

Second EU–US Joint Research Initiative Meeting
July 8 and 9, 2008
Eunice Kennedy Shriver National Institute of Child Health and Human
Development
6100 Executive Boulevard
Rockville, MD

This meeting was sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (HHS), in support of the Best Pharmaceuticals for Children Act (BPCA) Program.

Background and Purpose

The United States and the European Union (EU) have similarities and differences in research priorities and regulatory activities as they affect development of pediatric therapeutics. The similarities suggest that exploring joint funding of research proposals for pediatric clinical trials using off-patent medicines for children would offer benefits to both the United States and the EU. An initial meeting between NIH, the Directorate-General for Research and Technical Development (DG Research), the European Medicines Agency (EMA), and the Food and Drug Administration (FDA) held in London in January 2008 identified challenges and opportunities, with an agreement to enlarge the participants and develop a more detailed discussion.

The purpose of this meeting was to discuss regulatory and scientific prioritization processes in the United States and the EU and explore opportunities for potential collaborations to improve pediatric therapeutics through the EU–US Joint Research Initiative. Funding mechanisms were not discussed.

European-United States Discussion on Clinical Research Alignment

Steven Hirschfeld, M.D., Ph.D., Associate Director for Clinical Research, NICHD, NIH

According to Dr. Hirschfeld, NICHD's goals for the meeting were to discuss the following:

- Resource expectations
- Technical scientific review criteria
- Data standards and policy
- Ethical expectations.

Science for Global Health: Fostering International Research Collaboration with the EU

James Herrington, Ph.D., M.P.H., Director, Division of International Relations, Fogarty International Center, NIH

Dr. Herrington reviewed data on global disease burden in terms of reported mortality by cause. The data were compiled by the World Health Organization (World Health Report, 2004) and the

Fogarty International Center (Disease Control Priorities Project, 2006). In 2002, communicable, maternal, perinatal, and nutritional conditions accounted for 33 percent of reported mortality worldwide. Within the African Region, these conditions accounted for 72 percent of reported mortality. By comparison, these conditions accounted for only 6 percent of reported mortality in the European Region. HIV/AIDS, malaria, and diarrheal diseases accounted for 83 percent of this mortality; 5 percent was due to childhood cluster diseases (diphtheria, measles, pertussis, polio, and tetanus). In the European Region, 86 percent of reported mortality was caused by noncommunicable diseases. Cardiovascular diseases accounted for 60 percent of this mortality, and 22 percent was due to malignant neoplasms. Over the past century, life expectancy in the European Region and in much of the developed world has increased from about 55 years to about 75 years. Longevity, lifestyle changes, and environmental factors associated with economic development have contributed to the increasing rates of mortality due to noncommunicable diseases.

The United States has cooperative agreements with the EU to facilitate collaboration in biomedical and health research. The Agreement between the European Commission (EC) and the United States on Science and Technology Cooperation (signed in 1997 and renewed in 2003) allows NIH to enter into individual agreements with the EU. Through its intramural program, NIH has funded visiting fellows and guest researchers from 21 EU countries. In 2005, NIH provided \$8.3 million in funding for this activity. Between 2004 and 2006, NIH extramural grant awards and contracts provided more than \$1 billion to EU member states. Current areas of collaborations between NIH and the EU currently involve the National Cancer Institute (NCI), the National Library of Medicine, NICHD, the National Institute for Diabetes and Digestive and Kidney Diseases, and the National Heart, Lung, and Blood Institute (NHLBI). Under the EU's Seventh Framework Programme for research and technological development (FP7), areas of potential collaboration include bioinformatics; genomics and proteomics; addictions and behavioral medicine; cancer; cardiovascular and cerebral health; nanomedicines, materials, and production; and training of the next generation of researchers.

Pediatric Medicines and the Health Theme in the Cooperation Programme of FP7: I

Arnd Hoeveler, Ph.D., Head of Unit, Health Biotechnology, DG Research, EC, Brussels, Belgium

The EU is composed of 27 member states with 500 million inhabitants who speak 23 languages. Of these inhabitants, about 100 million are children. The EC and the European Parliament are the EU's primary decision-making bodies. The EC initiates discussions with the EU member states and the EU Civil Society with two aims: (1) developing a common regulatory framework for communication and codes of conduct to establish a consensus for EU direction and (2) financial support for research. This research support operates within a framework that is designed to support regulation. The EC is divided into departments known as Directorates-General. The Directorate General's mission is to:

- Develop the EU's policy in the field of research and technological development and thereby contribute to the international competitiveness of European industry

- Coordinate European research activities with those carried out at the level of the EU member states
- Support the EU's policies in other fields such as environment, health, energy, and regional development
- Promote a better understanding of the role of science in modern societies and stimulate a public debate about research-related issues at the European level.

FP7 is the EU's main instrument for funding research in Europe. FP7 is the natural successor to the Sixth Framework Programme (FP6) and is the result of years of consultation with the scientific community, research and policy-making institutions, and other interested parties. Since their launch in 1984, the Framework Programmes have played a lead role in multidisciplinary research and cooperative activities in Europe and beyond. FP7 continues that task and is both larger and more comprehensive than earlier Framework Programmes. Running from 2007 to 2013, FP7 has a budget of €50.5 billion over its 7-year lifespan, the largest funding allocation yet for such a program.

FP7 bundles all research-related EU initiatives together under a common roof and plays a crucial role in reaching the goals of growth, competitiveness, and employment. Other initiatives include a new Competitiveness and Innovation Framework Programme (CIP), Education and Training Programmes, and Structural and Cohesion Funds for regional convergence and competitiveness. The broad objectives of FP7 are grouped into four categories: Cooperation, Ideas, People, and Capacities. For each type of objective, there is a specific program corresponding to the main areas of EU research policy. All specific programs work together to promote and encourage the creation of European poles of excellence.

The Health Theme is a major theme of the Cooperation category, and the EU has earmarked €6.1 billion for funding this theme over the duration of FP7. The objective of health research under FP7 is to improve the health of European citizens, increase competitiveness of European health-related industries and businesses, and address global health issues, including emerging epidemics. In the Health Theme, FP7 supports basic and applied collaborative research. This research includes discovery activities, translational research, and early clinical trials (normally only phases I and II). Exceptions for pediatric medicines allow for phase III clinical trials. Collaborative research generally involves a consortium of partners from different countries. The EU contributes substantial funding for collaborative projects, but may not provide all.

Pediatric Drug Development: NIH–DG Research Cooperation—Summary of Prior Activities

Donald R. Mattison, M.D., Captain, U.S. Public Health Service; Senior Advisor to the Directors of NICHD and CRMC; Chief, OPPB, CRMC, NICHD, NIH

In 2007, NIH and DG Research began discussions concerning potential collaborations in pediatric drug development. The bases for these discussions were:

- Similar EU and U.S. legislation
- Established teams and networks with expertise in pediatric drug studies

- Developed populations with many healthy children, small numbers of ill children, and similar pediatric diseases.

The BPCA 2002 legislation mandated that NIH, FDA, and experts in pediatric research develop, prioritize, and publish an annual list of approved drugs. Considerations for listing drugs were the availability of information concerning the safe and effective use of the drug in the pediatric population, whether additional information is needed, whether new pediatric studies concerning the drug may produce health benefits in the pediatric population, and whether reformulation of the drug is necessary. A major focus of BPCA 2002 activities was identifying off-patent drugs that could potentially be used more effectively in children if additional studies were conducted. A challenge of these activities is ensuring the development of pediatric-friendly formulations.

In 2007, the focus of BPCA activities broadened from specific drugs to disease conditions and therapeutics. The BPCA 2007 legislation mandated that NIH, FDA, and experts in pediatric research develop and publish a priority list of needs in pediatric therapeutics, including drugs or indications that require study. It allowed NIH to award funds to entities that have the expertise to conduct pediatric clinical trials or other research. NIH may use contracts, grants, or other appropriate mechanisms to award funds. The new legislation considered:

- Therapeutic gaps in pediatrics, which may include developmental pharmacology, pharmacogenetic determinants of drug response, metabolism of drugs and biologics in children, and pediatric clinical trials
- Particular pediatric diseases, disorders, or conditions where more complete knowledge and testing of therapeutics, including drugs and biologics, may be beneficial in pediatric populations
- The adequacy of necessary infrastructure to conduct pediatric pharmacological research, including research networks and trained pediatric investigators.

New legislation governing the development and authorization of medicines for use in children was introduced in the EU in January 2007. This legislation—the Pediatric Medicines Regulation—introduces sweeping changes into the regulatory environment for pediatric medicines that are designed to better protect the health of children in the EU. The objective of the Pediatric Medicines Regulation is to improve the health of children in Europe by (1) facilitating the development and availability of medicines for children 0–17 years of age; (2) ensuring that medicines for use in children are of high quality, ethically researched, and authorized appropriately; and (3) improving the availability of information on the use of medicines for children, without subjecting children to unnecessary trials or delaying the authorization of medicines for use in adults. The Pediatric Medicines Regulation brings in many new tasks and responsibilities for EMEA, chief of which is the creation and operation of a Pediatric Committee to provide objective scientific opinions on any development plan for medicines for use in children.

The Agreement between the European Community and the United States on Science and Technology Cooperation provided the impetus for communication between DG Research and NIH. Director of DG Research Octavio Quintana Trias wrote to NIH Director Elias Zerhouni, M.D., and proposed a joint planning meeting. Dr. Zerhouni agreed that the initial meeting be

small and focus on procedural and planning activity. The meeting of representatives from NIH, DG Research, EMEA, and FDA was held in London in January 2008. The meeting participants identified the legislative commonalities and agreed that there are a range of overlapping areas, including the funding of organizations that are capable of designing, implementing, conducting, analyzing, and supporting pediatric studies that lead to the labeling and distribution of medicines that meet pediatric needs. The meeting participants identified commonalities as well as differences in the goals of pediatric drug testing legislation, approaches for prioritization, calls for research proposals, funding mechanisms (for example, contracts versus grants), and study monitoring.

Some of the goals for the July 2008 meeting were to:

- Share prioritization information
- Update current studies
- Describe areas in which study design has been challenging
- Share Written Requests (WRs)
- Share study designs
- Discuss the framework for a memorandum of understanding.

Pediatric Medicines and the Health Theme in the Cooperation Programme of FP7: II

Fergal Donnelly, M.D., Principal Scientific Officer, Health Biotechnology, DG Research, EC, Brussels, Belgium

The Pediatric Medicines Regulation has many business ends and objectives. Article 40 of the regulation is the main concern of the DG Research. Article 40 states that:

- Funds for research into medicinal products for the pediatric population shall be provided for in the Community budget in order to support studies relating to medicinal products or active substances not covered by a patent or a supplementary protection certificate.
- The Community funding referred to in paragraph 1 shall be delivered through the Community Framework Programmes for Research, Technological Development and Demonstration Activities, or any other Community initiatives for the funding of research.

The DG Research's total budget for pediatric medicines research is €30 million. In 2007, eight calls for research (requests for proposals [RFPs]) were issued. Funding per project was about €8 million–€12 million, with an EU contribution ceiling of about €6 million.

The topic for the third call is “adapting off-patent medicines to the specific needs of pediatric populations.” The text in the third call will reflect, to the extent possible, the joint agreed-upon priority list developed at this meeting. The intent is to address areas of U.S. and EU overlap regarding the molecules, therapeutic indications, and studies that will benefit children in the United States and the EU. The specific output is to develop a Pediatric Use Marketing Authorization (PUMA) for a compound or product that is on EMEA's Priority List of Molecules. The call will open September 2, 2008, and close December 5, 2008. During this open period, the priority list will be “frozen.”

Applications for the third call must be submitted electronically and in English. The submission includes administrative forms (part A) and technical content (part B). Part A requires a project summary, a list of participants, and a budget. The applicants must be consortia with at least three different entities from at least three different participating states. Part B requires descriptions of scientific/technical quality, implementation, impact, ethical issues, and gender aspects. Deadlines are strict, and it is highly advised to submit several days before the deadline.

Independent experts acting on their own behalf evaluate the proposals. They adhere to strict confidentiality and have no conflicts of interest. The first evaluation is basic eligibility, including minimum number of participants, relevance to the topic, and level of funding. The next evaluation is scientific and technical quality. The proposals are scored, and a consensus meeting is held in which a panel reviews the scores and issues a report. Contracts are negotiated with each consortium prior to award.

The results from the second call are as follows: 15 proposals were received, 8 proposals surpassed all evaluation thresholds, and 6 were retained for funding. There was good coverage of the ages and conditions listed and good coverage of malignant diseases, infectious diseases, and neonatology. The areas of ophthalmology, gastroenterology, and psychiatry received little attention; only one proposal involved cardiovascular medicine. New member states were significantly underrepresented. Commitment to seeking a PUMA was not clearly articulated. In many proposals, overambitious objectives were not matched by budget. Some investigators appeared in more than one project. Lack of clarity was apparent between the EMEA Priority List of Molecules and the Pediatric (Clinical) Needs List. Applicants showed a lack of familiarity with the realities of the drug development process.

Pediatric Therapeutic Research Initiative: Europe and the United States

Dianne Murphy, M.D., Director, Office of Pediatric Therapeutics, Office of the Commissioner, FDA

The purpose of the EU–US Joint Research Initiative is to coordinate and leverage the experience, science, and funding of pediatric therapeutic research in the United States and the EU. Coordinating and leveraging resources will help ensure safe, ethical, and scientifically sound implementation of pediatric programs. Cooperation between the EU and the United States is critical to achieve these goals. Understanding the respective legislative rules will facilitate this coordination. Understanding the differences in FDA’s and EMEA’s approaches to the off-patent process is important. Information exchanges and common ground for collaborative pediatric drug development programs are also important.

The Food and Drug Administration Modernization Act of 1997 mandated FDA to develop an annual list of products that needed pediatric information for labeling. The last FDA list was in 2001 and had more than 400 products (both on- and off-patent). BPCA 2002 released FDA from creating annual lists of these products. BPCA 2002 directed NIH and FDA to develop a list of drugs for which pediatric studies are needed for off-patent products. Developing this list has been a long, iterative process that required input from advisory committees, FDA divisions, the American Academy of Pediatrics, the U.S. Pharmacopeia, and academic experts. NIH publishes

the list of products needing additional information for labeling. Challenges to the process are (1) products constantly going off-patent and (2) some product forms going back on-patent.

Once NIH develops the priority list of off-patent drugs, it submits a Proposed Pediatric Study Request (PPSR) to FDA, which then issues a WR to the drug's developer requesting a pediatric study. If the WR is rejected, it is sent to NIH. NIH then issues an RFP and subsequently awards a contract for the study. In addition to contracts for studies, NIH awarded a contract for a coordinating center to ensure that data from trials will be developed, recorded, and submitted in a manner that meets FDA standards and requirements.

There are differences between NIH and the EU in the way studies are solicited. In its requests for contracts and grants, NIH is specific with regard to product and indication because the requests must reflect FDA's WR. If for some reason the study scope or requirements change, another WR must be issued and the process is repeated. The EU does not have such an iterative process. The EU issues announcements that are more general: Calls for Tender. The EU and the United States each develop its own drug priority list.

FDA and EMEA are leading present ongoing exchanges between the EU and the United States on development of pediatric trials at a global level. From August 2007 through May 2008, EMEA sent 201 Pediatric Investigational Plans (PIPs) to FDA. PIPs provide preliminary information on industry-requested indications, waivers, age groups, and so on. FDA reviews the PIP and determines whether WRs have been issued, whether there are ongoing Pediatric Research Equity Act studies, the status of internal studies, and safety issues. On several occasions, FDA has informed EMEA that a protocol is on hold because of a safety issue. Of the 201 PIPs, 79 were discussed, of which 29 were in-depth or expanded scientific discussions because of differences in things such as indications, endpoints, ages, the use of placebos, standards of care, and conduct of clinical trials.

There are two objectives of EMEA and FDA interactions:

- Regular exchange of scientific and ethical information on pediatric drug development programs in Europe and the United States to avoid exposing children to unnecessary trials
- Aim for global pediatric drug development, which does not mean the protocols will be exactly the same or the same questions will be asked.

The FDA and EMEA on-patent process of information exchange involves monthly teleconferences to discuss product-specific pediatric development (for example, PIPs, WRs, waivers, and deferrals). Documents are exchanged through a secure link (Eudralink). FDA and EMEA regularly exchange scientific information, including:

- Status of ongoing pediatric studies
- Results of studies conducted in pediatric patients, including negative studies
- Safety concerns, including clinical holds
- Plans for long-term safety monitoring
- Pending WRs
- Waivers (rationale and, for partial waivers, age cut-off for study)

- Deferrals (for example, the need for additional safety data in adults before initiating studies in pediatric patients).

With regard to future programs, FDA and EMEA have learned much from their on-patent interactions. A pediatric drug development program needs regular interactions and dedicated personnel. Technical experts may have different opinions and will influence how smooth and productive the collaborations are. There is a constant need for communication and familiarization about the program with each new product-area expert. Control of expectations is necessary.

Possibilities for future EU–U.S. collaboration include pediatric programs that:

- Share information on similar products
- Pool products and work to prioritize who does which product (The goal would be that ideally the data could be submitted to both EMEA and FDA; differences will exist.)
- Fund a common protocol
- Fund complementary parts of product development.

Review of Regulatory and Research Environment

Agnès Saint Raymond, M.D., Head of Sector, Scientific Advice and Orphan Drugs, Pediatric Medicinal Products, EMEA, London, UK

There are several differences between the United States and the EU in the legislative frameworks and regulatory approaches to pediatric drug development. Under BPCA 2007, pediatric drug studies for off-patent medicines are optional for drug companies, and, if requests for studies are rejected, NIH coordinates the studies through contracts. The EU approach is less restricted and has more opportunity for flexibility and creativity. In the United States, the primary tool is the WR; in the EU, the primary tool is the PIP. There are differences in incentives and rewards for companies that conduct pediatric trials of off-patent drugs. Under BPCA 2007, companies are granted 6 months of exclusivity. In the EU, companies are granted a 6-month patent extension for off-patent products and 10 years of data protection. From August 2007 to June 2008, there have been increasing numbers of indications in PIPs and waivers and increasing numbers of applications to the EMEA Pediatric Committee. There have been six applications for off-patent pediatric drugs.

PUMA is a special type of approval for pediatric products. It is optional and covers only pediatric indications and formulations. It requires agreement of development through the PIP. Product developers need to comply with the PIP, and the results need to be in the product information. The incentive is 10 years of data protection (as for new products in the EU).

PIPs and waivers are proposed by companies by the end of phase I for new products; PIPs for off-patent products may be submitted at any time. The plan is discussed, modified, and agreed upon by the Pediatric Committee. A plan can be imposed on a company, and a plan or waiver can be refused by the Pediatric Committee. PIPs are binding on companies, and the agreed-upon PIP or waiver is necessary to allow validation of the marketing authorization application (same for new indication, formulation, or route of administration). PIPs define the necessary data on

quality, safety, and efficacy for use in the pediatric population (0–18 years old). There is no explicit link with an adult indication. PIPs specify development timelines, including deferral of studies, and define age-appropriate formulations. The results according to agreed-upon plans serve as the basis for evaluation of approval.

On request from the applicant or initiative of the Pediatric Committee, there may be a waiver or deferral of a PIP for all or part of the pediatric population. Waivers may be for a class of drugs, indication, or specific product. There may be deferrals of initiation of studies and/or completion. Product development is most often a combination of a plan with deferrals and waivers (subset). PIPs are intended to support an indication in all subsets of the pediatric population and must adhere to the stated timelines. In practice, there is a discussion per indication of the development and formulation for each age group.

The main responsibility of the Pediatric Committee is to assess the content of PIPs and adopt opinions on them in accordance with EC regulations. This includes the assessment of applications for a full or partial waiver and assessment of applications for deferrals. The Pediatric Committee is composed of 5 members of the EMEA Committee for Medicinal Products for Human Use, 22 member state representatives, 3 members representing healthcare professionals, and 3 members representing patients' associations. Members of the Pediatric Committee are appointed for a renewable period of 3 years. Of the committee's 27 members, 17 are pediatricians; there is additional competence in pediatrics (for example, pediatric pharmacologists). Half the members are in academia.

There is a need to establish an EMEA network as part of EU and international pediatric research networks. Such a network would be a valuable tool for research including off-patent studies. The network would facilitate collaboration between academia and the pharmaceutical industry. The first steps in establishing an EMEA network is to identify existing pediatrics networks and define quality criteria for collaboration. The network could address issues such as pediatric formulations, better use of experimental (animal) models, and extrapolation from adults to children. There should be a global effort to avoid duplication of studies and waste of (precious) funding.

Resource Expectations for Generating Pediatric Label Changes

Steven Hirschfeld, M.D., Ph.D., Associate Director for Clinical Research, NICHD, NIH

There are multiple steps in the clinical study process. Resources and costs for the process are, in general, driven by the number of patients enrolled, the length of the study, and the number and complexity of assessments. To plan pediatric studies that might lead to labeling changes, estimating the necessary resources and costs is critical. Publicly available data were analyzed for this purpose.

Investigators from the Duke Clinical Research Institute (DCRI; Li et al. Economic return of clinical trials performed under the pediatric exclusivity program. *JAMA* 2007 Feb 7; 297(5):480–8) collected data from 59 final study reports submitted to FDA between 2002 and 2004. Key elements of the clinical trial design and study operations were obtained, and the cost of

performing each study was estimated. The reports encompassed 137 trials and about 23,000 children. The median trial enrollment was 116 (range = 10–795). The median trials per product was two (range = one–eight). Nine products were analyzed in detail. Median costs by study type were \$9 million for a single dose pharmacokinetics (PK) study, \$2.3 million for a multidose PK study, and \$6.5 million for an efficacy study.

FDA data were analyzed. The data came from studies submitted and granted exclusivity from 2002, when the data became publicly available, through early 2007. The analysis included 195 studies, 33 drug classes, and 12 therapeutic areas. There were 73 products, 59 with label changes. The studies were classified as PK (single or multidose), PK/pharmacodynamics (PD), PD, and efficacy. Of the 195 studies, 20 percent were PK, 18 percent PK/PD, 29 percent PD, and 33 percent efficacy. Fifty-four studies were randomized, of which 33 were used for efficacy. The analyses show a median of 2.6 studies per product and median of 357 patients per product. The youngest age groups had the fewest number of products studied. The 11- to 16-year-old group had the greatest number of products studied. This pattern holds for distribution of age groups per study type. Mean numbers of patients by study type were 33 for PK, 68 for PK/PD, 157 for PD, and 249 for efficacy.

Based on the data analyses, the general trends were as follows:

- About 90 percent of submissions are granted an incentive.
- About 80 percent of products granted an incentive have a label change.
- There is no difference in the number of studies, the number of patients, or disease class between products that had a labeling change and those that did not.
- The youngest children are generally studied the least, but all age groups are represented.

With regard to resource expectations, (1) the number of studies is generally between two and three per product, (2) the number of patients correlates with the study outcome type, and (3) there is a trend toward fewer patients with more objective outcome measures and less available therapeutic alternatives.

Supporting New Studies for Old Medicines: The Prioritizing Work of the Pediatric Committee at EMEA

Daniel Brasseur, M.D., Ph.D., Chair, Pediatric Committee, EMEA, London, UK

The Pediatric Committee revised the priority list for studies into off-patent pediatric medicinal products. The objective of the revision was to provide the basis for the work program for the third call of FP7. This program ensures that funds are directed into research of medicinal products with the highest need in the pediatric population. The revision strategy was as follows:

- Develop a list of pediatric diseases and conditions
- Set priority criteria for conditions and priority criteria for products
- Propose criteria and rating (points)
- Check information from published literature (general reviews of therapeutics in the various domains) and textbooks to identify products of interest
- Prepare a database.

The priority process was as follows:

- Examine major conditions within each pediatric specialty (for example, cardiology, oncology, and pain)
- Establish therapeutic needs within each domain
- Score the needs according to predefined criteria for eligible condition and for product
- Check and confirm validity of criteria in databases
- Set a score (can be positive or negative).

Experts were consulted about the priority process. There was initial disbelief in the procedure, but there was no outcry in view of the outcome. Ultimately, there was large support of the exercise and reasonable agreement with the priority list produced by NIH and FDA in 2003.

A critical analysis of the priority list revealed the following issues:

- There was a choice of frequent diseases because of the Orphan Regulation.
- Neglected diseases are part of other DG Research programs.
- Evidence for available treatment could not be assessed.
- Emerging therapies in life-threatening conditions should receive some priority.
- Products of interest may actually be newer ones.
- There was no analysis of the need for pediatric formulations.
- Establishing the cutoff value was a matter of practicality and feasibility.
- The prioritizing method is not appropriate for cancer products.
- Areas where no therapeutic agents have been assessed correctly were completely left out (for example, rheumatology).
- The process focused solely on off-patent products and not on future developments needed in certain therapeutic areas.

About 300 pediatric conditions were identified and classified by therapeutic areas. The proposed criteria to rank priority for eligible conditions are seriousness (lethal or debilitating), high prevalence (relative to children), diseases affecting all age ranges, and diseases affecting newborns. Criteria for addition to the priority list are main therapeutic needs, specific safety concerns limiting use, information needed from clinical studies, and identification of endpoints for measuring efficacy.

BPCA Overview

Perdita Taylor-Zapata, M.D., Pediatric Medical Officer, OPPB, CRMC, NICHD, NIH

Initially signed into law 2002, BPCA encouraged pediatric drug testing through incentives to private companies and authorized a research program through HHS. Legislation directed HHS, acting through NIH, to establish a research program for drug testing and drug development. This program consisted of a drug development program to conduct clinical trials of primarily off-patent drugs where the WRs were rejected by the pharmaceutical companies. BPCA was delegated to NICHD to administer the research program, with consultations and contributions from other NIH Institutes and Centers (ICs) with pediatric research portfolios. NICHD developed and continued an annual cycle of data gathering, expert consultation, and critical analysis with experts in pediatrics to prioritize drugs, primarily off-patent drugs, to be studied.

In 2005–2006, in consultation with experts in pediatric research, NIH and FDA started receiving input from experts to consider changing the paradigm of prioritization from an annual cycle of individual drug/indication approach to a condition-based or therapeutic area-based approach.

NIH has made significant progress in the prioritization of off-patent drugs needing study in children. As of June 2008, 106 drugs have been discussed with experts (NIH ICs, FDA, academia, and industry) and 61 drug/indication pairs have been identified and listed as off-patent priority drugs requiring further pediatric studies. NICHD has responded to 80 percent of WRs received; 20 percent represented challenges. Fifteen clinical and/or preclinical studies are underway.

In September 2007, Congress reauthorized BPCA as part of the FDA Amendments Act of 2007. The focus of the new legislation required a shift from prioritizing drugs to identifying gaps in pediatric therapeutics including drugs or indications that require study. The steps to date that the NIH has taken to implement the new legislation include:

- Redirecting prioritization to focus on needs in pediatric therapeutics
- Identifying gaps in knowledge of drugs
- Identifying biologics or devices used in pediatric care
- Identifying diseases and conditions that bring children into contact with the health care system
- Determining studies (and/or therapeutic approaches) that would have a public health benefit.

The 2008 prioritization process will continue in the format of evaluating therapeutic classes of drugs for the determination of labeling and scientific gaps in knowledge. NICHD will prioritize therapeutic areas over the next 4 years based on the following:

- Building on the current foundation established by the 2002 BPCA implementation
- Evaluating the currently listed drugs and therapeutic areas under BPCA 2002 for additional or new therapeutic gaps
- Changing the listing process from an individual drug/indication approach to listing needs in pediatric therapeutics
- Determining new areas of need in pediatric therapeutics.

The prioritizing process will include:

- Defining boundaries of therapeutics and therapeutic needs
- Gathering data to assist in determining gaps in therapeutic areas and/or drugs through epidemiology studies and literature summaries
- Consulting with experts in pediatric research to assist in determining gaps in therapeutic areas and/or drugs
- Consulting with FDA Pediatrics and Review Divisions in determining labeling and study design gaps
- Prioritizing through the development of priority categories for therapeutic areas and priority scores for drugs.

A preliminary BPCA list of needs in pediatric therapeutics is being prepared based on research conducted under BPCA since 2002, expert opinion, and incorporating public health issues that are prevalent and/or increasing in pediatric therapeutics. Each year a “priority category” will be selected. Examples include areas of high prevalence in the pediatric population, areas with high morbidity and mortality, areas with public health impact, and areas with limited availability of treatment alternatives. For each therapeutic area or indication identified within a priority category, reviews of published literature and analyses of medical claims databases will be performed to determine disease burden, health services use by pediatric patients, and gaps in knowledge within a therapeutic area. For each therapeutic area or indications selected, evaluation of the needs within special populations, including neonates and adolescents, will be conducted.

Off-patent and off-label drugs, biologics, and/or devices will be identified by the three-tiered outreach process described above and finalized through consultation with the FDA. Priority scores will be assigned based on the following:

- Level of evidence of available—PK, safety, or efficacy data
- Frequency of drug use in the pediatric population
- Severity of the disease for which the drug is being used
- Potential benefit that the study of the drug will provide to the public and research communities—with particular emphasis on the impact of improving knowledge of the drug across multiple specialties.

Based on all collected data, therapeutic areas and drugs with a public health challenge/benefit are finalized and prioritized for study based on feasibility, relevance to mission of NIH/BPCA, identification of health disparities, and innovation in research. Diversity in the types of research has been proposed and includes epidemiology research, basic science and mechanistic research, and clinical trials. Still in question are formulations and manufacturing research.

United States: Steps to Award, Study, Monitoring, and Data Submission

Anne Zajicek, M.D., Pharm.D., Associate Branch Chief, Pediatric Medical Officer, OPPB, CRMC, NICHD, NIH

Dr. Zajicek briefly reviewed the PBCA list prioritization process. NIH requests input on therapeutic needs and associated medical treatments that are proposed by stakeholders. NIH holds the annual list prioritization meeting. Stakeholders are invited, and therapeutic areas and associated treatments are discussed by experts. BPCA 2002 mandated that NIH and FDA develop a master list of all off-patent drugs that lack adequate pediatric labeling. However, in the 2002 legislation, the definition of “off-patent” was unclear. BPCA 2007 (FDA Amendments Act of 2007) clarified the definition of “off-patent” as a drug that has no listed patents or has one or more listed patents that have expired. In addition, the 2007 legislation calls for a list of priority areas in pediatric therapeutics; requires consideration of available information, therapeutic gaps, potential health benefits, and adequacy of infrastructure for research; and allows NIH to submit a PPSR to FDA as a draft WR.

NIH publishes the annual priority list in the Federal Register. FDA, with input from NIH, writes the WR for a drug on the priority list. FDA sends the WR to the New Drug Application (NDA)

or abbreviated New Drug Application (aNDA) holder. The WR describes studies needed to improve the label for pediatric prescribing.

FDA has issued WRs for the following off-patent drugs:

- Lorazepam
 - Sedation
 - Status epilepticus
- Nitroprusside
- Azithromycin
 - Ureaplasma pneumonia
 - Chlamydia
- Baclofen
- Lithium
- Lindane
- Rifampin
 - Methicillin-resistant *Staphylococcus aureus* (MRSA) endocarditis
- Central nervous system (CNS) shunt infections
- Meropenem
- Vincristine
- Actinomycin-D
- Ampicillin
- Griseofulvin
- Methotrexate
- Daunomycin

Industry declined the WRs for all of these drugs except lindane.

Under BPCA 2007, NIH can fund studies through grants, cooperative agreements, and contracts. The contracting process begins when FDA refers a WR to NIH. NIH develops an RFP, with the project officer writing the scientific portion including the statement of work and technical evaluation criteria. The RFP solicitation is published in Federal Business Opportunities (www.fedbizopps.gov) with a 30- to 90-day timeline. A Special Emphasis Panel is convened to evaluate the proposals. The panel includes experts in pediatrics, clinical pharmacology, statistics, therapeutic area, ethics, and others. A determination is made about responsiveness of proposal, a score is given to the proposal based on the technical evaluation criteria, and a determination is made about score in the competitive range. The government and the offeror(s) may negotiate prior to contract award.

There are three components of BPCA oversight: NIH, FDA, and Congress. An NIH data and safety monitoring board (DSMB) oversees performance of all BPCA studies. Contractual guidance on timelines and activities include contract length (2–5 years), study start-up, investigator meeting, weekly calls with study steering committee, and weekly calls with project coinvestigators. The data coordinating center ensures 100 percent source document verification and adherence to Good Clinical Practice guidelines. FDA oversees all studies performed under Investigational New Drug Application (IND). BPCA legislation requires progress reports to Congress. NIH responds to congressional questions on a regular basis. NICHD provides briefings and testifies before various congressional committees as required.

Data from BPCA studies are evaluated by FDA. The data submitted to FDA goes to a public docket, with NIH-proposed labeling changes. Data evaluated by FDA include medical, clinical pharmacology, statistics, pharmacology/toxicology, chemistry, manufacturing, and controls. Data may be audited for accuracy. NIH submissions are discussed by FDA's Pediatric Review Committee. Data submitted to the FDA docket may receive public comment. Labeling changes are negotiated between FDA and the NDA holder.

BPCA authorized an annual budget of \$200 million, but Congress did not appropriate any funding. As a result, NIH has provided \$25 million per year for BPCA activities. NICHD has

provided \$7 million of the funding. The remaining \$18 million is provided by 19 other NIH ICs with interests in pediatric medicine.

NICHD has contracts with RTI International and Westat for pharmacoepidemiology work and a contract with Premier Research Group for the data coordinating center. Data coordination work includes generation of case report forms, database construction, review of informed consent forms, site regulatory document verification, data monitoring, and DSMB monitoring. The cost of the 5-year contract is \$20.5 million.

BPCA clinical projects are as follows:

- Lorazepam for sedation (PK, safety, and efficacy)
- Lorazepam for status epilepticus (PK, safety, and efficacy)
- Nitroprusside (reducing blood pressure during surgery to reduce blood loss)
- Lithium (defining treatment of mania in children with bipolar disorder)
- Baclofen (treating spasticity, most commonly from cerebral palsy)
- Meropenem (treating serious intra-abdominal infections in infants).

Studies being conducted under intra-agency agreements are as follows:

- Hydroxyurea (sickle cell treatment; NHLBI)
- Oncology trials (NCI)
 - Vincristine (data extraction, catheter-clearing experiment, PK modeling of published data, prospective PK study)
 - Actinomycin-D (data extraction, catheter-clearing experiment, PK modeling of published data, prospective PK study)
 - Methotrexate (neurocognitive outcomes)
 - Daunomycin (disposition and body weight)
- Methylphenidate project (PK/PD in preclinical model, cytogenetics)
- Ketamine project (neuroapoptosis in preclinical model).

Meropenem and BPCA

Danny Benjamin, M.D., Ph.D., M.P.H., Associate Professor, Duke University Pediatrics; Chief, Division of Quantitative Sciences; Director, DCRI Clinical Research

In the RFP for the BPCA meropenem study, the scope of work requested single-dose PK analysis, multidose PK analysis, and an efficacy trial with 600 infants with documented necrotizing enterocolitis. Response to the RFP involved an iterative and cooperative process among FDA, NICHD, and the offerors, which were a group of investigators from the Pediatric Pharmacology Research Unit (PPRU) and neonatologists. Negotiations led to a revised scope of work that included a PK and safety trial analyzing first dose and steady-state kinetics in 200 infants with suspected or proven necrotizing enterocolitis. From these 200 infants, both first dose and steady-state samples will be collected from 144 infants. Steady-state samples only will be collected from the remaining 66 infants. The study will analyze the safety and PK of one or two dosages, depending on the preliminary efficacy data.

The study is an open-label design. Meropenem can be used for suspected necrotizing enterocolitis, as add-on therapy or as monotherapy. Because the PK is not known, the collaborators agreed to use an aminoglycoside in conjunction with meropenem. This approach is ethically in the best interest of the study and is written in the informed consent. Four groups of infants will be enrolled: (1) premature and young postnatal age, (2) premature and old postnatal age, (3) near-term and young postnatal age, and (4) near-term and old postnatal age. Premature infants are defined as ≤ 32 weeks gestation, and neonates are defined as ≤ 2 weeks postnatal age.

Based on the original study design, there were 20 sites and a 10-month enrollment period. Enrolling 200 would require one infant per study site per month. A 20-percent float enrollment was agreed upon, which allowed enrollment to extend to 12 months. A 10- to 20-percent float on the number of sites was agreed upon, which allowed 25 sites. It was anticipated that the first patients would be enrolled 9–10 months after the contract began. The original application for the contract was October 2005, and the protocol was established at that time. The contract was signed in September 2007. The first six sites are operational; enrollment began in June 2008. All sites should be operational by the end of August 2008. The IND was submitted in December 2007. Because the protocol was submitted in December and not shortly after the contract was awarded in October, it cost the study a month or two on the timeline. However, the study is currently ahead of schedule and on budget. The contract ends in September 2009.

The lessons learned to date are to remain focused on the contract details and strict adherence to the timeline. Secondary protocols must be fully written and approved before being submitted to institutional review boards. Secondary protocols must not affect the timeline of the primary protocol. Although the primary protocol did not include cerebrospinal fluid sampling, the project officer and investigators agreed that these samples should be collected. It is anticipated that about 20 samples will be collected. The current mechanism for NIH studies requires a small business group as the coordinating center; these small groups have small staffs. DCRI has coordinating center capability with 900 staff members dedicated exclusively to clinical research. The institute is fundamentally a helper to the NIH small business mechanism. The institute has extensive experience with clinical studies, with enrollments from 12 patients to 41,000 patients. One-third of the studies have enrolled more 1,000 patients. Given this experience, the institute is fully capable of coordinating the meropenem study's 25 sites. The study has benefited from the trust and established working relationships among NICHD project officers, DCRI, and the study investigators at the PPRU sites.

Future contracts would benefit from a lead-in phase (that is, a “precontract”) for protocol development. The protocol would be reviewed and revised, for example, by FDA, NICHD, and EMEA. Upon protocol approval, the contract for implementation would be awarded and the study would begin. This approach would allow earlier IND submission. Studies should have dedicated contract management staff, and there should be a system for contracting late sites. Multisite studies should include repeat sites, new sites to expand networks, and backup sites.

Pediatric Antihypertensive Clinical Trial Design

Danny Benjamin, M.D., Ph.D., M.P.H., Associate Professor, Duke University Pediatrics; Chief, Division of Quantitative Sciences; Director, DCRI Clinical Research

Duke University investigators analyzed raw data from 12 safety and efficacy hypertension studies conducted between 1998 and 2005. The FDA-provided data were combined into a common data set. Trial design, safety, and dose response were analyzed. Half of the trials failed. Half of the trials were type C design in which subjects were randomized into low-, medium-, or high-dose groups. There were subsequent placebo control and open-label phases. Dose response was primary endpoint. Half of the type C trials failed.

In the 2- to 4-week placebo control phase, there were no differences in adverse events between the placebo control arm and the product arm. Based on the analysis, placebo controls in pediatric hypertension trials are safe. The type C trials had the same design, the same inclusion–exclusion criteria, and similar patient populations. Successful trials had several design components in common. They all used diastolic blood pressure as the primary endpoint, had a larger range in amount of agent given to low-dosage versus high-dosage groups (20- to 30-fold difference between high and low doses), and used pediatric formulations in the efficacy trial. The placebo withdrawal phase was important to demonstrate blood pressure lowering response despite lack of dose response for most agents. Based on the analysis, failed trials would have been successful if they had dosed on a milligram-per-kilogram basis and used a large dosing variance being high and low dose.

Recommendations for future pediatric clinical trial design are as follows:

- Develop an exposure–response model using adult and pediatric data to perform clinical trial simulations of pediatric studies and explore trial designs and analysis options
- Design pediatric trials by leveraging previous quantitative knowledge
- Routinely collect blood samples at informative time points to assess PK in each subject to ascertain exposure–response analysis.

Off-Patent Anticancer Drugs: The Needs

Gilles Vassal, M.D., Ph.D., Pediatrician Oncologist and Professor of Oncology, Department of Pediatric Oncology, Director, Direction of Clinical and Translational Research, Institut Gustave Roussy, Villejuif, France

About 75 percent of pediatric cancers can be cured. Cytotoxic chemotherapy—particularly off-patent medicines—plays a major role in pediatric chemotherapy. Although some labeling may be inappropriate, there is no need for additional studies for most of the drugs (for example, carboplatin, cisplatin, cyclophosphamide, and busulfan). The needs for study are age-appropriate formulations for oral anticancer drugs, chemotherapy in infants, and epidemiology of long-term sequelae.

Ongoing projects selected in the September 2007 FP7 call are addressing the needs for age-appropriate formulations of mercaptopurine, cyclophosphamide, and temozolomide. Age-appropriate oral formulations are needed for the following pediatric anticancer drugs:

- Retinoic acid
- Etoposide
- Vinorelbine
- Methotrexate
- Thioguanine.

Age-appropriate formulations for oral use are likely to lead to PUMAs and will generate additional PK data, especially in younger populations. There is no current need for international cooperation. Although there are marketing issues, these formulations should eventually be available in the United States and Europe for pediatric cancer patients.

According to NCI Surveillance, Epidemiology, and End Results data, there were 12,800 new pediatric cancer cases in the United States in 1998. The incidence of pediatric cancers in Europe was about the same. There are about 2,500 deaths per year in the United States and Europe. Cancer in infants accounts for 10 percent of all pediatric cancers. The incidence is 233 per million infants. The three most common types of infant cancers are neuroblastoma, leukemias, and CNS tumors. Because of differences in survival rates between infants and all children, there is a need for more efficient and safer treatments. Five-year survival rates for all children compared with infants are:

Cancer type	All Children	Infants <1 year
▪ Neuroblastoma	45 percent	80 percent
▪ Leukemias	75 percent	33 percent
▪ CNS tumors	65 percent	45 percent

There are several reasons to study chemotherapy in infants. Issues of safety have been reported. Little is known of the maturation of physiological processes involved in drug disposition in the first year of life. There is a need for PK, PD, and pharmacogenomic (PG) data in infants to define safe and effective dose of off-patent cytotoxic agents. Because pharmacological studies in a rare population are very difficult to run, there is a need for innovative population PK designs. Experiences with pharmacological studies should be applied to studies of neonates. There is a need to embed them into prospective clinical trials and open them in qualified centers. Interfant-06 (International Collaboration Treatment Protocol for Infants Under One Year with Acute Lymphoblastic or Biphenotypic Leukemia) is an example of a prospective international collaboration in clinical research in infants. This collaboration could provide needed data on chemotherapy in infants. In addition, there are several ongoing prospective trials of neuroblastoma patients in the United States and Europe (International Society of Paediatric Oncology European Neuroblastoma Research Network), as well as ongoing international cooperation on staging and evaluation of response to carboplatin, cisplatin, cyclophosphamide, vincristine, doxorubicine, and etoposide. Linking pharmacologic trials to existing protocols will increase the feasibility and likelihood of recruiting patients and generating data.

Dr. Vassal proposed a joint United States–EU call for a project to explore the pharmacology of anticancer drugs in infants with cancer (solid tumors and leukemias) to recommend the dose of several medicines:

- Actinomycin-D
- Doxorubicine

- Busulfan
- Carboplatin
- Cisplatin
- Cyclophosphamide
- Cytarabine
- Daunorubicin
- Etoposide
- Fludarabine
- 6-Mercaptopurine
- Methotrexate
- Thioguanine
- Vincristine

Subpopulations may be required to take into account the time-dependent maturation of physiological processes involved in drug disposition in the first year of life.

Prioritization in Pediatric Oncology: Off-Patent Anticancer Drugs

Victor M. Santana, M.D., Director, Division of Solid Malignancies, Oncology Department, St. Jude Children's Research Hospital

Childhood cancer is viewed as a “life continuum” disease—from diagnosis and treatment throughout the lifespan. Care in pediatric oncology is multidisciplinary, and clinical research serves as the cornerstone of therapy. There is a long interval between intervention and outcomes. Many of the issues in pediatric oncology relate to the cytotoxic drugs that are used. There is a tension between safety and efficacy because of the drugs’ narrow therapeutic window and acute and delayed toxicity. Half of the cancers diagnosed in the 0- to 14-years-old age group are brain tumors and acute leukemias. Many of the other half of the diagnoses involve solid tumors.

In the United States, about 8,700 new cases are diagnosed annually in children younger than 15 years of age; 12,400 cases are diagnosed in persons younger than 20 years of age. About 1,700 children younger than 15 years of age and 2,300 children/adolescents younger than 20 years of age die of cancer each year in United States. Some children who are cured experience diminished quality of life because of the long-term effects of their cancer diagnosis and treatment. Current therapy is at near-maximal intensity, and new treatment strategies are needed to improve outcome for these children.

Prioritizing drugs and protocols at St. Jude Children’s Research Hospital solid tumor program involves a number of considerations:

- Patient population—frequency and severity of the condition
- Unmet needs—available alternatives
- Current knowledge—successful approaches in adults, existing pediatric data, activity, safety
- Scientific importance
 - Compelling preclinical rationale
 - Novel mechanisms of action or new schedules and dosing
 - Analogues of known effective agents with improved toxicity profile
 - Relevance to other conditions or tumor types
- Impact—new population, frequency of use
- Feasibility—number of patients, accrual goals, and costs
- Use of preclinical models to inform decisions—appreciation of their value and limitations
- Ethical considerations.

Five off-patent oncology drugs are being studied through the BPCA mechanism: methotrexate, daunomycin, vincristine, actinomycin-D, and 13-cis-retinoic acid. Methotrexate and daunomycin are being studied at St. Jude Children's Research Hospital, and a PPSR is being developed for a third: 13-cis-retinoic acid. The methotrexate study is evaluating neurocognitive outcomes of pediatric patients with high-risk acute lymphoblastic leukemia. The study will explore the relationship between neurocognitive testing and diffusion tensor and magnetic resonance imaging. The daunomycin study is investigating PK, safety, and efficacy in the treatment of childhood cancers and the relationship to body weight. In addition, the study will explore the correlations with age, gender, race, and ethnicity. NCI and the Children's Oncology Group (COG) are collaborating with these studies.

13-Cis-retinoic acid (isotretinoin) is a vitamin A derivative that causes *in vitro* neuroblastoma differentiation. In a clinical trial of pediatric patients with high-risk neuroblastoma, the drug improved overall long-term survival rates. However, 13-cis-retinoic has variable PK, and the formulation is suboptimal for young children. The drug is a liquid formulation in a soft gelatin capsule. The capsule can be pierced and chewed; older children can be trained to swallow it. For younger children, the liquid must often be squeezed into food, which increases dosing variability. Out-of-capsule administration may be associated with decreased 13-cis-retinoic levels, and extemporaneous liquid formulations have been associated with toxicity, likely due to metabolism to all-trans retinoic acid (tretinoin). There are several possible studies to consider for BPCA. Data could be obtained to enable 13-cis-retinoic acid labeling changes that would include recommended dosing and approaches to use of the existing formulation in pediatric oncology, which may require a successful supplemental NDA. PK and possibly PG studies could allow for PK- and/or PG-guided dosing. Further studies on administration route (in or out of capsule) effects on PK are needed. A stable formulation suitable for young children and safe for handling by women of childbearing potential would be optimal. Specific safety concerns about CNS effects should be explored.

Off-Patent Anticancer Drugs: Actinomycin-D (AMD) and Vincristine (VCR)

Peter C. Adamson, M.D., Chief, Division of Clinical Pharmacology and Therapeutics, The Children's Hospital of Philadelphia

Most chemotherapies share a common toxicity: myelosuppression. This toxicity limits the ability to deliver therapy, but from a therapeutic drug-monitoring standpoint, a quantitative marker of toxicity (blood counts) can be used to individualize therapy. The toxicity can be managed because it can be easily measured and intervened. Actinomycin-D's myelosuppressive effects are often accompanied by hepatotoxicity. However, vincristine is neurotoxic, and there are no good measures of its peripheral toxicity.

Like most anticancer drugs, actinomycin-D and vincristine are dosed per body surface area (BSA). This dosing approach, however, is not used for infants and toddlers. The dosing approach for this age group becomes arbitrary and is inconsistent across diseases. For some drugs, there is an age cutoff for shifting the dosage based on BSA to body weight (per kilogram). The age cutoff may vary from 1 year to 3 years. The shift from BSA to per kilogram generally lowers the dose. Another dosing approach uses body weight, not age, as the cutoff to shift from per

kilogram to BSA. In a third approach, the dose is simply cut in half for children younger than a certain age (for example, 1 year). Because of these arbitrary approaches, some children are undertreated and some receive toxic doses. The lack of understanding of the appropriate administration of vincristine and actinomycin-D is related to mortality, particularly in infants and toddlers.

Although there have been many studies of anticancer drugs, few phase III trials have used a drug development approach where the key variable is a specific drug's effect on outcome, not a specific regimen's effect. Prior to 1997, improvements in treatment regimens and drug dosing continued to decrease overall mortality rates. Since 1997, there has been no improvement in overall mortality rates, primarily because no new anticancer drugs have been developed.

To successfully evaluate vincristine neurotoxicity, actinomycin-D hepatotoxicity, and PK of both drugs in children, investigators realized that a number of approaches would be necessary. The first step was to reanalyze source data from previous clinical studies. Data—much of it on paper—were extracted from the National Wilms Tumor Study database for toxicity. Although vincristine is administered as a single drug, actinomycin-D is not. It is administered with vincristine. The pairing of these two drugs provided an opportunity to study them at the same time. An assay was developed to quantitate both drugs at the same time in the same microvolume of plasma. A challenge to collecting samples in infants and toddlers is venous access. Cancer patients generally have a central catheter, and parents are reluctant to allow a peripheral intravenous line. Therefore, to improve participation in a study, samples would need to be collected from the same catheter through which the drugs are administered. The challenge with this approach is contaminating the PK samples drawn from the catheter. The second step in the study of vincristine and actinomycin-D was overcoming this challenge by conducting catheter-clearing experiments, which are almost completed. This approach still needs to be validated with other drugs because of the possible interaction between different catheters and the drugs. The other approaches involve (1) PK modeling of published vincristine and actinomycin-D data to design a prospective PK study and (2) a prospective PK study.

There are other challenges to the vincristine and actinomycin-D studies. Clinicians who use the drug may not appreciate the fact that, although vincristine has been used for 50 years, its appropriate administration in certain settings is not fully understood. Another challenge will be enrolling patients who may already be enrolled in a number of other protocols. Because clinical research is a cornerstone of pediatric oncology, cancer patients are often enrolled in multiple protocols. Winning over clinicians may be more challenging than winning over families. The final challenge to the studies is patient accrual.

Priorities for Studies of Off-Patent Pediatric Drugs: Areas of Overlap

Criteria for addition to the priority list are main therapeutic needs, safety concerns limiting use, information needed from clinical studies, and measurable outcomes. Four therapeutic areas were addressed: pain/analgesia, infectious disease, cardiovascular disease and nephrology, and neurology.

Pain/Analgesia. The off-patent drugs discussed and the decisions made are as follows:

- Fentanyl—study
- Ibuprofen—should not be studied
- Midazolam—should not be studied
- Morphine—study
- Propofol—should not be studied.

Infectious Disease. The off-patent drugs discussed and the decisions made are as follows:

- Amphotericin B—should not be studied
- Azithromycin—study
- Ciprofloxacin—being studied, share data
- Clindamycin—study
- Fluconizol—being studied, share data
- Meropenem—study.

Cardiovascular Disease and Nephrology. The off-patent drugs discussed and the decisions made are as follows:

- Dobutamine—study
- Dopamine—study
- Epinephrine—study
- Hydrochlorthiazide—study
- Milrinone—study
- Spironolactone—do not study.

Neurology. The off-patent drugs discussed and the decisions made are as follows:

- Diazepam—being studied
- Lorazepam—being studied.

Establishing Joint Priorities

General Issues. The following general issues/topics were identified:

- Scientific issues
 - Neonates—PK, PG, PD
 - Endpoints for clinical studies
 - Safety and long-term follow-up
 - Study design issues; compatible designs to meet FDA and EMEA data submission requirements
 - Breast milk
 - Placental transport and metabolism
 - Populations
- Processes
 - Informed consent
 - Coordinating data collection and submission
 - Technical evaluation of applications
- **IP** and products—formulations

- Age groups, gender differences (PK, PD, PG).

Pain. The following issues/topics in the area of pain were identified:

- Validated pain assessment/pain scoring instruments by age groups or developmental stage
- PG
 - Developmental expression of enzymes involved in metabolism and disposition
 - Developmental expression of receptors that mediate drug effects
- Safety and efficacy
- Drugs for possible study:
 - Morphine—joint working group, quality and quantity of existing data, dosing in neonates, long-term follow-up, methodological issues in clinical trials
 - Fentanyl.

Infectious Disease. The following issues/topics in the area of infectious disease were identified

- MRSA as an indication
- Clindamycin—treatment of MRSA (bone, joint, and soft tissue infections; bacteremia)
- Azithromycin—treatment of Chlamydia pulmonary infection, pneumonia, bronchopulmonary dysplasia (BPD); long-term outcome studies; share single-dose PK data
- Meropenem—share data (necrotizing enterocolitis, neonatal meningitis)
- Trimethoprim-sulfamethoxazole—possible study by the United States.

Cardiovascular Disease and Nephrology. The following issues/topics in the area of cardiovascular disease and nephrology were identified:

- Hypertension treatment—hydrochlorothiazide
- Treatment of neonatal shock
 - Dopamine
 - Dobutamine
 - Epinephrine
 - Milrinone
- Problems of definition—shock, blood pressure, long-term outcomes
- Use of new technologies—Doppler flow analysis.

Neurology. The following issues/topics in the area of pain were identified:

- Neonatal seizures
- Seizure endpoints
- Status epilepticus treatment with lorazepam—share data.

Oncology. The following issues/topics in the area of oncology were identified:

- Oral formulations
- Specific studies of neonates, infants, and toddlers—PK, PD, and PG
- Long-term outcomes
- Steroid toxicity
- Drug interactions.

Recommendations

Long-Term Follow-up

- Define/establish long-term outcome measures (for example, neurocognitive); identify sequellae, markers
- Define “long term”
- Determine what is feasible for a long-term outcome project
- Use of alternative methods for monitoring efficacy.

Other Areas to Consider

- Define terms—BPD outcomes/pulmonary function, shock, neonatal blood pressure range
- Refine measures of efficacy
- Cost-efficient measures
- Juvenile animal models
- Differences in gender, race, and ethnicity
- Studies of adolescents
- Data sharing
- Sharing of progress of studies
- Compatibility of data formatting and descriptors
- Avoidance of duplication of effort
- Data mining and scientific pooling
- Descriptive studies on the influence of maturation on PK on an age continuum (a basis for future modeling)
- PK/PD modeling and simulation
- Innovative statistical methods
- Innovative noninvasive methods (for example, neuroimaging, stable isotope labeling, microdosing)
- Endpoints, biomarkers, surrogates—validation
- Devices for children (for therapy and drug administration).

Drug Studies

- Morphine PK, data review
- Age-appropriate pediatric formulations.

Collaboration/Communication

- Establish a mechanism for frequent information exchange between NIH and DG Research
- Establish working groups
 - Specific drugs
 - Age groups
 - Formulations
- Prepare a publication on the meeting.

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