**Best Pharmaceuticals for Children Act**
**Annual Prioritization Meeting**
**November 19, 2009**
**Natcher Conference Center**
**Bethesda, 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 in support of the Best Pharmaceuticals for Children Act (BPCA) Program. The purpose of the meeting was to prioritize topics of study for pediatric therapeutic areas based on recommendations from experts in pediatric medicine and research.

## Welcome

*Anne Zajicek, M.D., Pharm.D., Acting Branch Chief, OPPB, CRMC, NICHD, NIH*

Dr. Zajicek welcomed the participants and referred to the larger context of this meeting, which included a discussion of prioritization in pediatric pharmacology by various groups on November 18, as part of the Methodologies to Set Priorities for Child Health Clinical Research Meeting. She explained the goals of the meeting: to implement prioritization requirements of BPCA, discuss problematic elements and possible solutions, and propose potential therapeutic areas for 2010, as required by the Act.

The mission of the OPPB is to (1) promote new research in basic and translational pharmacology with a focus on pregnant women and children; (2) identify, prioritize, and sponsor basic, translational, and clinical research and research strategies to improve understanding of interactions between therapeutics, disease, pregnancy, and development; and (3) facilitate training that enhances pediatric and obstetric pharmacology expertise. The OPPB has a grants portfolio and issues program announcements requesting applications for two networks: (1) the Obstetric Pharmacology Research Units Network and (2) the Pediatric Pharmacology Research Units Network.

The 2002 BPCA directed the NIH, and specifically the NICHD, to annually develop a priority list of prescription drugs used to treat children but that lacked pediatric labeling. The 2007 BPCA reauthorization legislation expanded this mandate; the law now requires the NIH to develop a priority list of needs in pediatric therapeutics. In the past 7 years, the OPPB has funded clinical trials across a large spectrum of pediatric diseases and clinical settings as well as epidemiologic and pharmacoepidemiologic research of diseases and therapeutic areas. During this time, the research conducted under the auspices of the BPCA has unmasked other gaps in pediatric research, including a need for pediatric formulations, preclinical studies, and outcome measures. In addition, the BPCA-related research and studies have revealed a need for more training in clinical pharmacology.

Dr. Zajicek listed and summarized the BPCA-sponsored clinical trials, which include studies of lorazepam, nitroprusside, lithium, oral baclofen, meropenem, morphine, azithromycin, and oseltamivir. The OPPB, using BPCA funds, is cofunding with the National Heart, Lung, and Blood Institute a study of hydroxyurea in very young children with sickle cell disease, a drug development project with the National Institute of Mental Health (NIMH) for fragile X, and a series of projects with the National Cancer Institute involving vincristine, actinomycin-D, methotrexate, daunomycin, and isotretinoin.

BPCA also cosponsored preclinical studies of (1) methylphenidate and potential cytogenetic abnormalities and (2) ketamine and neuroapoptosis. The OPPB cofunded training in pediatric clinical pharmacology with the National Institute of General Medical Sciences. A loan repayment program now exists for trainees in pediatric clinical pharmacology.

Problem areas include the lack of trained pediatric investigators, lack of networks capable of recruiting patients, need to develop a working relationship between medicine and engineering, and need for outcome measures, especially in neonatology, cardiovascular areas, and neurology. Prioritization is fairly difficult to quantify and relies on feasibility. It is difficult not to short-change infrequent, difficult-to-study therapeutic areas. Therefore, a bell curve might be a way to envision low-frequency, high-severity, emergent projects included in an ancillary fashion.

## Overview of Past Prioritization Process
## Introduction of 2009 BPCA Therapeutic Area Working Groups

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

Dr. Taylor-Zapata referred to the meeting participants as stakeholders in the prioritization process regarding pediatric therapeutics, which involves the use, effectiveness, and side effects of drugs for different age ranges in various formulations, including liquids, pills, and injections. After summarizing the legislative history from the 1930s through the 2002 and 2007 BPCA legislation, Dr. Taylor-Zapata reviewed the evolution of BPCA Program.

In 2003–2004, the NICHD developed an annual cycle of data gathering and consultation with experts in pediatrics in an effort to prioritize the study of primarily off-patent drugs. Beginning with a master list of 246 off-patent drugs, the U.S. Food and Drug Administration (FDA) issued written requests to drug companies, which had 30 days to agree to conduct the studies. If industry declined to conduct the studies, the NIH would develop requests for proposals to study the drugs.

In 2005–2006, the NIH and the FDA began to receive input from experts to consider changing the approach of the annual cycle from an individual drug/indication approach to a condition-based or therapeutic-area-based approach. In 2006–2007, a drug list with associated therapeutic areas emerged.

The NIH has made significant progress in the prioritization of off-patent drugs that need study in children under the BPCA. A total of 131 therapeutics have been discussed with experts thus far, and 91 drug/indication pairs have been identified and listed as priority drugs requiring further

pediatric studies. The NICHD received 24 written requests, 19 clinical and/or preclinical studies are underway via contract or grant, and 18 clinical and translational science awards have been made.

A paradigm shift from drugs alone to therapeutic areas resulted from the 2007 BPCA legislation. The NICHD was mandated to determine, develop, and prioritize a list to be used to identify needs in pediatric therapeutics and promote further research to address gaps, with a focus on developmental pharmacology, pharmacogenetic determinants of drug response, metabolism of drugs and biologics, and pediatric clinical trials. Prioritization also involves pediatric diseases, disorders, or conditions for which more complete knowledge and testing of therapeutics might be beneficial to pediatric populations. Another concern is the adequacy of necessary infrastructure to conduct pediatric pharmacology research, including research networks and trained pediatric investigators. In addition, the OPPB's work under BPCA involves mechanisms and partnerships, proposed pediatric study requests, information dissemination, and training.

In terms of lessons learned regarding the prioritization process, the NICHD encountered the pervasive lack of preclinical, phase 1, and phase2 clinical trial data; the issue of extrapolation; the unforeseeable nature of some clinical responses in immature individuals; unanticipated adverse reactions; the threat of effects on growth, development, or health long after the drug's administration; how pediatrics lags behind in advances in science and technology; and the lack of a long history of product development in pediatrics. Other lessons learned involved the lack of epidemiology data for the drug and the condition; lack of information on the natural history of the disease or treatment effect; need for upfront pharmacokinetic expertise; practicalities of pediatric trials, especially randomized controlled trials; lack of information on drug safety; and limited commercial motivation.

After highlighting a number of challenges in pediatric drug development, Dr. Taylor-Zapata turned to the topic of framing the new prioritization process and stated the goals for the 2009 annual meeting: (1) updating and reporting on current BPCA Program activities; (2) developing goals, outcomes, and evaluation for the prioritization process; (3) incorporating a broad range of stakeholder opinion; (4) determining new areas of need in pediatric therapeutics based on the therapeutic areas and the associated drugs that are problematic for pediatricians; and (5) developing a short list of pediatric protocols that can be pursued in the near future.

Dr. Taylor-Zapata referred the participants to the 2010 Worksheet for Prioritization in their packets and explained the creation of the three BPCA working groups after the development of the *Priority List of Needs in Pediatric Therapeutics* at the 2008 annual prioritization meeting. In consultation with the FDA, the NICHD prioritized three therapeutic areas for future study consideration for 2009. Three working groups were developed to discuss the needs in the following areas: (1) therapeutic needs in adolescent medicine, (2) safety and efficacy of cough and cold medicines in pediatrics, and (3) safety of atypical antipsychotics in pediatrics.

## Adolescent Therapeutics Working Group Presentation

*Presenter: Michael G. Spigarelli, M.D., Ph.D., Associate Professor of Pediatrics and Internal Medicine, Clinical Trials Office, Department of Pediatrics, Cincinnati Children's Hospital Medical Center*

*Respondents: Jeffrey S. Barrett, Ph.D., F.C.P., Children's Hospital of Philadelphia*

*Janice E. Brunstrom-Hernandez, M.D., Washington University School of Medicine, St. Louis Children's Hospital*

*Phillip Brian Smith, M.D., M.P.H., Duke Clinical Research Institute*

Dr. Spigarelli began his presentation with a definition of the term "adolescence" and explained that issues involved in adolescent therapeutics include population, care providers, and conditions. Obesity is an ever-increasing issue, with 20 percent of teenagers obese. In addition, in the past 15 to 20 years, the number of adolescents with newly diagnosed type 2 diabetes has increased from less than 5 percent to 30 to 50 percent of the diagnoses of diabetes in children.

The Adolescent Therapeutics Working Group cited as its first priority to understand the effects of both pubertal development and body weight on the pharmacokinetics, pharmacodynamics, and pharmacogenetics of pharmaceutical agents in children and adolescents. Particular emphasis is on understanding the effect of stage of sexual maturity and body weight on drug distribution and metabolism; pharmacogenetic changes in the expression of drug metabolizing enzymes in adolescents related to age, family history, and pubertal maturation; extent and mechanism, risk factors, and consequences of weight gain seen in older children and adolescents treated with antipsychotics, parenteral contraceptives, and other agents associated with weight gain; and impact of adherence on the pharmacotherapy and therapeutic outcome in adolescents because adolescents frequently are responsible for managing their own medications and treatments.

Study design is a needed area of improvement in adolescent therapeutics. Systematic improvements, expertise development, and a comprehensive approach are needed. Study design considerations include assent versus consent, regulatory issues, and pregnancy risk. Study design also must take into account dosage scaling, developmental considerations, pubertal staging, and the intrusiveness and inconvenience of the trials.

Dr. Spigarelli cited the advantages of studying adolescents. They are a highly motivated study population that tends to recruit additional participants. They also are technically savvy in the use of e-diaries, text messaging, and cell phones. In addition, if an adolescent has a chronic disease, there is typically only one. Finally, adolescents are honest and have adherence rates similar to adults.

The second priority is to develop a protocol across review divisions within the FDA to evaluate the endocrine and metabolic, psychological, and reproductive impact of pharmacotherapy in adolescents, with particular emphasis on psychotropic and other drugs frequently used in adolescents. Concerning dosing information, dosing must fit the individual and be logically designed and carefully determined. It also must promote the elimination of errors.

The third priority is to develop an understanding of how and where to distinguish between pediatric (preadolescent) and adult dosing guidelines for all drugs used in adolescence. In particular, this priority involves determining when weight- and/or age-based dosing regimens are no longer applicable and whether development of the specific adolescent dosing guidelines must be considered for the therapeutic agents most commonly used within adolescents and young adults.

Dr. Spigarelli noted that the Adolescent Therapeutics Working Group felt that adherence and adherence readiness of the adolescent are a key component of effectiveness for those drugs that demonstrate efficacy in the general adult population.

The respondents raised the following issues and concerns:

- Dr. Barrett stated that drug utilization patterns must be defined in various age categories and across the country and that pharmacoepidemiologic studies should look longitudinally at how members of this subpopulation take drugs and their attitudes toward taking drugs. Data are needed on the interface of best practices with adverse effects in this subclass. Also needed is more integration of metabolomics to discriminate subpopulations, identify biomarkers with the most utilized drugs, and define covariant relationships with other demographics. In addition, studies are needed to examine diurnal variation, hormonal response, and behavior with difficult-to-manage drugs in this population. Other goals might be to educate this population on how to take drugs more effectively and to consider diet and racial/ethnic differences in trials on weight and obesity. Stratification might be necessary in terms of enrollment strategies in the design of these trials.
- Dr. Brunstrom-Hernandez emphasized the primary importance of addressing the issue of adherence. An attempt should be made to divide adolescents into different categories and to choose a particular drug to study from the point of view of adherence. Also, education should be provided about over-the-counter (OTC) drugs for adolescents. Pharmacogenetics can provide a broad screening, without adherence issues, to understand the populations that might do better with one type of drug versus another.
- Dr. Smith stated that the FDA's adverse event reporting system provides valuable data and that the working group should outline therapeutic areas it is interested in.
- Maria Trent, M.D., M.P.H., noted that developing novel delivery systems for common medications is extremely important in terms of meeting goals around adherence to medication. Long-acting, sustained-release, and/or alternate delivery systems (for example, patches) for medications to treat common conditions may improve longitudinal clinical outcomes for patients.

Meeting participants raised and discussed the following issues:

- In response to a question about the extent to which already-existing data should be used, the working group urges researchers who are designing trials that include adolescents to retain the age and puberty status of individuals among the data.
- Priority-setting includes the need for education, which indicates the importance of establishing partnerships with professional societies, educational groups, and other organizations to move the agenda forward.

- A question involves whether, in obesity studies, doses should be based on meters squared instead of pounds. The response was that the scaling issue is important in pharmacology. A child is not a small adult; an adolescent is neither a large child nor a small adult. Adolescence is an individual stage of development.
- Leptin, which is necessary but not sufficient for the onset of puberty, increases as obesity increases and is therefore a link to early onset of puberty.
- Studies should narrow the range between the onset and completion of puberty. When studying the impact of pubertal development, drugs with different metabolic pathways should be chosen. Studies can be designed to address drug biotransformation, pharmacogenetics, and disease states and to examine the role of genetic variation and age-dependent changes in drug clearance by selecting from the extremes of a genotypic population at different ages.
- Child psychiatry is a specialty that should be involved, alongside pediatrics, in the prioritization process for adolescent therapeutics. However, a major problem is that it can take 3 to 9 months for a patient to get an appointment with a psychiatrist.
- Weight changes the way drugs are metabolized. One-third of adolescents who are obese also have fatty liver.
- Adolescents with chronic kidney disease are on multiple medications throughout the day. The question is how they should be dosed so as not to interfere with their activity, cognition in school, and diet. The problem is failure to identify how both disease states and drugs influence neurocognitive function in adolescence. Only vague and subjective measures exist. Some tools used to examine function after brain injury might augment understanding of how disease and drugs influence adolescents.
- The age range of adolescence should not be restricted. The focus should be on the biology of the children who will be given the medications.
- A question is often posed regarding whether puberty is changing over time. What is being seen is a change not of puberty itself but of the appearance of pubic hair before breast development in girls, which is definitely related to the weight epidemic.

## Cough and Cold Therapeutic Working Group Presentation

*Presenter: Ian Paul, M.D., M.Sc., Associate Professor, Departments of Pediatrics and Public Health Sciences, Penn State University College of Medicine*
*Respondents: Gregory B. Hammer, M.D., Stanford University School of Medicine*
*Robert J. Leggiadro, M.D., University of Medicine and Dentistry of New Jersey*
*Lynne G. Maxwell, M.D., FAAP, Children's Hospital of Philadelphia*

Dr. Paul began his presentation by providing information about upper respiratory infections (URIs), which are the most common reason for acute care physician visits in the United States each year. No cures are available for colds, but many OTC medications claim symptomatic relief. Billions of dollars are spent each year in the United States on OTC cough and cold medications. A recent study found that 10 percent of children use cough and cold medications each week nationwide.

Four different classes of oral drugs are marketed for URIs: (1) antitussives, (2) decongestants, (3) antihistamines, and (4) expectorants. The rules governing these medications were set in 1976 with the FDA monograph on OTC cough, cold, and allergy products. However, 33 years after the

FDA announced that no data exist for the use of these medications in children, dosing information is still lacking. The traditional dosing of cough and cold medicines for children is based entirely on the adult dose. The lack of dosing information has contributed to some of the safety concerns about these drugs. There are more than 7,000 emergency department visits per year by children younger than 12 years old due to adverse events associated with cough and cold medications. Surveillance efforts have been ongoing by industry and the Centers for Disease Control and Prevention (CDC). Safety concerns led to a series of public health advisories and FDA hearings regarding these medications. The most recent outcome is that industry voluntarily changed the labels on these OTC products to say "do not use under age 4."

Besides safety concerns, concerns about the efficacy of these medications have existed for some time. In 1997, the American Academy of Pediatrics issued a policy statement on the use of codeine and dextromethorphan in cough remedies for children, saying that "indications for their use in children have not been established." In 2006, the American College of Chest Physicians also issued a policy statement denying the efficacy of these medications in children. In 2008, the British Thoracic Society stated that "over-the-counter medications are as effective as placebo for acute cough with head colds in children."

Many problems exist in interpreting the data about cold and cough remedies. The endpoints for efficacy are unclear, and validated tools for measuring outcomes are lacking. Information about correct doses and outcomes related to single versus multiple doses is still not available.

The working group considered several questions in determining priorities in this therapeutic area. The questions related to the evidence gap, the affected ages, current and future research, what is achievable within BPCA, areas with the highest impact, and areas that will move science and clinical care forward. The working group proposed four broad priority areas and constructed a timeline for reaching the goals. The priority areas are (1) development of clinically meaningful endpoints for cough and cold medications in children younger than 12 years of age, and validated tools to measure them; (2) pharmacokinetic studies, including the study of pharmacogenetic variability, in children younger than 12 years of age, including infants; (3) efficacy studies (randomized, masked, placebo-controlled trials) of orally administered OTC cough and cold ingredients in children younger than 12 years of age; and (4) studies to elucidate the primary biochemical mediators of cough and cold symptoms to identify new targets for drug therapy.

Dr. Paul stated that these drugs will continue to be used by a large percentage of children despite a lack of science to justify their use or doses administered. Surveillance and safety efforts currently being undertaken by industry and CDC for OTC medications should continue. Funding is needed to determine pharmacokinetics, dose, pharmacogenetic impact, and efficacy. This effort fits within BPCA because these drugs are off patent and have no market exclusivity. Because the drugs are more than 50 years old, there is a need for innovative tools for symptom and outcome measurement, new targets for treatment, and new drugs to be developed. This effort fits within BPCA's preclinical data collection mission.

The respondents raised the following issues:

- Dr. Hammer proposed working with engineers to develop a marker for a reduction in mucus as an objective endpoint for efficacy of cough and cold remedies. The issue involves the extent to which the giving of drugs by parents should be promoted and whether an effort should be made to try to influence that process. A question arises about the ethics of marketing drugs for use in small children without any demonstrated benefits in adults, much less in children. A wellness index might be developed with targets such as being able to sleep at night. Pharmacokinetic studies might measure the concentration of the drugs in body fluids other than blood, such as mucus. Overall, efforts should be refocused to discourage the use of OTC drugs with doubtful efficacy and adverse effects in children. Dr. Paul stated that some efficacy data exist for some of the medications under discussion in adults. The need for objective endpoints is crucial, the idea of the wellness index implies subjective endpoints, and the question remains concerning significance. Quality of life is the issue; coughs and colds disrupt sleep, children's function in school, and adults' function at work and hence involve costs.
- Dr. Leggiadro added that if studies go forward, specific indications for specific conditions would need to be worked out along with specific drugs and formulations. Ethics issues would have to be addressed again because of morbidity and mortality with the use of these drugs. The biggest issue would be reconciling this need with other, more pressing needs and proposals on the table.
- Dr. Maxwell stated that why parents give these drugs to their children is not known. Use of these drugs in children of all ages should probably be discouraged, but this practice is entrenched among parents. Also, the drugs are formulated by companies as combinations; therefore, the various components must be balanced concerning side effects. In addition, to assess efficacy, symptom entry criteria are needed. Recruiting, enrolling, and assessing these children in the outpatient setting are difficult.

Meeting participants added the following comments:

- In the past year, industry has conducted a number of pharmacokinetic studies of common cough and cold ingredients in pediatrics, resulting in some progress toward addressing basic pharmacokinetic work on OTC medicines. All of the OTC drugs should not be lumped into one group because they have different mechanisms of action. The prescription medications have been studied for efficacy, and those efficacy parameters can be used to study OTC medications. Because opinions vary widely from parents' anecdotes to individuals who claim that these medications are dangerous, each of the different classes of OTCs should be studied for efficacy and safety.
- OTC cough and cold medications are marketed under a monograph that the FDA is in the process of revising. A draft rule will be issued and, when the monograph becomes final, the off-patent/on-patent distinction will not apply. In terms of the decision-making process of prioritization, until the new draft monograph is released, what studies industry will undertake will not be known. Once the studies are completed, industry can either submit the required data to the monograph or submit the data individually under new drug applications. The second option would prevent other companies from being able to use the data and market the product under the monograph. It is a complicated process that the NIH should consider as it

makes funding decisions because it is possible that many of the studies that are recommended would in fact be conducted by industry.

- A task group comprising the makers of OTC cough and cold products is committed to examining the most common active pharmaceutical ingredients (APIs) in children, focusing on OTC doses. Four work strings are (1) pharmacokinetic studies in children 2 years and older, including teenagers, for all eight substances; (2) analyzing and pilot-testing methodologies to recruit children at the right symptom level; (3) efficacy studies in 6- to 12-year-old children; and (4) a multiyear safety surveillance study.
- Pharmacokinetic and safety and efficacy studies make a great deal of sense, but marginal benefit will result from efficacy studies because it will be difficult to decrease use even if the studies show no efficacy. Therefore, the fourth priority of the working group, which involves novel approaches, should be advanced to first place to benefit children and pediatricians. Dr. Paul stated that the issue involves whether people would be willing to pay for an expensive prescription drug for an illness that will resolve on its own in 2 to 3 days.
- Certain design issues should be considered. For example, how should combination products be studied? Also, antihistamines are effective for adults but only if started in the first 24 to 48 hours of the illness. How can children be recruited in that phase? The issue involves the timing of treatment in respect to efficacy. In terms of tolerability as opposed to safety, the FDA Adverse Events Reporting System (AERS) is inadequate. There are issue with the use of placebos in pediatric studies. These issues should be considered in the design of pediatric studies in general.
- Regarding safety and the institutional review board process, the question involves how these studies should be done to determine a target dose at an early stage of illness. Creative solutions are needed to ensure that pediatric studies will result in useful information about dosing, toxicity, and endpoints.
- URIs are not one disease, which makes it difficult to design a study with a clear endpoint. Access to the medications is another issue for study. Would more appropriate use result if parents needed access to health care providers for prescriptions? Another issue is abuse of the medications that are easy to access.
- If the studies are industry sponsored, {the respondent} questions arise regarding the integrity and quality of the data. Industry-sponsored studies might encounter a bit of skepticism. The response is that if industry studies are published transparently, they are trustworthy. There are two types of industry trials—those generated by contract research organizations and those that are investigator-initiated. The quality of data from investigator-initiated trials can be uneven. Good clinical practice calls for an audit of the raw data, which makes the data reliable. The FDA's perspective is that uncertainty about industry trials is unfounded because the FDA follows auditing procedures to ensure the quality of data. Moreover, data from industry are usually generated from multicenter studies, and those data must be reproducible across study sites.
- Endpoints should be focused on patients who are critically ill (for example, with diabetes, cardiac problems, or adrenal issues) because the benefit-risk profile is different in those patients and that is where the most impact will be felt.
- The issue of dose ranging is an important component in designing an efficacy trial; if the monograph dose is carried forward, depending on the results, it is possible that efficacy might not result.

- Coughs and colds are high prevalence and have a moderate morbidity. If the stakeholder's purpose is to be translational, it must be recognized that parents buy these medications. Information, education, and marketing must be included in an examination of this issue. A legitimate purpose is to decrease morbidity from the treatments that are available. If adherence and efficacy are not demonstrated for combination drugs, then single medication preparations should be made available.
- The issue of transparency and publication bias can be avoided if trials are registered on clinicaltrials.gov.
- The FDA monograph is being revised based on new evidence since 1976; however, very few studies are available to update the monograph. The question is whether another 33 years will pass without studies and children will continue to receive these cough and cold medications under a new monograph that is not based on new information. Regardless of what the monograph revision calls for, parents will still want to treat their children with medications for coughs and colds.

Dr. Trent added the following comments:

- Most young children have 6–10 URI-type infections per year, with each lasting 10–14 days. One respondent suggested that a product that safely reduced symptoms be developed. The leader of the working group countered that parents would not pay for a medication that reduced symptoms by, say, 20 percent. This may be true, but based on the stated observation that parents continue to use the medications and OTC cough and cold preparations for children is a billion dollar business would seem counter to that prediction.
- One area of research that has been missing from all three groups is economic analysis with contingent valuation (preference assessment) with consumers. This research would allow for calculation of the utilities for cough and cold medication reductions to be used in analyses to determine thresholds for cost-effectiveness of such an intervention. A modest (20 percent) reduction in cold symptoms may actually mean fewer missed days for children in daycare, fewer work days missed by parents, and lower medical costs for children with chronic diseases affected by a concurrent upper respiratory disease such as asthma. Adding the parental utilities for the health states associated with URIs, a prescription medication that reduced the symptoms and/or infectiousness of URIs may indeed be a cost-effective strategy using a population-based approach. Tamiflu, which reduces symptoms associated with influenza infection, could be used as a model for further developing this idea. Abandoning the evaluation of product development as suggested by the FDA representative would not solve the issues raised by continued use of cough preparations in young children and/or the clear need for parents/patients to reduce symptoms associated with URIs—even though they will eventually go away.
- The same notion holds true for development of new products for adolescent medication delivery. For example, development of a drug/device that delivered antibiotic treatment for pelvic inflammatory disease over a 2-week period would ensure that adolescents—now almost exclusively treated as outpatients and who have poor adherence to care—completed a successful course of therapy. Alternatives for combined administration of HIV medications that did not involve oral consumption and/or were sustained release would potentially improve the safety, side effect profile, and adherence for adolescents with HIV/AIDS.

- Training programs in health economic methods and biomedical research with particular focus on drug development/delivery should be included in the priorities related to the BCPA program.

## Antipsychotics Safety Therapeutic Working Group Presentation

*Presenters: Robert L. Findling, M.D., Rocco L. Motto, M.D., Professor, Director, Division of Child and Adolescent Psychiatry, University Hospitals Case Medical Center, Case Western Reserve University*
*Merrily Poth, M.D., Professor, Departments of Pediatrics and Neuroscience, Uniformed Services University of the Health Sciences*
*Julie M. Zito, Ph.D., Professor of Pharmacy and Psychiatry, Department of Pharmaceutical Health Services Research, School of Pharmacy, University of Maryland, Baltimore*
*Respondents: C. Patrick Reynolds, M.D., Ph.D., Texas Tech University Health Sciences Center School of Medicine*
*Philip D. Walson, M.D., Georg-August University Medical School*
*Teri Moser Woo, Ph.D., CPNP, University of Portland*

Drs. Findling, Poth, and Zito presented information from the findings and recommendations of the Antipsychotics Safety Therapeutic Working Group. Dr. Findling gave background information about commonly prescribed atypical antipsychotics (AATPs) with FDA approval for various indications. These medicines are used for serious conditions based on short-term studies by NIMH and the pharmaceutical industry.

Dr. Poth pointed out that the working group comprises individuals from the FDA, academia, and industry. She presented a report from the committee, which held five group conference call meetings, discussed the available data, and shared questions regarding the use, effectiveness, and adverse events of AATP drugs in children and adolescents.

The working group arrived at consensus regarding a number of conclusions. AATP drugs are widely used in children and adolescents for a variety of indications, most of which are off label; in addition, these drugs are often used in combination with other pharmaceuticals. Findings from clinical trials on the efficacy and safety of these drugs are often unrelated to community practice patterns. Although clinical trials assess both the efficacy and safety of AATPs in children and adolescents, a number of limitations exist for assessing drug safety, including relatively short-term studies, small numbers of subjects, many exclusions, and high dropout rates. Therefore, clinical trial data on efficacy and safety are limited in generalizability and lacking in long-term safety information. Available data suggest efficacy for the currently approved indications, but little published data exist to support the multitude of other uses of these drugs. Compared with adults, the incidence of adverse drug events, such as increased lipid levels and weight gain, is higher in many respects in children and adolescents.

Findings from the available data show that weight gain is a common adverse drug event with AATP drug use and may be extreme. One study of 4- to 19-year-old mental health clinic patients reported substantial drug-specific weight gain ranging from 4.4 to 8.5 kg in 10.8 weeks. Some of

these patients develop other aspects of metabolic syndrome, with potentially significant implications for future health.

Diabetes and diabetic ketoacidosis (DKA) may occur with use of these drugs; however, the frequency of this occurrence is unclear. Although most of the diabetes data are from studies in adults, a number of deaths have been reported in children with DKA, even though fatality is rare in other children with diabetes. Some subjects who become glucose intolerant or diabetic are not overweight, raising questions about the prevalence of regular monitoring of AATP-treated youth for changes from baseline health status in relation to length of AATP exposure.

Research should focus on reducing pediatric AATP knowledge gaps, including gaps involving long-term safety; risk moderators, such as age group and gender; comparative safety data (for example, community versus clinical trial population); new users versus prevalent users of antipsychotics; adverse drug event risks in children who are already overweight or youth with serious comorbidities; and adverse drug event risks for AATP combinations with other drugs.

Inadequate utilization, efficacy, or safety data exist on adjunctive AATP therapy with drugs to control weight gain. Longer term data also are needed on efficacy and adverse events, and longitudinal cohorts should be formed from retrospective data sources. In addition, large cohorts should have broad community-treated populations with various indications for use across youth age groups.

Studies also should be conducted to examine interactions of AATPs with other drugs commonly used in combination (for example, stimulants, selective serotonin reuptake inhibitors, and anticonvulsant mood stabilizers). Studies also are needed to tease out the determinants of efficacy and to identify factors increasing the likelihood of significant adverse drug events (including extreme weight gain, diabetes, and hyperlipidemia).

In addition, studies are needed on mechanisms of metabolic side effects of AATPs, for example, identification of possible changes in neuroendocrine systems associated with weight gain and diabetes and measures of known orexigenic hormones and other systems associated with extreme weight gain. If changes in these measures are found, they might be able to be used to predict problems.

The working group consensus is that data are needed to illuminate both the effectiveness and safety for specific AATPs in children and adolescents. Funding of studies to collect such data, including both retrospective and prospective long-term studies, should be a priority for the FDA and the NIH. Questions to be addressed include (1) the absolute incidence and time course of adverse drug events; (2) the mechanisms of adverse drug events, particularly metabolic abnormalities; and (3) the balance between adverse drug events and efficacy in specific groups (different age and racial/ethnic groups, the poor and near-poor, and disabled youth).

Dr. Zito presented information about pediatric drug safety research design options. The clinical question is “What is the safety profile for AATP use in U.S. children and adolescents?” The quantitative research question is “What is the incidence of metabolic and endocrine

abnormalities (for example, weight gain, liver function abnormalities, and hyperlipidemia) in relation to length of exposure (the main independent variable) and conditional on observed practice patterns, comorbidities, concomitant psychotropic medications, and health status?"

Available data sources include the FDA's AERS database, which showed increased pediatric reports for sedation, weight gain, liver function, and tardive dyskinesia compared with adults. Meta-analysis of clinical trial data and federal probability sampling surveys are other data sources. Administrative claims data from insured populations are available from Medicaid, commercial insurance, and health maintenance organization and preferred provider organization providers. In addition, national pediatric utilization profiles are available from the NIH.

Examples of potential risk study designs include a study funded by the FDA and the Agency for Healthcare Research and Quality to assess cardiac risks in 500,000 insured youth taking medications for attention deficit hyperactivity disorder (ADHD). This retrospective analysis will be based on claims data from a consortium of treatment settings. Another more controversial classic case-control study published this year found 1.4-percent frequency of stimulant exposure in pediatric sudden deaths compared with 0.4 percent in auto accident passenger deaths. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study in 2006, an effectiveness trial for adult schizophrenia, showed that second-generation antipsychotics were more expensive without benefit of improved efficacy. Another publicly-funded, 8-week trial for early-onset schizophrenia and schizoaffective disorders, published in 2008, showed no significant difference in symptom response to molindone, olanzapine, and risperidone. Finally, as already noted, a 2009 trial on weight gain in a systematic community-treated sample showed an average weight gain of 8.5 kg in 10.8 weeks in olanzapine users.

The working group proposes a mixed-model design approach. Stage 1 of the design includes claims data analysis to show national patterns of use of AATPs to identify the size of the AATP-exposed population; the length of exposure; the age, gender, race/ethnicity, diagnosis-specific, comorbidity, and severity subgroups; and the extent of the outcomes of interest. The goal is to combine data sets from different treatment settings to identify at-risk populations and generate hypotheses. Stage 2 would be a prospective clinical cohort study at experienced regional academic research sites that enroll youth to meet the targeted exposure criteria based on prior AATP exposure.

A mixed model includes a number of limitations. It requires a pilot study to assess feasibility. Also, the possibility of a lack of engagement, enrollment, and continuation must be addressed. In addition, comparisons are always tricky, and lumping and splitting always raise questions. The strengths of the mixed model are that it can be used to develop the infrastructure for safety monitoring, it is committed to benefit-risk assessment in community-treated individuals, and there is no good alternative if long-term safety is the issue.

Prioritization should be voted on according to three criteria: (1) relevance, (2) feasibility, and (3) benefit. All three criteria are met by studying AATPs because of the need to understand long-term safety, the fact that completed studies prove feasibility, and the awareness that the 1 to 2

million youth who are receiving AATPs currently could benefit from increased knowledge from future studies.

The working group ended its presentation with a reference to its nine recommendations:

1. Funding is needed to implement the working group's recommendations.
2. Data and studies are needed for understanding pediatric AATPs, particularly use over the long term.
3. The FDA should make short-term data available for secondary studies by investigators from the field.
4. A review article should be drafted summarizing current knowledge and recommended directions.
5. The working group, the NIH, and the FDA should collaborate to identify the relevant variables to be included in electronic medical records.
6. The working group should learn more about AERS so that recommendations can be developed regarding its use for monitoring serious adverse event reports associated with pediatric AATPs.
7. A design should be developed for studies of risk factors/predictors of adverse events and the effects of long-term use of AATPs.
8. Animal models should be explored to address issues of toxicity, particularly with long-term use.
9. The working group has an important purpose and would like to continue its activities.

The respondents raised the following issues:

- Dr. Reynolds noted that two of the recommendations concern the FDA's AERS. A question is whether the AERS data will be available to the working group and whether the working group understands the AER process. One or more of the working group members could work with the FDA on a short-term sabbatical to gain access to understanding the process. Dr. Poth mentioned that AERS is helpful for identifying targets but not for quantifying the events reported. Dr. Reynolds also noted a paucity of information on the pharmacokinetics of AATPs in children, a fact that should be incorporated in the recommendations. Dr. Findling responded that the real issue involves the cause of the huge gap between subject variability and the pharmacokinetic parameter estimates. Dr. Reynolds stated that the polypharmacy in these patients is considerable and, therefore, the possibility for drug interactions is immense. He asked whether the pharmacokinetics data in this age population address that fact. Dr. Poth responded that they do not and stated that the working group's intent was to point out that these drugs are being used commonly in ways about which nothing is known. The question should be addressed. Dr. Reynolds noted the possibility of designing a study to address these concerns.
- Dr. Walson made a number of points, including that, although the new BPCA calls for condition-based use of drugs, the AATPs are being used for behavior problems. Flexible funding should be used for the recommended review article. Proposed Pediatric Study Requests (PPSRs) should be developed, and a written request, formulary, and increased training are needed. According to the BPCA, the NIH is supposed to develop data monitoring methods. A specific recommendation should be that the databases include weight and pharmacokinetic data. Also needed are clinical trials that examine pharmacokinetic and

pharmacodynamic predictors of efficacy. The issue of dropouts should be dealt with, and working with behaviorists is probably more productive than dispensing drugs to individuals; therefore, the working group should consider multimodal therapies instead of merely drugs. What is needed is a measure of exposure in individual patients.

- Dr. Woo stated that in primary care, it is rare that children are on only one medicine. Some real-world studies are needed to examine children with multiple comorbidities who are on multiple drugs long term. Long-term and short-term endocrine effects should be studied in adolescents. Kaiser has a dataset on body mass index in these youths.

Participants added the following comments:

- In terms of genetics, industry-sponsored trials get pharmacogenomic samples. Also, current studies at the FDA allow coprescriptions and therefore enable a prospective look at the difference in weight gain between youth who are either on or off stimulants with an AATP. A great deal of information is available from autism and bipolar trials in children. Access to the FDA would help to answer many questions about weight gain in children.
- Regarding poly-prescribing, it is difficult to get meaningful data to address the single agent responsible for weight gain or any other side effect.
- With the exception of agitation in autism, on-label psychiatric medication in children and adolescents is for diagnosis rather than symptoms. However, one of the more common reasons for referral for medication is aggression and agitation. Therefore, should these behaviors be legitimate targets for development of medications?
- A 2006 study showed a sixfold increase in the use of AATPs in the past decade. At any given time, at least 500,000 children are taking AATPs. An Iowa City study of 99 children on risperidone for an average of 2.9 years found substantial metabolic abnormalities. A recent Canadian study found a ninefold difference in metabolic syndrome in in-patient children taking AATPs compared with children who were not taking AATPs. The rate of metabolic syndrome in the in-patient subjects taking AATPs was 27 percent.
- In a large prospective epidemiologic study of these agents, to what extent should alternatives to AATPs be examined? Are the proposed PPSRs the correct mechanism for this area? The broader question of safety has been framed. PPSRs are usually targeted toward developing information on an indication. Other contracting-style mechanisms could be used.
- Regarding the collection of safety data, many of these medications are used off label; therefore, there are no data from clinical trials about their safety. Complications often are discovered by individuals who do not prescribe the medications and who do not submit adverse event reports. Mechanisms should be developed to encourage physicians to file reports to be included in the AERS database, which can be mined on a regular basis.
- There are concerns about the clinical side effects of antipsychotic medication, which can cause elevations in prolactin. Elevations in prolactin can cause clinical symptomatology in patients (galactorrhea) and/or result in reproductive dysfunction. Determining the impact of these side effects and establishing thresholds for alternate management should be set.
- Use of these medications for mood stabilization and behavioral control rather than for symptomatic treatment of psychotic states has become commonplace. Clearer strategies for prioritizing use of these medications based on behavioral profiles is indicated—particularly given acknowledged delay for a formal evaluation by a child psychiatrist in nonemergent situations.

- A part of the issue in managing patients on atypical antipsychotic medications may be the observed disconnect between the psychiatric provider and the medical primary care provider. A team-oriented approach to care that involves the primary care physician as a part of behavioral and medication management may facilitate improved outcomes for patients on these medications.
- The notion of developing new medications to counteract the side effects of atypical antipsychotic medications seems counter to the goals of BCPA activities. Development of drugs with similar efficacy profiles, but improved safety and side effect profiles, would be in order.

## Review of Day 1 Discussion—Prioritization Methodology

*Charlie Bruetman, M.D., M.B.A., Vice President, The Lewin Group*

Dr. Bruetman presented a summary of the key areas discussed during the previous day's meeting on BPCA general prioritization. He explained that the approach to prioritization includes a consideration of end-user involvement, expert involvement, and partnerships and collaboration. The process should be dynamic and flexible, and priorities should be reviewed annually. The process also involves objective criteria, including feasibility, unmet need, potential benefit, existing evidence, cost-benefit, and alignment with the mission.

Challenges to the prioritization process include the difficulty in quantifying some topics, applicability across activities, consideration of rare diseases, priority cutoff, and limited resources. Based on discussions with multiple organizations, four guiding principles have been developed for the prioritization framework: (1) well-defined process, (2) well-defined objective criteria, (3) legitimacy and fairness, and (4) expert involvement.

## Pediatric Devices—Feasibility
## Pediatric Anesthesia—Extrapolation

*Anne Zajicek, M.D., Pharm.D.*

Another section of the same law that reauthorized the BPCA, the Food and Drug Administration Amendments Act (FDAAA) of 2007, newly authorized the Pediatric Medical Devices Act. Some devices are related to problems encountered on a daily basis (for example, devices for delivering oxygen such as tubing length and face masks). Other devices are related to prioritized therapeutic areas (for example, retrofitting devices to children versus creating a newly designed device). Length of use of the device is another concern (for example, short-term use of a nebulizer for an asthma attack versus long-term use of a limb-lengthening device). Other issues involve the approval pathway through the FDA and funding through private versus public versus public-private partnerships.

The FDAAA of 2007 requires that an application for a device include a description of any pediatric subpopulations that suffer from the condition that the device will treat, diagnose, or cure. The Act required the Secretary to submit a plan for expanding pediatric medical device research and development by March 2008.

After defining "device," Dr. Zajicek listed the NIH components of a pediatric device plan: (1) development of a model that would permit private or public-private funding following initial proof of concept, (2) identification of the key elements of the transition from early-phase studies to marketing development, and (3) a publicly funded project that would be expected to meet the scientific objectives as well as the identified business development objectives to be considered feasible and of sufficient priority to merit funding.

Dr. Zajicek called for cooperation between schools of medicine and schools of engineering to create needed medical devices, such as formulation devices to pulverize tablets and coat them to mask bitterness, better fitting face masks, retractable tubing, more sensitive negative pressure sensors, and smaller batteries. Other ideas for devices include devices to measure cough, sleep, compliance, growth and maturation, alternate ways of drawing blood, blood pressure, activity levels, and pulmonary function.

In terms of a business model, Dr. Zajicek described the NIH's Small Business Innovation Research grant program. The FDA's Center for Devices and Radiologic Health (CDRH) could be consulted for advice about the approval of devices. For the transition from mockup to production, a public-private partnership could be sought with an industrial design firm.

Regarding extrapolation, Dr. Zajicek questioned the process of extrapolating data from juvenile animals to young children or adult animals to human adults. She described two preclinical trials involving methylphenidate and ketamine, in which nonhuman primates were used as a human model. The question involves studying a drug commonly used in children in terms of exposure, for example, to a single dose of ketamine or three injections over a period of a half hour for fracture reduction. What is the relationship between the animal results and what happens in humans when the drug is used in a very limited way? And what short-term and long-term outcomes should be examined?

Meeting participants discussed the following issues and made the following comments:

- Regarding device safety in pediatric patients, an adverse event system is in place for each FDA Center. Companies and hospitals are required to report serious and life-threatening adverse events related to devices. The FDA also has an active surveillance system that operates through the academic facilities. A sub-network of MedSun at the FDA is called KidNet, a program that hospitals can join. Clinical trials involving implantable subcutaneous continuous monitoring devices or implantable lenses should be a high priority for BPCA.
- Some pseudodevices classified as hydrogel dressings are regulated by CDRH and are used widely in infants and young children as multi-ingredient drugs; however, there are minimal data and understanding about them.
- Some devices in common use in pediatrics, for example, as delivery mechanisms for ADHD treatment, can help to determine compliance with drugs that must be taken multiple times a day or involve potential substance abuse issues.
- Pediatric-friendly techniques are needed for procedures such as lap band surgery for adolescents.
- Color-coded markers for syringes and cups, as well as small dispensable tablets, are needed to ensure safety and compliance in dosing.

- Massachusetts Institute of Technology's Health Science Technology Program is a joint engineering and medical school program that develops specific medical technologies. Programs such as this across the country should be asked to address issues involving devices.
- The machines used to do continuous renal replacement therapy on neonates and children with liver transplants are geared for adults; they should be made more efficient for use in children.
- Investigators at the Children's Hospital of Philadelphia would like more regulatory guidance and input on study design for an efficacy trial involving a malabsorption blood test to guide the use of enzymes in cystic fibrosis.
- Regarding extrapolation, in the rhesus monkey model used in the study at the National Center for Toxicological Research described by Dr. Zajicek, a 9-hour exposure to ketamine resulted in abnormal apoptosis. Researchers have demonstrated that ketamine exposures cause severe disruptions in the performance of identical cognitive function tests in both monkeys and children. Windows of sensitivity have been identified in the animal models.
- Safe Kids is following up children exposed to ketamine and other drugs for cognitive development and behavior.

## Endocrine Drugs—Epidemiology and Safety Evaluations

*Scott Rivkees, M.D., Associate Chair of Pediatric Research; Director, Yale Child Health Research Center; Chief, Section of Developmental Endocrinology and Biology; Professor of Pediatrics, Department of Pediatrics, Yale School of Medicine*

Dr. Rivkees presented information about pediatric endocrinology and pharmaceutical-related needs on behalf of the Lawson Wilkins Pediatric Endocrine Society. In the United States, there are about 1,000 pediatric endocrinologists with 2.5 million patient visits per year. Their areas of focus include growth, puberty, thyroid, adrenal, pituitary, and bone as well as diabetes and obesity. Increased interactions with industry have resulted in new therapeutics for growth, puberty, and diabetes.

After describing a past interaction with BPCA involving propylthiouracil-induced liver failure in children, Dr. Rivkees listed some specific needs: (1) the need to define the incidence and prevalence of pediatric endocrine conditions such as growth hormone deficiency, precocious puberty, and hypopituitarism; (2) the need to define treatment practices, including care patterns, regional variability, and differences in treatment depending on whether children have Medicaid or commercial insurance; (3) the need to define off-label treatment practices; (4) the need to define complications of therapy; and (5) the need for postmarketing drug surveillance.

## BPCA Prioritization Framework: Moving Forward

*Presenter: Clifford Goodman, Ph.D.*
*Respondents: Victor Santana, M.D., St. Jude Children's Research Hospital*
*Robert M. Ward, M.D., FAAP, F.C.P., University of Utah*
*J. Steven Leeder, Ph.D., Pharm.D., Children's Mercy Hospitals and Clinics, University of Missouri, Kansas City*

Dr. Goodman presented the OPPB's goals and methodology for revising the prioritization process, reviewed the guiding principles of the prioritization framework, introduced the draft

BPCA prioritization framework based on the guiding principles, and solicited feedback on the draft framework.

The desired outcomes of the BPCA prioritization process are to (1) implement a simple and transparent process to support funding decisions, (2) align the organization to a common direction and objectives, and (3) create a prioritized list of pediatric needs that closely aligns with BPCA's mission and goals. The four steps to creating a prioritization process are to (1) understand the importance of establishing a prioritization process, (2) review other prioritization frameworks, (3) create guiding principles for the prioritization framework, and (4) apply the guiding principles to the BPCA prioritization framework.

The four guiding principles of the prioritization framework include (1) a well-defined process, which entails having a systematic approach with clear objectives and outcomes; (2) well-defined objective criteria; (3) legitimacy and fairness, which embody transparency, stakeholder input, a dynamic process, and leadership; and (4) expert involvement to inform and contribute to the process and add credibility.

There are two main phases in the prioritization process. Phase I entails therapeutic areas, which are general categories with multiple pediatric needs to be addressed in Phase II. A therapeutic area can be a group of conditions, a subgroup of the population, or a setting of care. Phase II involves more specific pediatric needs, including research associated with a particular drug, biologic, or device.

There are five key steps to both phase I and phase II of the prioritization process. Phase I prioritizes nominations for therapeutic areas by (1) gathering nominations, (2) convening key stakeholder representatives, (3) applying threshold criteria to the nominations, (4) scoring the therapeutic areas based on the criteria, and (5) identifying the top therapeutic areas. Phase II prioritizes pediatric needs within the selected therapeutic areas using the same steps as phase I.

After reviewing each of the five steps of phase I and phase II in more detail, Dr. Goodman pointed out that the second principle involves applying the same criteria to both therapeutic areas and pediatric needs. The threshold criteria are relevance to the BPCA mission and goals and non-disqualifying ethical concerns. The prioritization criteria are urgency of need, feasibility, impact, evidence, and population. Dr. Goodman described how each nomination is scored either 0 or 1 according to the two threshold criteria; a nomination that does not receive a 1 or "yes" score for both criteria is excluded from the prioritization process. Each nomination is then scored 1 through 9 on each of the five prioritization criteria. The OPPB applies the weights to calculate a weighted score for each nomination.

Legitimacy and fairness, which is the third principle, includes transparency, broad stakeholder input, dynamic process, and leadership. The fourth principle, expert involvement, involves three unique groups: (1) OPPB pediatric pharmacology experts, (2) key stakeholder representatives, and (3) knowledgeable experts.

Dr. Goodman compared the current BPCA process with the draft framework to show their similarities. The enhancements include incorporation of broad stakeholder input in both phase I and phase II though solicitation of nominations, incorporation of key stakeholder representatives to score therapeutic area nominations, a scoring algorithm incorporated into the process as a decision tool, criteria applied in two steps (threshold and prioritization), and a transparent prioritization process.

## Continued Discussion of Future Prioritization

*Moderators: Clifford Goodman, Ph.D., and Perdita Taylor-Zapata, M.D.*

As an introduction to the discussion of prioritization factors to consider, Dr. Taylor-Zapata noted that in many therapeutic areas, the general themes are the same, namely, lack of pharmacoepidemiology data (disease course, disease pattern, natural history of the disease, drug use, drug effect); lack of efficacy data (specifically outcome measures and endpoints); and lack of drug safety data (in particular, long-term drug safety data).

The respondents raised the following issues:

- Dr. Santana issued a caution about steps 3 and 4 of phase II regarding certain conditions that occur at very low frequency and therefore do not meet the scoring system. Another process should be derived for these low-scoring conditions. His second comment involved step 4 and the five weighted criteria. Four of the criteria are objective and amenable to robust data scoring systems, but the first one—the urgency of need score—has a very high weight; subjectivity should be removed from this system. Another concern involves defining when and how the model will be revisited to assess its success. Dr. Goodman stated that to be fully dynamic and transparent, the process will be revisited. He explained that priority-setting processes are not the answer; rather, they are tools and support for decision-making. Regarding evidence and urgency of need, Dr. Goodman explained that urgency is very important in this context and that quantification is desirable.
- Dr. Ward stated that labeling is a surrogate for a well-done study. It defines efficacy, safety, kinetics, and adverse effects. The sample size must be adequate to analyze the endpoints with valid statistics, and the label disseminates this information to all prescribers. Dr. Ward asked how the process can be modified to be more efficient and more productive. He answered that question by stating that the FDA and the NIH must play to their missions and strengths. The NIH advances and funds science and uses translational studies to apply laboratory findings. Its studies follow guidelines more than regulations. In contrast, the FDA protects the public health and determines the safety and efficacy for all drugs to support a label. Its labeling studies adhere to good clinical practices and good laboratory practices, and those requirements are strictly enforced to protect public health. The FDA and the NIH should use their strengths to increase pediatric labeling, and research organizations should contract with the NIH to conduct pediatric labeling studies.
- Dr. Leeder stated that the new focus on therapeutic areas allows for addressing broader needs. The concern about urgency of need raises a question about future needs; for example, statin use might grow over the next few years. Researchers should be thinking in terms of establishing safe and effective doses. Also, the multiplicative effect across diseases contributes to being able to generate information to affect a broader population of patients

than would a focus on a single agent. Another point regarding impact can be illustrated by the obesity epidemic, in which effective treatment earlier in life might affect morbidity and mortality during the course of the disease over a period of 25 to 30 years. In phase II of the prioritization process involving pediatric needs, the means are available to determine whether metabolomic changes associated with hypercholesterolemia in children are different from those in adults. Cholesterol might be more important in children than in adults. The use of statins in children means adding a foreign compound into a dynamic system of growth and development. Cholesterol will be the backbone for many of the steroids and hormones that those children will need as they grow and develop. It is unknown what effect perturbing cholesterol synthesis will have downstream of the event being inhibited. Dr. Goodman stated his agreement with all of Dr. Leeder's points.

Participants added the following comments:

- The FDAAA of 2007 also reauthorized the Pediatric Research Equity Act (PREA), which requires pharmaceutical companies submitting new drug applications to provide pediatric data if the drug is likely to be use in a pediatric population. When thinking about prioritization, one should consider PREA as a mechanism for obtaining the desired studies. Drug companies can be required to study drugs with new or supplemental applications. A new indication, active ingredient, formulation, dosing regimen, or route of administration triggers PREA and allows the FDA to require studies. Those studies would not have to be publicly funded.
- The NICHD should take the next step and work with other NIH Institutes and Centers (ICs) and foundations to amplify the pediatric importance of newer drugs (for example, in children with cancer). Translational researchers and pharmacologists are needed to do this work. The NICHD also should act as an advocate for the prioritized drugs for funding and mobilizing resources. Dr. Goodman noted that people from appropriate NIH ICs would be involved as experts in the prioritization process.
- National patterns of medication use for pediatrics should be advanced so that clinicians in practice can begin to see that use often does not follow expectations and that new drugs often are slow to be adopted. Dr. Goodman remarked that prioritization must be a data-driven process. The Medicaid databases, linked with commercial databases, can give a picture of a national pattern of utilization that reveals noteworthy disparities.
- Niacin is effective in lowering cholesterol. How can the use of this inexpensive and benign OTC drug be expedited? Dr. Goodman referred to the recent study comparing drugs used for hyperlipidemia on the basis of safety and efficacy. He pointed out that those studies involved adults, not children.
- A new era of targeted therapy and personalized medicine will be the next step. How will it apply to pediatrics? In the future, the priorities and new areas of need might not be aligned with therapeutic areas such as asthma, neonatology, or adolescence. They will be more cross-cutting. It might be worth trying to develop research models to validate predictive and prognostic tools, surrogate markers, and biomarkers and to determine ways to incorporate genomics and pharmacogenomics in cross-cutting ways. Investment in some of these areas, which embody the essence of personalized therapy, should start in pediatrics. Therapeutic areas could be replaced with mechanisms of action. In the context of the priority-setting framework, one could conceive of a therapeutic area theme, for example, pharmacogenomics

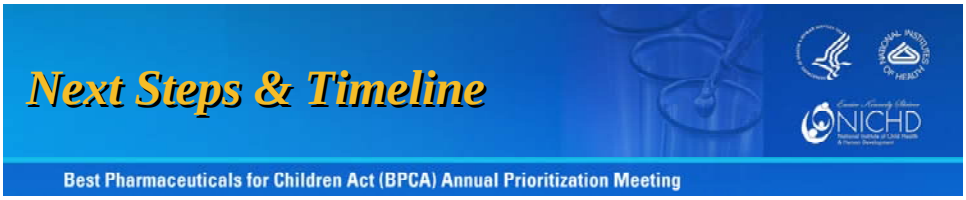
in pediatric oncology. Pharmacogenomics will narrow the target population but be much more effective within that group. However, this change would affect the urgency-of-need criterion within the prioritization process.

- Regarding the issue of subgroup and personalized medicine, the prioritization process should include methods for targeting hard-to-reach groups with high-impact diseases to determine whether health care disparities involve access and education or real subgroup differences.
- A new therapeutic area, namely, inflammatory skin disease in children, should be included. Also, it should be noted that maintenance of certification in most specialties includes quality improvement, whereby practicing physicians are required to participate in data collection. In addition, one must realize that patients must be incentivized to participate in studies.
- Work is being done to guarantee that pediatrics will be represented in the FDA's Sentinel Initiative, a national electronic system that will transform the FDA's ability to track the safety of drugs, biologics, and medical devices.

## BPCA: Future Developments

*Perdita Taylor-Zapata, M.D.*

Referring to next steps and the timeline (see below) Dr. Goodman included in his presentation on the BPCA prioritization framework, Dr. Taylor-Zapata stated that the NICHD faces the challenge of implementing the prioritization process in a clear and defined way. Flexibility is built into the process to enable diversification and expansion of the studies. The NICHD understands that it needs public and private partners to collaborate in these endeavors. Input also must be incorporated from parent and advocacy groups. The implementation of the prioritization process must be completely transparent.




- **OPPB to consider input while finalizing prioritization framework**
- **Final prioritization framework to be applied beginning with 2010 list of Pediatric Needs**

| Prioritization Framework Steps | 2010 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec |
| **Phase I** | ▼ | — | — | — | — | ▼ | | | | | | |
| 1) Gather nominations | ▼ | — | ▼ | | | | | | | | | |
| 2) Convene stakeholder reps | | ▼ | ▼ | | | | | | | | | |
| 3 & 4) Prioritize Therapeutic Areas | | | | ▼ | ▼ | | | | | | | |
| 5) Finalize Therapeutic Areas for 2010 | | | | | | ▼ | | | | | | |
| **Phase II** | | | | | | | ▼ | — | — | — | — | ▼ |
| 1) Gather nominations | | | | | | | ▼ | — | ▼ | | | |
| 2) Convene workgroups | | | | | | | | ▼ | ▼ | | | |
| 3 & 4) Prioritize Pediatric Needs | | | | | | | | | | ▼ | ▼ | |
| 5) Finalize Pediatric Needs for 2010 | | | | | | | | | | | | ▼ |

- To advance therapeutic areas, endpoints and outcome measures must be determined, training must be carried out, pharmacokinetic and pharmacodynamic information must be obtained, and infrastructure must be leveraged for completion of the relevant studies. The NICHD has worked with a number of Institutes on a number of studies in an effective and efficient way, partnered with industry to talk about pediatric formulations, worked with foundations and societies, and collaborated internationally. Dr. Taylor-Zapata asked the participants to include their feedback and input about new therapeutic areas on the Worksheet for Prioritization in their packets. The priority-setting process under discussion will be instituted in 2010, but elements of this process have been used in the past. The process will be evaluated in a year.

## Closing Remarks

*Anne Zajicek, M.D., Pharm.D.*

Dr. Zajicek thanked the participants for their feedback and input over the past 2 days regarding the prioritization process. She referred to her notes for the day to mention issues related to the complexity of written requests, resulting questions regarding outcome measures, the need to evaluate devices in clinical trials, and problems involved in the therapeutic areas, including off-label practices, the need for data-sharing, the issue of pharmacoepidemiology in pediatrics, the coordination of data and infrastructure globally, and the synchronization of databases. All of these areas represent a work in progress.

Dr. Zajicek stated that the prioritization process will be examined in light of the past 5 years of prioritization. She asked the participants to fill out the Worksheet for Prioritization to give input regarding the prioritization method. More targeted discussions will take place regarding the three working groups' recommendations.

## Participants

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