the U.S. Pharmacopoeia list requiring pediatric formulations are available in Europe.

According to an opinion-based estimate from the Economics Working Group, the “price” to develop pediatric formulations for off-patent drugs is about \$8 million–\$15 million for chemistry, manufacturing, and controls (cost per drug plus cost of trials). Because of this, there is a need for prioritization.

Barriers to performing trials on off-patent drugs include:

- Feasibility
 - Number of patients available
 - Number of patients required
 - Study design issues
- Lack of adequate efficacy endpoints
- Lack of pediatric clinical trialists
- Established standard practices
- Cost of trials and number of drugs for study
- Specific drug and indication
- Regulatory agency requirements (for example, FDA written request).

Possible scientific and education roles for a GCPP include:

- Establishment of international collaborations with emphasis on providing the scientific underpinnings to perform drug trials in pediatrics (biomarker development, mechanistic PK simulation strategies, *in vivo-in vitro* correlations, application of pharmacogenomics and proteomics)
- Development of training programs in pediatric pharmacology worldwide.

Possible roles of GCPP members include:

- Advocacy
- Scientific collaboration to advance knowledge in pediatric pharmacology
- Development of joint programs
- Development or participation in drug studies (emphasis in pharmacologic studies)
- Sharing of resources, databases
- Identification of common issues related to implementation of U.S. and European legislations (lists of off-patent drugs for study, studies feasibility, issues of study design, pediatric formulations and regulatory and ethical challenges)
- Identification of research needs in developmental and clinical pharmacology
- Advocate for incorporation of funding to support translational research
- Advocate partnerships of major research funding organizations (NIH, INSERM, National Research Council of Canada, British Research Council, and others).

According to Dr. Giacoia, there is a strong need to work together to:

- Establish a working group with representatives from funding agencies for BPCA regulatory agencies (FDA, EMEA) and investigators to harmonize approach to study of off-patent drugs
- Develop a common strategy to avoid duplication of efforts
- Harmonize study designs according to developmental age and therapeutic groups
- Develop guidelines for ethical approaches to studies and ethical informed consent process.

Differences between developed and developing countries:

	<u>Developed Countries</u>	<u>Developing Countries</u>
▪ Effect of increase in world population		
▪ Relative increase in number of children	↑	↑ ↑ ↑
▪ Access to life-saving medicines	80 percent	20 percent
▪ Proportion of global medicines sales	79 percent	21 percent
▪ Prevalence of disease		
– Neglected diseases: tuberculosis, HIV, malaria, and others	Low	High
– Childhood cancer: proportion of total cases per year	10 percent	90 percent
– Survival rate of childhood cancer	80 percent	20 percent

Problems and issues not related to GCPP:

- Lack of adequate supply and distribution of drugs
- Lack of accessibility to care

- Lack of physicians, pharmacists and other health professionals
- Patent related issues (trade-related aspects of intellectual property rights)
- Counterfeit drugs
- Lack of appropriate formulations
- WHO essential drug list not specific for pediatrics
- Drug development for the treatment of “neglected diseases”
- Training of pharmacists and other health care personnel
- Training of health personnel in the conduct of drug trials
- Training of physicians in pediatric pharmacology
- Ethical issues and informed consent.

Dr. Giacoia characterized WHO essential medicines:

- Essential medicines are those that satisfy priority health care needs of population
- Selected according to disease prevalence, evidence and efficacy
- 2005 list = 312 drugs; on-patent approximately 20
- “Should be available at all times in adequate amounts, in appropriate dosage forms, at a price that the community can afford”
- No essential list specific for pediatrics
- Dr. Cranswick and WHO list (May 2006)
- Lack of appropriate pediatric dosage forms.

Dr. Giacoia listed the following needs for formalizing a GCPP:

- Learning realities of pediatric therapeutics in developing countries
- Identification of teachers and partners
- Identification of ongoing programs /networks for which a GCPP can add value
- Development of plan to integrate and coordinate activities
- Development of a feasible organizational structure
- Identification of resources to sustain administrative component or use an established system.

Possible roles of members of GCPP for developing countries include:

- Advocacy
- Technical support and training
- Information exchange
- Development or participation in drug studies (emphasis in pharmacologic studies)
- Collaborations with local, national, international groups and organizations, and pharmaceutical companies.

Dr. Giacoia asked the following questions about a GCPP:

- Is it desirable?
- Is it feasible?
- What is the role of a GCPP?
- How is it going to be organized?

The key issues for a GCPP are:

- Integration

- Harmonization
- Avoidance of duplicative efforts
- Establishment of alliances
- Interaction or integration with established groups.

Work Group I: Issues and Priorities for Developed Countries

Facilitator: Dr. Reed; Recorder: Michael J. Rieder, M.D., Ph.D., FRCPC, FAAP

Participants discussed training issues. Replying to Dr. Choonara's question about the extent to which pediatric clinical pharmacology is recognized as a specialty in the United States, Philip D. Walson, M.D., stated that the American Academy of Pediatrics (AAP) does not recognize it, and Dr. Reed explained that board certification is not in place.

Dr. Reed noted his concern about the lack of awareness about the value of clinical pharmacology. Specialists in this area are not present on hospital floors for consulting. Dr. Reed proposed that succinct letters be written to medical school department chairs noting that clinical pharmacology is "alive and well."

The discussion turned to developing techniques in pediatric clinical pharmacology. Dr. Walson noted that FDA does not accept suitable surrogate endpoints in pediatric clinical trials, insisting instead on the use of adult endpoints.

Replying to Dr. Reed's request, John T. Wilson, M.D., [correct? Or was it Dr. Walson?] commented on training issues. He said that each undeveloped country has its own needs and own political and social structures. Countries offering training need to recognize this. For example, training someone in a developing country about a technique that requires the use of expensive equipment probably does little good. Edmund Capparelli, Pharm.D., added that exchange programs need to be started.

Dr. Reed noted that concerns in developed countries, such as those about formulation, would also benefit developing countries. Dr. van den Anker referred to the BPCA Web site, www.circlesolutions.com/bpca, which discusses NICHD's Pediatric Formulation Initiative.

Dr. Reed said that the only meeting attended both by physicians and pharmacists is held by the American Society for Clinical Pharmacology and Therapeutics. He added that because of concerns he had noted previously about the costs of this society and its direction, the American College of Clinical Pharmacology is moving to fill the gap for physicians and pharmacists to meet.

Dr. Walson noted that AAP has committed millions of dollars to advocacy and is doing an excellent job. It has trained members of its Committee on Drugs and its Section on Clinical Pharmacology and Therapeutics to advocate. AAP is allowed to advocate whereas other groups are not. It has been effective in conveying that it speaks on behalf of children without having a separate agenda, a powerful message to Congress. Dr. Walson added that he was unfamiliar with

AAP counterparts in European countries. Dr. Choonara observed that the problem in Europe is that pediatric health professionals cannot compete with pharmaceutical industry lobbyists.

Dr. Choonara discussed the MICE initiative to set up a fund to study off-patent drugs. It is unclear that MICE will be funded. The European Union might support the initiative through general research budgets but not through a specifically designated fund. Pharmaceutical companies are not interested in funding it.

Dr. Rieder stated that the Canadian Paediatric Society has lobbied for increased investigation, but the society works slowly and lobbying government in Canada is more restricted and is much less effective than in the United States. However, Health Canada, a Canadian federal department, was embarrassed that the United States has moved forward and has established a pediatric office. Although the office director lacks experience in pediatric issues, she is dynamic. Dr. Rieder said that he and others will meet with Health Canada within the next month or so to discuss the future of the pediatric office. He added that one of the outcomes of this meeting should be to determine the details of a global consortium.

Dr. Walson asserted that it took 25 years for AAP to agree that it is unethical not to study drugs in children. AAP's position had been that pediatricians should explain to parents that they (pediatricians) were not knowledgeable about the use of medications to treat children. Dr. Walson suggested that the AAP's advocacy groups meet with other advocacy groups to discuss techniques of successful advocacy. He mentioned that a German television program was more successful than any advocacy effort in the United States. In this program, well-respected German pediatricians explained to parents that pediatricians are not knowledgeable about the use of medications to treat children.

Participants discussed a lobbying effort in Australia. A participant stated that the chief lobbyist is effective and has primarily directed his efforts to Australian state governments. However, the effort has changed the Australian federal government's approaches to legislation. Various participants were impressed with the efforts of the chief lobbyist.

Participants discussed lobbying efforts for pediatric pharmacology in the 25 member countries of the European Union. Dr. van den Anker and Dr. Choonara agreed that efforts should be directed to the European Union and not to individual members. Participants noted that an initiative exists but were not aware of the identity of the person in charge.

Dr. Choonara noted that two major applications from ENDIC received favorable scientific review but did not go further politically. The reason why the applications did not go further is that the ENDIC and another group, ESDP, have noted that medicines are used off-label for children. The group that raised the issue is not the group that will be funded. The European Union funded another group, TEDDY, resulting in a scientifically poor project that is repeating studies that Dr. Choonara and others did about off-label and unlicensed drug use in children. Dr. Choonara had no idea why this other group is repeating the studies.

Dr. Wilson noted that in relation to information transfer and advocacy, WHO organized a task force about drugs in human milk, publishing two books on the subject. The task force had effective meetings about what was needed. He wondered how the WHO accomplished this, suggesting that it could serve as an example for a group to examine the use of medicine for children.

Dr. Reed said that Dr. Wilson brought up a broader perspective by mentioning WHO, which has seldom been mentioned during the meeting and which has not had much emphasis on pediatrics. Dr. Reed added that the American Society of Clinical Psychopharmacology refused to consider pediatric pharmacology initiatives, and those interested in advocating in this area have had trouble finding a home. He suggested that rather than having fragmented efforts, it would be better to have one effort within WHO, which might be viewed as less political and self-serving. He added that Dr. MacLeod is becoming active in WHO. Dr. MacLeod is a persuasive champion and an effective leader. Dr. Reed agreed with Dr. Choonara's comment that organizing within WHO should not be limited to seeking improvements only in developed countries. Dr. Reed added that he was not aware of efforts in developed countries to embrace responsibility for undertaking studies benefiting developing countries unless money was to be made, such as in improving infant formulas.

Dr. Giacoia raised the issue of involvement of international pediatrics associations. Dr. Walson believed that the International Pediatric Association is better suited to championing the cause of studying the use of medications for children, and other participants agreed. Dr. Walson also believed that the idea of forming a committee of specialists is an obvious one, but who has the time to form it needs to be determined. Dr. Reed said that an invitation has been made to form a liaison group, particularly with the PPRU Network, and that he planned to discuss these matters with Dr. Giacoia after the meeting.

Dr. Walson stressed his belief that initiatives in pediatric pharmacology should be taken out of North America, in part because strength in pediatric pharmacology resides in Europe, not in the United States. It would not be worthwhile, therefore, to develop an infrastructure in North America that already exists in Europe. For this reason, he inquired if the NICHD can redirect funding to support activities in Europe. He recalled the saying, "There is no limit to what you can do if you don't care who gets credit."

Dr. van den Anker, president-elect of the ESDP, said that the ESDP is not going to become a global consortium. If, however, sufficient North Americans presented scientific work at the ESDP meeting, then a debate could start about the ESDP's forming a European section in other organizations, especially in the International Union of Pharmacology.

Dr. Reed suggested that a change in the focus of clinical pharmacology training is needed in the United States. Dr. Walson believed that the only way for change to occur in the United States would be to change the training of subspecialists as clinical pharmacologists, as per a statement from Dr. Giacoia. Dr. Walson's institution and others have done this, and funding is available.

Dr. Walson asked if NIH support is available to train Americans outside the United States. Dr. Giacoia replied that NIH could support this if U.S. organizations partnered with funding agencies outside the country. Dr. Walson asserted that trainees would come if funding was available. He noted that colleagues at his institution in Cincinnati, who are well supported by the NIH, will not travel to Canada or Europe, where the patients are and where disciplinary strengths lie. The NIH could encourage international collaborative studies. The NIH Roadmap for Medical Research does not indicate high priority for such international collaborations, and some investigators do not want to do collaborative research. Issues such as concerns about institutional review boards, overhead expenses, and spending U.S. tax money abroad will need to be dealt with.

Dr. van den Anker agreed with Dr. Koren's view that the GCPP should not run global pediatric clinical trials, a huge undertaking. Instead, the consortium could consider other matters, such as pharmacokinetic studies and differences in ethical approaches in different countries. In developing a global consortium, European centers offer strength in pharmacoepidemiology in relation to drug use, medication errors, and adverse events. Different European centers have different strengths, as is the case in the United States.

Dr. Rieder noted that U.S. scientists are successful in molecular biology research because they focus on one molecule in one gene. To understand how this relates to community services, one needs to understand that investigators in the United States are not rewarded for doing efficacy studies in large populations or for looking at broader issues of drug use, such as medications for children. This situation has arisen in the United States partly because NIH has supported molecular biological studies whose results are published in prestigious basic science journals such as *Nature* and *Cell*. The funding situation is changing, but within the constraints of decreasing overall support. In contrast, investigators in Europe and Canada have had broader interests.

Bringing the discussion to a close, Dr. Giacoia asked whether other issues should be mentioned. Dr. Choonara suggested that too great an emphasis in the United States is on pharmaceutical company studies that bring in income but do not generate scientific research. Dr. Walson said that pharmaceutical company studies are not particularly profitable, and that without an infrastructure for those studies, investigator-initiated studies cannot be done. Company studies and investigator-initiated studies cannot be separated. He lauded the recent development of Current Procedural Terminology codes for clinical trials, of interest for budgeting the funding of trials.

Dr. Capparelli stated that pharmaceutical companies have embraced clinical pharmacology during the last few years with respect to modeling simulations and understanding disease, to determine best use for study compounds. As has been discussed during the meeting, it is important to understand how disease processes (presentation and progression) change developmentally, even when studies in children are done with the same endpoints as studies in adults. This issue needs consideration to enable linking data across studies to answer broader questions. The pediatric literature is "littered" with small, fragmented approaches that sometimes arrive at contradictory conclusions simply because of differences in methods.

Dr. Walson added what he described as another controversial statement: The problem with incorporating science arises not from industry but from FDA. FDA has ill-considered guidelines, such as the ones insisting on repeating adult studies in children. While agreeing with other participants that FDA's leadership is changing, Dr. Walson said that FDA line officers who meet with industry are not changing.

Work Group I members were Lisa Bomgaars, M.D.; Edmund Capparelli, Pharm.D.; Dr. Choonara; Dr. Giacoia; Dr. Jacqz-Aigrain; Dr. Reed; Dr. Rieder; Perdita Taylor-Zapata, M.D.; Dr. van den Anker; Philip D. Walson, M.D.; and John T. Wilson, M.D.

Work Group II: Setting Priorities and Establishing Linkages with Developing Countries

Facilitator: Dr. MacLeod

Dr. MacLeod explained that there are a number of pragmatic pediatric pharmacology initiatives underway, and many of them have been underway for a long time. What the initiatives lack, however, is an integration of scientific expertise that exists internationally. A mechanism is needed to integrate the expertise in a practical manner, similar to what IPA has done. To this end, Dr. MacLeod urged the work group to develop tangible recommendations that would lead to greater influence of pediatric pharmacology in developing countries. The goal of these recommendations is to make better use of pediatric medical therapies.

Dr. Yaffe noted that it would not be difficult to develop a list of essential drugs, based on the list of NICHD-identified off-patent pediatric drugs. He cited an example of France conducting clinical trials to collect data on such drugs. FDA has a stated policy for accepting drug studies conducted outside the United States, but so far, FDA has refused to accept data from these studies for approval of labeling changes. This could be a problem for developed countries. Dr. MacLeod noted that the International Conference on Harmonization has made progress in data acceptance issues and includes most of the countries in the developed world. Although developed countries are interested in approving pediatric medical therapies, developing countries are more focused on access to drugs.

Dr. Koren reminded the work group that training is achievable and could be a tangible recommendation. The participants cannot expect to understand all of the international issues in all developing countries, but the participants know how to train pediatric pharmacologists. The training should be applicable to each country's situation with its regulatory agency. Training should be straightforward and "down to earth." He cited his experience with training foreign students: Once they complete their training and return to their respective countries, they should be encouraged to stay in touch with the core training group and to stay informed of research activities. This approach maintains international communication and collaboration. Students do not need to visit North America for training. Training programs can be developed and implemented in developing countries. Different modes of training should address the specific needs of each developing country. Training should be a lifelong endeavor.

Dr. MacLeod noted that in a previous position (Dean of Health Sciences at McMaster University), he helped found the International Clinical Epidemiology Network. There are many similarities between clinical epidemiology and clinical pharmacology, primarily in integrating disciplines. Dr. MacLeod described how the Rockefeller Foundation developed training centers in 1980 in 26 developing countries. These centers focused on clinical epidemiology and received about \$10 million per year for 20 years. Today, there are several hundred people who were trained through this network. The Rockefeller Foundation approach would serve as a good model for a global pediatric clinical pharmacology initiative.

Dr. Yaffe commented that there should be standards for training in pediatric clinical pharmacology, and the participating countries need to agree on the standards and ensure adherence to the standards.

David Knoppert, M.Sc.Pharm., suggested that the work group develop a written mission statement or vision statement. He also suggested that any global pediatric clinical pharmacology initiatives involve pediatric pharmacists, that they be as inclusive as possible, and that linkages be developed with large pediatric clinical pharmacist organizations. The meeting should produce a specific mandate, with an action plan. Both the Rockefeller Foundation model and the Boston University model would serve well for a global consortium on pediatric pharmacology.

Dr. Hoppu suggested that it might be more effective to train adult pharmacologists from developing countries to learn pediatric pharmacology. He said that it is important for government regulatory agencies to recognize and understand the issues of pediatric medical therapies. Dr. Hoppu noted that there are two subgroups within developing countries: the poorest countries (where children's medical therapy issues are barely recognized) and the more developed countries (where there is more awareness of children's medical therapy issues). The work group could make different recommendations for each subgroup. Finally, Dr. Hoppu urged the work group to attach its recommended activities to existing organizations, programs (both private and governmental), and foundations such as the Gates Foundation. The global consortium could help convince these entities to fund pediatric pharmacology initiatives.

Dr. Mirochnick said that the world is a complicated place, with great variation across and within countries. Developing countries have different capabilities. For example, Thailand and Brazil have capabilities that are much different than those in African countries. The different capabilities need to be recognized and incorporated into the recommendations for developing countries. In addition to training, the global consortium on pediatric pharmacology should focus on research and advocacy. There are specific needs for pediatric formulations from drug companies. Some formulations that are suitable for adults are not suitable for children.

Dr. MacLeod said it is important to understand that of the 6.5 billion people in the world, about half are under the age of 16. There is a great need for children's medical therapies in the developing world. Another program to which a global consortium on pediatric pharmacology could link is the Program for Appropriate Technology (PATH), which is associated with the Gates Foundation. PATH has focused on delivery of vaccines and is looking at relatively simple approaches that will make a difference to large numbers of people. Dr. MacLeod commented that

training of people with appropriate skills is a technology that can pay huge dividends. Dr. Koren reiterated that training should be tailored to the specific needs of each developing country.

Vinod K. Bhutani, M.D., explained that many developing countries have suffered from decades of loss of academic infrastructure, so that training of medical students, young physicians, and postgraduates is lacking. Many developing countries require the building of a sustainable infrastructure for academic training. Partners should be sought to help build a sustainable infrastructure, and the leaders for academic training should be identified to lend their expertise. Dr. Bhutani recommended that principal investigators and researchers be allowed to design and develop their own research agendas. Dialogues are required, and international partnerships and collaborations need to provide a forum for such dialogues. From a community perspective, there should be more focus on patient safety. Promoting patient safety should be part of the global consortium's mission statement.

Dr. Schaller said that educating adult pharmacologists is a good idea, but that any time adult and child services are mixed, the children's services generally suffer. Dr. Schaller said that an individual from WHO—Chris Nelson—set up pediatric bacterial meningitis surveillance units in several African countries to identify specific pathogens and, therefore, develop pathogen-specific vaccines. Dr. Nelson recruited one pediatrician from each country's leading hospital and taught the pediatricians to perform lumbar punctures on all children who appeared to have bacterial meningitis. This activity was well received in the participating countries, and several of the pediatricians presented at the Union of African Pediatric Societies. Dr. Schaller said that this initiative is an example of how a small amount of training can make a large contribution.

Zhiping Li, M.D., agreed that training is very important in developing countries. She explained that the presentations in this meeting were enlightening and served as training for her. She now has a better understanding of global pediatric clinical pharmacology activities. It is important to understand the needs of trainees in developing countries. The meeting in Shanghai will provide much training for its participants. Dr. Li agreed with Dr. Hoppu that governmental support is essential in developing countries.

Dr. MacLeod made two observations: (1) The Rockefeller Foundation's clinical epidemiology network had a large impact in China and India because of the large populations in those two countries, and (2) it is much more difficult to work in and have an impact in an African nation such as Uganda.

Dr. Koren said that there are many types of expertise that vary from institute to institute. If the global initiative recommends training, then it needs to develop a script. For example, what types of training should be considered? What is the right term (therapeutics)? Should there be an emphasis on toxicology? According to Dr. Koren, adverse drug events and toxicology must be part of the training. Standards for training can be established through collaborations with other organizations such as the Global Forum on Health (GHF). Dr. MacLeod said that GHF activities are focused on the 90 percent of the world's population (mostly women and children) that lives in the lower income/resource poor bracket. Health improvement is a global issue.

Dr. Mattison synthesized the work group's discussions up to this point:

- Need to create a voice for children, across and within countries and governments, organizations, and professional societies
- Need to create awareness of children's health issues
- Need to create training opportunities
- Recommendations should be achievable
- Recommendations should be recorded (that is, written) and disseminated
- Individual tasks should be assigned.

Dr. Hoppu suggested that GCPP get the topic of pediatric clinical pharmacology on the international agenda. For example, the Finnish government has proposed that pediatric medical therapies be placed on the agenda for the next WHO general assembly. This proposal is supported by other Scandinavian countries. International issues of children's medicines should be established through a WHO resolution. With regard to pediatric pharmacology, Dr. MacLeod noted that there is a lack of engagement by UNICEF and that this organization seems to lack knowledge about children's drug therapy issues. Dr. Schaller said that UNICEF has asked to join a meeting with IPA and WHO in Geneva, Switzerland, in April.

Dr. Knoppert explained that a method for advocacy would be to approach ministers of health in each country and urge them to contact WHO and UNICEF to inform them about pediatric pharmacology issues. Dr. Knoppert reiterated the need to develop a written GCPP mission statement or vision statement, with mandates and charges to fulfill the GCPP mission.

Dr. Koren agreed on the need for concrete ideas and a plan of action, but he emphasized that GCPP needs more than one area of focus. Training is needed to address essential medicines for children. Evidence-based pediatric pharmacology needs to be integrated into training. Dr. Koren said that it is not as important to change the labeling of drugs as it is to change pediatricians' practices. Clinical evidence needs to be synthesized to show pediatricians that the process works. Pediatricians should be taught how to analyze new pediatric pharmacologic data; they need to understand and learn how to conduct meta-analyses and systematic literature reviews.

Lynne M. Mofenson, M.D., commented that GCPP has a new role of advocacy to WHO and UNICEF. There needs to be a focus on appropriate formulations for children, such as liquid formulations that do not require refrigeration and solid formulations that can be crushed so they can be sprinkled on food or mixed with water. Several participants said that developing appropriate formulations for children is expensive and is generally not a high priority of pharmaceutical companies. Dr. Knoppert said that pharmacies at different hospitals are doing different activities and approaches for drug formulations. This information could be collected and synthesized to develop lists of stability of different formulations. Dr. Mirochnick commented that advocacy could play a role in developing appropriate children's drug formulations. Dr. MacLeod suggested that GCPP could join with IPA to advocate to WHO and UNICEF to raise awareness of children's drug therapy issues. The only other existing potential international advocacy organization is IUPHAR.

Dr. MacLeod synthesized the work group's discussions and listed major activities for setting priorities and establishing linkages with developing countries:

- Advocacy and raising awareness of pediatric pharmacology
- Need to identify essential drug therapies for children
- Need for drug formulations that are more suitable for children
- Addressing issues of drug safety, safe medication practices, toxicology, and antenatal drug risks
- Need for training and building capacity.

Work Group II members were Dr. Bhutani, Dr. Hoppu, Dr. Koren, Dr. Knoppert, Dr. Krotoski, Dr. Li, Dr. MacLeod, Dr. Mofenson, Dr. Mattison, Dr. Mirochnick, Dr. Nakamura, Dr. Schaller, and Dr. Yaffe.

Work Group I Summary Report

Dr. Rieder summarized the work group's discussions. There are three key priorities to address the pediatric pharmacology challenges for developed countries:

- Human resource development (training)
 - Multidisciplinary focus
 - Broad-based
 - Noninstitutional services
- Child-specific development of techniques and technologies
- Consortium development.

Aspects of training development include:

- Centers/expertise for training
- Attracting trainees
- Tailoring training programs to the unique needs of the individual trainee, notably for trainees who are returning to the developing world
- Having pediatric clinical pharmacology recognized as a specialty in the United States
- Creation of a Web site for education, information exchange, and sharing of training resources.

Aspects of techniques and technologies development include:

- Use of suitable end-points
- Development of child-friendly formulations
- Special elements in clinical trials design
 - Statistical analysis, PK studies.

Steps forward in training development include:

- Highlight issue for U.S. department chairs
- European inventory of training programs completed
- Development of an inventory of North American training inventory
 - Drs. Reed and Rieder
- Publication of United Kingdom/Canadian training objectives

- Drs. Choonara and Rieder.

Steps forward for the development of techniques and technology include:

- Workshop on pediatric formulations in September
 - Jorg Breitzkreutz
 - www.circlesolutions/bpca.com
- Addressing the information gap in pediatric clinical pharmacology
 - Dedicated Web site; a pediatric pharmacy advocacy group?; linkage to other Web sites?
- Creation of a functional global consortium with meetings, Web sites, journals (some of which already exist).

Work Group I summarized consortium efforts for development and advocacy:

- In the United States, AAP has been very effective
- European situation more fragmented
- Canadian situation lobbying less well organized.

Steps forward for consortium development include:

- Need to identify potential members
- Roles
 - Sharing resources and techniques
 - Helping collaborations, training
- Great potential
- Much of what is needed is already in place
- What is needed is a mechanism to coordinate this effort.

Work Group I recommendations for consortium development include:

- Do not reinvent the wheel
- Need to identify key needs in different regions and what regions have to offer
 - Challenge to the group
- Need to identify key partners in different regions and champions
 - Academic organizations
 - Professional groups
 - Governmental and supragovernmental groups
 - Nongovernmental organizations.

Work Group I urged pediatric pharmacologists to participate in the following meetings:

- Stockholm in June 2006
- Shanghai in June 2006
- Toronto in September 2006.

Work Group II Summary Report

Dr. Mattison noted that there was a fair amount of overlap in the discussions of the two work groups. He reported that none of the members of the developing countries work group can honestly speak for those countries or realistically address the issues in those countries. The work

group attempted to be pragmatic in its discussion and sought to capitalize on existing international organizations (for example, IPA, WHO, ESDP) as potential platforms for advocacy and education of children's drug therapy issues. The work group recognized the importance of training and the various ways that training could be implemented. However, without knowing the specific needs of each individual developing country, the work group did not recommend any specific training approaches. Needs assessment would be required, and the differences among developing countries should be recognized. The work group agreed that specific tangible steps need to be assigned to individuals for further development.

Dr. MacLeod explained that the work group's discussions revolved around one central principle: Better drug therapy for children is a necessary condition for improving world health. Advocates of children's health need to raise awareness of this central principle. BPCA has been a major catalyst in raising awareness of pediatric pharmacology issues, as have efforts in Europe, Japan, Canada, and Australia. Efforts in developed countries, however, affect only 10 percent of the world's children. Dr. MacLeod summarized the work group's discussions as follows:

- Identifying essential medicines for children and the need to work with international organizations such as IPA and WHO; clarifying what an essential medicines for children list should be; identifying important diseases in developing countries; developing treatment guidelines; developing a drug information database
- Developing suitable and appropriate formulations for conditions and children such as liquid formulation that do not require refrigeration; tablets/capsule/solid formulations that are the appropriate size for children; more stable, longer shelf life
- Improving drug safety
- Developing training and building capacity; working in a cooperative model such as that used in the Rockefeller Foundation's International Clinical Epidemiology Network; producing health care providers with very practical skills; developing better information for prescribing drugs for children; tailoring training to the needs of the trainees and their regions.

Discussion of Work Group Reports

The participants agreed that advocacy for children's drug therapy issues is extremely important in both developed and developing countries. The participants acknowledged that many pharmacology programs are having difficulty recruiting students for graduate programs. Dr. Mattison described the recruiting of pediatric clinical pharmacologists from general pharmacologists as being in "meager shape." The recruitment of adult pharmacologists may be a more realistic alternative. There is a need to attract subspecialists, and clinical pharmacology needs to be recognized as a subspecialty. Dual board training should be encouraged.

The participants discussed training issues for pharmacologists and clinical pharmacologists. They noted that there are differences in meaning for these professions in different countries, and there needs to be a common label across countries. Nonphysician pharmacologists and physician clinical pharmacologists can serve an important role in pediatric pharmacology. The participants noted the extent to which pharmacology is taught in medical schools and how this instruction is received by students. Several participants suggested that medical school change the way pharmacology is taught. Although there have been problems with recruiting appropriate trainees,

the participants agreed on the importance of attracting qualified trainees to improve medical therapies for children.

Dr. Li stated that China has good training for pediatric clinical pharmacology, but there is a need to understand how the greater scientific system functions; there needs to be a more holistic perspective to improving children's health. Dr. Mirochnick commented that because of the variability of conditions within countries, training needs to be flexible, perhaps regionally oriented. Dr. Bhutani explained that a lack of infrastructure inhibits the sustainability of training and that organizations such as GCPP, IPA, and WHO need to work with governments to improve pediatric pharmacology curricula. Several institutions that are ready to implement training and capacity building were mentioned. The recipients of training in developing countries need to be identified.

The participants discussed the essential medicines for children list. Development of this list has been considered for a number of years, yet it has not moved forward. Developing this should be a multidisciplinary effort and will involve hard work and cooperation among a number of organizations. The essential medicines list should focus on improving survival among children. Specific guidelines for treating children should be developed.

The participants agreed that a task force to design an international training program would be beneficial. There should be at least two approaches: one for developed countries and one for developing countries. Training programs would be tailored to national or regional needs.

Dr. Jacqz-Aigrain stressed the importance of establishing an international registry of pediatric clinical trials, including areas other than pediatric clinical pharmacology (for example, pharmacogenetics). Dr. Koren suggested registration would be required for publishing results of such clinical trials. Dr. Hoppu reminded the participants that such an endeavor would not occur without adequate resources and a formal organization to solicit or provide funding. A clinical trials registry would improve information exchange and would increase potential opportunities for international collaboration. Collaboration, in turn, would improve education and training.

Where to Go From Here?

Dr. Giacoia asked the meeting participants about the feasibility of moving forward with GCPP activities. He asked: What can GCPP accomplish? What can GCPP do to follow through on today's meeting? How can GCPP fulfill its goals and activities? Dr. Giacoia noted that this meeting is a step in the beginning of the process. Dr. Giacoia expressed his hope that the proceedings of this meeting would be published in PPDT. Dr. Giacoia stated that GCPP needs to identify actions plans to address the following topics or "modules":

- Funding
- Advocacy
- Training
- Technology development
- Drug safety.

Agenda for the ESDP Meeting

Drs. van den Anker and Choonara

Dr. Giacoia asked the meeting participants to identify topics that GCPP can discuss and address during the ESDP meeting in Stockholm, Sweden. Dr. Choonara noted that because the agenda is already set, the only time GCPP members can meet is a 2-hour period on the afternoon of Friday, June 16. The advantage of this time is that ESDP will have had its annual general assembly on the preceding day. During the general assembly, it will be proposed that ESDP form an affiliation with IUPHAR. Such an affiliation would allow a possible expansion of GCPP membership. However, Dr. Choonara asked who would participate in the GCPP meeting (that is, would everyone be welcome or would it be only representatives from various organizations?).

Dr. Giacoia commented that he would like the meeting to be open, but GCPP is not ready to make a presentation. The consortium needs to develop its mission statement, refine the modules, and begin developing the action steps. Dr. Koren suggested that participants in today's meeting be assigned to develop a core of ideas for each module. In this way, GCPP would be able to develop a solid protocol that could be submitted for funding.

Dr. Choonara suggested that GCPP develop the modules before the meeting, then take advantage of modern technology and disseminate the materials among the GCPP members for review prior to the ESDP meeting. This would result in a shorter meeting in Stockholm. Dr. Choonara proposed that GCPP could establish an international society for pediatric pharmacology that incorporates ESDP within it such that ESDP would be the European section within the society. The meeting participants discussed the pros and cons of Dr. Choonara's proposal.

Dr. Mattison offered a simpler and more pragmatic approach for the Stockholm and Shanghai meetings. He suggested that a "snapshot" of GCPP be presented to determine international interest. GCPP might prepare a first draft of its mission and modules to seek reaction and gather input. Then, if there is sufficient global interest in pediatric clinical pharmacology, GCPP can move forward with its mission and activities. Dr. Mattison said that developed and developing countries have common concerns for pediatric pharmacology, such as advocacy and training, to generate interest from many meeting participants. The GCPP's draft will evolve as it receives input from meetings.

In a further discussion about potential invitees to the GCPP meeting in Stockholm, Gregory L. Kearns, Pharm.D., Ph.D., said that there is a pediatric section within the American Society for Clinical Pharmacology and Therapeutics (ASCPT) that recognizes the importance of clinical pharmacology from a global perspective. The pediatric section of ASCPT would likely want to be involved with GCPP. ASCPT is the largest clinical pharmacology organization in the United States with about 2,400 members. About 1,400 members will attend the society's annual meeting this year.

Drs. Hoppu and MacLeod said that the participants of this meeting will be quite different from the Stockholm meeting participants. Because of this, GCPP might be better served to narrow its focus on two or three modules for this meeting.

Dr. MacLeod explained the benefits of GCPP developing relationships with IPA and IUPHAR to provide an international voice for pediatric clinical pharmacology. These organizations would provide links with pediatricians and pediatric expert bodies in the world. GCPP presence at the ESDP meeting will provide an opportunity to identify the global need to improve the health of children.

Dr. Choonara urged the North American members of GCPP to discuss their approaches and activities that would be different from those of their European counterparts. There needs to be a unified voice from North America. Dr. Rieder proposed that the North Americans be members of European pediatric pharmacology societies.

Dr. Mattison summarized the GCPP agenda at the ESDP meeting in Stockholm:

- Present a summary of today's meeting
- Describe the GCPP's potential activities and how they can improve children's health
- Ascertain the level of interest from Stockholm meeting attendees
- List and develop modules and action steps
- Present and discuss the GCPP mission statement
- Gather input from ESDP.

IUPHAR Meeting

Dr. MacLeod

Dr. MacLeod said that this meeting will be similar to the Stockholm meeting but with a slightly different focus. There will be about 250 attendees—200 from China and 50 international participants. About 60 percent of this meeting will be devoted to pragmatic issues, with the remainder presenting new science. The meeting content will be a mixture of educational transfer event and an original science meeting. During this meeting, Drs. MacLeod and Schaller will attempt to present the agenda for an essential medicines project with IPA. There is hope that WHO will have mandated development of an essential medicines list by the time this meeting is held.

In response to a question from Dr. Mattison, Dr. Choonara said that PPDT would be interested in publishing an article about the mission of GCPP. Dr. Reed commented that such an article could address both a “call to arms” and a report on the lack of advocacy for pediatric clinical pharmacology. Dr. Reed suggested that an article on GCPP should be published in a journal with a broader base than that of PPDT. There needs to be a mechanism for action and several avenues for communication. AAP may be able to provide the resources to disseminate information on pediatric clinical pharmacology. *Lancet* was suggested as another possible avenue for communication on GCPP.

Summary of Meeting and Action Plan

The meeting participants agreed to create task groups for each module to develop lists of action step to define GCPP's goals. The task groups and cochairs are as follows:

- Training—Drs. Reider and Choonara
 - Comparison of training programs in Canada and the United Kingdom
 - Short-track programs (for example, for physicians conducting clinical trials)
 - Developing countries—Drs. Koren and MacLeod
- Techniques/methodological approaches—Drs. Capparelli and Walson [correct?]
 - Innovative ways to conduct pediatric clinical pharmacology trials
 - Population PK, prestudy modeling, dry-spot technology, pharmacogenomics
- Advocacy—Drs. Giacoia and Hoppu
 - Non-drug regulatory policy
 - History
 - Essential drug lists
- Pediatric formulations and essential medicines issues—Drs. Knoppert, MacLeod, and Cranswick.

The meeting participants agreed that the whole GCPP group will review the results of each task force before presentation at the Stockholm meeting. The draft materials will be presented at the Stockholm and Shanghai meetings.

Participants

Vinod K. Bhutani, M.D., Stanford University

Lisa Bomgaars, M.D., Baylor College of Medicine

Edmund Capparelli, Pharm.D., University of California, San Diego

Imti Choonara, M.D., MRCP, Derbyshire Children's Hospital/University of Nottingham

George P. Giacoia, M.D., NICHD, NIH, DHHS

Kalle Hoppu, M.D., Helsinki University Central Hospital, Helsinki, Finland

Evelyne Jacqz-Aigrain, M.D., Ph.D., Hôpital Robert Debré, Paris, France

Gregory L. Kearns, Pharm.D., Ph.D., University of Missouri, Kansas City; Children's Mercy Hospitals and Clinics

David Knoppert, M.Sc.Pharm., M.Sc., FCCP, M.Sc., London, Ontario, Canada

Gideon Koren, M.D., FRCPC, University of Toronto, Hospital for Sick Children, Toronto, Canada

Danuta M. Krotoski, Ph.D., NICHD, NIH, DHHS

Jan L. Leahey, NICHD, NIH, DHHS

Zhiping Li, M.D., Children's Hospital, Fudan University, Shanghai, China

Stuart MacLeod, M.D., Ph.D., British Columbia Children's Hospital, Vancouver, British Columbia, Canada

Donald R. Mattison, M.D., NICHD, NIH, DHHS

Mark Mirochnick, M.D., Boston University School of Medicine

Lynne M. Mofenson, M.D., NICHD, NIH, DHHS

Hidefumi Nakamura, M.D., Ph.D., National Children's Medical Center, Tokyo, Japan

Jennifer S. Read, M.D., M.S., M.P.H., NICHD, NIH, DHHS

Michael D. Reed, Pharm.D., Case Western Reserve University School of Medicine

Michael J. Rieder, M.D., Ph.D., FRCPC, FAAP, University of Western Ontario, London, Ontario, Canada

Jane G. Schaller, M.D., University of British Columbia, Vancouver, British Columbia, Canada
Leslie Serchuck M.D., NICHD, NIH, DHHS
Perdita Taylor-Zapata, M.D., NICHD, NIH, DHHS
Johannes N. van den Anker, M.D., Ph.D., Children's National Medical Center
Philip D. Walson, M.D., Cincinnati Children's Hospital Medical Center
John T. Wilson, M.D., Louisiana State University Health Sciences Center
Sumner J. Yaffe, M.D., University of California, Los Angeles
Anne Zajicek, M.D., Pharm.D., NICHD, NIH, DHHS