Dr. Taylor-Zapata welcomed everyone to the meeting and reviewed logistics, noting that the meeting minutes will be posted on the BPCA Web site. She noted that the goals for the meeting are to (1) educate those new to the BPCA process and update those who are already familiar with it, (2) engage in the discussion of topics and/or drugs of interest in prioritized therapeutic areas, and (3) encourage continued participation with the NICHD in identifying the future research agenda for the BPCA program. She gave an overview of the day’s agenda and moved to presentations.

BPCA Updates, NIH Perspective
Anne Zajicek, Pharm.D., M.D., Branch Chief, OPPTB, NICHD, NIH

Dr. Zajicek thanked everyone for their work and involvement with the BPCA. She said legislation has been permanently authorized for the U.S. Food and Drug Administration (FDA) and was authorized for the National Institutes of Health (NIH) for the next 5 years.

It is the BPCA’s responsibility to prioritize the 2002 master list of all off-patent drugs based on availability of safety and efficacy data, whether additional data are needed, whether new studies produce health benefits, and whether drugs need to be reformulated. The 2007 and 2012 therapeutic areas included therapeutic gaps, which led to renaming the branch the “Obstetric and Pediatric Pharmacology and Therapeutics Branch.” Other therapeutic areas included (1) the potential of health benefits for research, including (1) the tension of frequency of disease versus severity of disease; (2) the adequacy of necessary infrastructure, as some infrastructure is needed for performing pediatric clinical trials; and (3) the need to increase the number of people who are capable of conducting these trials.

Dr. Zajicek asked Dr. George Giacoia to speak briefly about the National Institute of General Medical Sciences (NIGMS) T32 Training Grants for pediatric pharmacologists. Dr. Giacoia said the NIGMS and NICHD are developing a virtual network of 11 T32 programs—three are under the NICHD and the rest are in the NIGMS program in pediatric pharmacology. They have developed a core program in pediatric pharmacology that is ongoing and a lecture series given by webinar that will continue through April. In addition, the NICHD is trying to work with other important areas that have not been addressed, especially the areas of asthma, diabetes, and
psychiatric disorders and encourage interaction between experts. The goal is to affect the marriage between pediatric clinical pharmacology and subspecialties. The webinars have been extremely successful.

Dr. Zajicek said the BPCA has prioritized many therapeutic areas, and its roles are to prioritize drugs, to develop Proposed Pediatric Study Requests (PPSRs) or implement Written Requests (WRs) from the FDA, to serve as a sponsor, to publish study results, and to submit data to the FDA and hopefully affect label changes.

Legacy clinical trials that have been completed through individual contracts include lorazepam for sedation; lorazepam for status epilepticus; meropenem; nitroprusside for blood pressure control; lithium for mania (which completed recruitment on November 30, 2012); baclofen; vincristine; actinomycin-D; daunomycin (through the Children’s Oncology Group [COG]); azithromycin for ureaplasma urealyticum pneumonia and prevention of bronchial pulmonary dysplasia (BPD) (funded under a grant); morphine for neonatal pain (funded under a grant); methotrexate for high-risk acute lymphocytic leukemia and neurocognitive changes (done through COG); and hydroxyurea, including some trials that are finished and some that are not.

For hydroxyurea, the Baby HUG trial (for babies 9 months to 17 months with sickle cell disease) is completed and there have been pre-Investigational New Drug (IND) meetings with the FDA. The Pediatric Trials Network (PTN) is doing a relative bioavailability study comparing the liquid that was used in the Baby HUG trial, and the National Heart, Lung, and Blood Institute (NHLBI) is conducting a Baby HUG follow-on study to study mutagenicity and carcinogenicity.

The BPCA is mandated by legislation to report data to the FDA in two forms: first, through an unblinded, open, named IND submission, and second, through a public docket where data are cleaned and de-identified. The process is as follows: (1) the NIH generates the BPCA data, (2) the Clinical Study Report (CSR) is submitted, and (3) the de-identified data are submitted in PDF form. The FDA then opens the docket and the de-identified data are submitted to the docket—that signifies Time 0. The FDA Review Division reviews the submission and has ongoing conversations with the NIH. At the end of the 180-day time clock, the FDA negotiates a label change with the New Drug Application (NDA) holder.

Submissions that have been submitted to the Review Division include meropenem, nitroprusside, hydroxyurea (though it is missing the relative bioavailability study), and metronidazole. Docket submissions include meropenem and nitroprusside. Planned data submissions for the first quarter of 2012 include baclofen, hydroxyurea, and acyclovir (through the PTN).

As an example of the submission process, the BPCA had a pre-IND meeting on November 30, 2012, with the Cardio-Renal Review Division for the Sodium Nitroprusside study. A CSR was submitted to the division and there were two studies for the nitroprusside trial. Study 1 was submitted on November 29, 2011, and Study 2 on March 12, 2012. De-identified data were submitted to the docket on August 31, 2012; the 30-day public comment period took place from October 3 to November 2, 2012; and an audit occurred for the high-enrolling site for Study 2 the first week of October 2012. In short, the process is working.
Dr. Zajicek reminded attendees of the importance of good laboratory practice and good clinical practice during these trials. She said that an ongoing issue with the NIH is the need to adhere to both the academic bar and the regulatory bar. She explained that the big legislative change in 2012 was inclusion of the word “neonate.” Studying neonates has been an ongoing battle. The first list of drugs from 2002 and 2003 included several drugs used for neonates for indications that do not exist in adults, such as BPD. Problems surrounding studying neonates include the lack of labeling, feasibility, recruitment, the ability to extrapolate data from children to adults, and clinical trial endpoints. Some sort of biomarker or surrogate marker as a marker of neurodevelopment needs to be developed. She did note that the BPCA trials have been relatively successful at recruiting neonates. The azithromycin and morphine trials are for neonates only; the lorazepam for sedation trial had a neonate enrollment of 7 to 10 percent; and lorazepam for status epilepticus and nitroprusside both enrolled neonates.

The PTN has been extremely successful in recruiting neonates, and most of the network’s clinical projects are neonatal trials, including those for acyclovir, fluconazole, metronidazole, and sildenafil (in an opportunistic format). The PTN contracted with the Pediatrix Database to study neonatal intensive care unit (NICU) use and adverse events associated with proton pump inhibitors and octreotide (which the FDA had an interest in), and to look at opportunistic data collections, including scavenged samples.

The BPCA and Neonatal Research Network co-funded a study of the safety and efficacy of a hypothermia cooling device. The BPCA is continuing data collections and co-funding with other NIH Institutes, including the NHLBI Pediatric Respiratory Outcomes Program, looking at the use of various medications in children at risk of having BPD. It is also co-funding, with the National Institute of Neurological Disorders and Stroke, the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs Trial.

As a case study of where things can fail, Dr. Zajicek discussed the study to treat neonatal hypertension. The researchers developed a factorial design project to look at hydrocortisone and dopamine. A total of 336 infants were screened and 10 were enrolled. Issues with the trial included eligibility (including indomethacin as a contraindication for use with hydrocortisone) and consent issues. Among the questions that arose were: How is blood pressure measured in the NICU? Have these methods been standardized or validated in this population? What is normal neonatal blood pressure at a given gestation or postnatal age? What is the definition of hypotension? These are all problems because one needs to know what normal blood pressure is to know whether there is a change. She said the editorial that accompanied this paper in a 2012 issue of The Journal of Pediatrics noted the use of this pilot feasibility study is valuable for assessing feasibility and noted the importance of potential alternatives to prerandomization informed consent.

Neonatal research needs include improved feasibility; innovative clinical trial designs, including use of observational data gathering; consent issues; determining the rationale for extrapolation from preclinical models (children/adults); and validating clinical trial endpoints, including the
use of biomarkers that connect mortality, morbidity, or neurodevelopmental status with trial results, because it is so difficult to follow children for years.

Many of the PTN sites are the same as the Clinical and Translational Science Awards program sites, so the PTN is indeed using the infrastructure that the NIH is paying for. As for other types of data collection, the one absent space is the outpatient clinic, which is where most people get their medical treatment. To get at some trial data, the NIH worked with the Health Resources and Services Administration to co-fund a grant with the American Academy of Pediatrics’ Pediatric Research in the Office Setting. The grant (Comparative Effectiveness Research through Collaborative Electronic Reporting) was used to get information about use and adverse events related to asthma and second-generation antipsychotic medications.

The BPCA Program continues its work with pediatric formulations. The BPCA has an interagency agreement with the FDA to develop a global platform to guide formulations development and an algorithm to make pediatric formulations a little easier and less “hit or miss.”

In conclusion, the BPCA has developed strong NIH and Department of Health and Human Services partnerships. There has been slow, but steady, progress in completion of clinical trials and data submission for labeling. There also exists a continued need for access to observational data for efficacy and safety in children and a need for a coordinated plan of action to address the needs of neonates.

**Participant Questions**

Dr. Philip Walson asked whether, when the holder of the IND receives the data, it is voluntary or mandated that the holder include the data. Can the holder refuse to change the label? Dr. Zajicek responded that the legislation states there is to be discussion and negotiation about a label change. If the IND holder does not want the change, a pediatric advisory committee would likely be convened to discuss the issue. Dr. Walson then asked that the National Association of Children’s Hospitals and Related Institutions be involved with attempts to get outpatient data, as it has huge outpatient clinics with electronic records.

Dr. Heber Neilsen asked whether the new health care law provides an opening to get long-term data from electronic records, such as is possible in Scandinavia. Dr. Walson responded that anyone who wants the data from the Scandinavian countries can get it through a proposal for data mining, but that a European small business has to be involved in the request. Dr. Zajicek asked Dr. Neilsen to send her an e-mail so she can give him a more detailed and accurate response to his question.

**BPCA Updates, U.S. Food and Drug Administration (FDA) Perspective**

*Mary Dianne Murphy, M.D., F.A.A.P., Director, Office of Pediatric Therapeutics, Office of Special Medical Programs, Office of the Commissioner*
Dr. Murphy began by responding to Dr. Walson’s question to Dr. Zajicek. She said there is a mechanism for mediating a refusal of the IND holder to accept the data for its label. In those instances, the debate would go to a public advisory committee.

She said she is glad that after 15 years there is permanent authorization of this legislation, but also noted that a report is due in 4 years, so the group needs to continue submitting studies and data. She said she appreciates all the data and important information that have already been submitted.

Dr. Murphy noted that she will not provide the details of the new Food and Drug Administration Safety and Innovation Act (FDASIA) legislation. Obviously the impact of moving pediatric studies to the end of phase 2 makes the FDA much more aligned with the European submission requirements. Further guidance and regulation will be published in the next year. She said she included in her handouts the “who, where, and what” of what is involved in the FDA because the information is not all available in one place.

The FDA is now part of the law, which is important for industry. The FDA is driven by the Prescription Drug User Fee Act timelines, so making this legislation a permanent part of FDA law means that pediatric studies and labeling have to be addressed during drug development. Pediatrics can no longer be an afterthought. This legislation transforms the approach to product development. The legislation is also important for researchers, as more pediatric networks with specific expertise in product development trials are needed. Europe has legislation mandating pediatric expertise for trials and the United States also needs to. Ultimately, it is better if the countries do research together—the FDA meets every month with Europe, Canada, and Japan through teleconferences—although there are many fundamental scientific differences in approaches to trial design. Researchers can work on minimizing differences, but the networks are not in place for the United States to be involved in these studies. Advocacy groups can make a big difference, but there needs to be less fragmentation among them. Patients may want to think about how they can empower themselves and participate.

**Issues and Gaps: Future Focus.** The infrastructure, knowledge, and people exist to get this work done, but an issue is how long-term studies should be addressed. Such studies are really difficult, because somehow researchers have to look at the impact of the chronic use of drugs on children who are still developing. There have been suggestions for programs such as disease registries, so that all children with a disease will go into the same registry, regardless of the drugs they are taking. There must be better long-term plans for safety. There is also a need for validated endpoints, networks to be in place, and better databases. The current databases are just not effective or useful for pediatrics.

**Transparency and Pediatrics.** There is little business incentive to develop pediatric products, so when a trial fails, there is no motivation for companies to invest in finding out why or resolve the reasons that contributed to the failed trial. A failed trial means it was not able to prove whether or not the medication worked. Many of these trials have such small numbers of participants that it is difficult to figure out why the trial failed. With adult trials that fail, the companies take the time to figure out the problem, spend more money determining the endpoint,
and decide on the right dose. Pediatric trials get one shot to get it right, so they need to be even better designed than adult trials.

Failed adult trials are considered by the FDA to be commercial confidential information, meaning it is a criminal offense to reveal this information unless others have made it public. Legislation allows information about pediatric trials conducted under BPCA or the Pediatric Research Equity Act (PREA) to become public, but only after being redacted. Often so much of the information is redacted that the final data are useless, but it is getting better in terms of the quality of information and raw data that are being released on the Internet.

Pediatric legislation began in 2002 by requiring posting of the clinical and biopharmaceutical summary of all pediatric exclusivity trials. In 2007, this was expanded to include the complete review, not just the summary, of trials required under PREA and statistical reviews. The WR also must be made public, although it will not show all the information.

**Failed Trials and Transparency.** Dr. Murphy spoke about lessons learned from various clinical trials that failed. For the hypertension trials, researchers failed to get the dose right, so maybe researchers should consider diastolic blood pressure as a co-primary endpoint. It may also be time to think about other co-primary endpoints with pediatric trials. With migraine trials, there was a high placebo rate. They tried all kinds of trial modifications, but could not overcome the differences in the pediatric expression of the disease until they had an enrichment approach to these trials. For general anxiety disorder, there were different pharmacokinetics (PK) over age groups and by gender.

As of 2012, of the more than 400 products with new pediatric labeling, only about two dozen included neonates. Of the products which had studies that included neonates, over two-thirds of the trials failed to demonstrate efficacy. One assessment found around half of the products studied under pediatric legislation are not even used in neonates.

**Length of Pediatric Studies.** A look at the nearly 509 studies for pediatric labeling changes made under BPCA and PREA between September 2007 and December 2010 showed that the range of study length was .004 months to 120 months. The median length of the studies was 4.75 months and the mean was 8.64 months. Most of these studies are weeks or months long, not years. Generally, they do not follow children over an extended time to include various developmental and pubertal stages, and that needs to change in the future.

**Progress.** Progress has been made in that there are many more pediatric resources at the FDA. However, there is still a lack of depth in some areas for pediatrics. The first trials under the docket process from NIH contracts and other funding mechanisms are now being submitted to the FDA. It will be a real learning process to figure out how to get that information into the labels. Academia has hopefully realized that product development, and the necessary clinical trials, is a specialized area of research. Industry is making investments in pediatric product development by way of human resources.
There is recognition that development of endpoints for neonates and young children is a fundamental area of research needed for product development in these populations. There is now better understanding, because each trial—even failed ones—teaches researchers something. In the past, protocols were simply followed, but researchers now need to think about where the science currently stands. The hope is that all pediatric protocols are obsolete and no longer useful due to progress in the science and changes in the approach.

Dr. Murphy said the FDA struggles with how to give guidance that is useful, but not limiting. However, there is better understanding of why there are differences in response to therapy between adults and children, and communication is improving among the various players. The FDA is now attending academic meetings, presenting at the meetings, and letting academicians know why it is important for them to participate. Transparency of data is helping the effort.

Congress is requiring the FDA to provide a report in 2016 about what progress has been made. Because it takes about a year to get the document together, there are actually only 3 years to complete all the trials. After that an ongoing report will be required every 5 years. It is difficult to change a law, but if something is really broken, the opportunity will be there to discuss changes to the legislation.

There is a huge amount of information on the FDA Web site at www.fda.gov/pediatrics—the site has links to meetings, safety issues, information about hundreds of products, study characteristics, formulations platform, and more.

**Participant Questions**

Dr. Jeffrey Barrett asked whether the FDA has thought about metrics other than counting labeling and whether there is a more objective measure. He asked whether there is another method to communicate with Congress that might be more effective. Dr. Murphy responded that the FDA advocates should not stray too far from labeling because there is always a need to develop more science. That science then must be translated into something that will have a public health impact, and people must be told how to use the products better. Thus, labeling is the number one priority. However, the FDA does count other things—it counts what is learned from failed trials, scientific advances, efficiencies, and pathophysiology; but the law has said that the labeling is the FDA’s deliverable. Dr. Barrett said he understands this is part of the process and is an outcome, but he is concerned about educating the lay community about the value of this information and explaining why these studies need to be done. Labeling is just one entity used to characterize it. Dr. Murphy said the FDA did a focus group with parents, and they said they never thought of going to the FDA or looking at the labeling, so more work needs to be done with advocacy groups to educate and inform parents. They need to understand their child is being treated with less knowledge than they will be once the product is labeled.

Dr. William Rodriguez noted that many articles are available about failed trials and adverse events and how they led to changes in labeling. Dr. Murphy discussed an article that noted “what you read isn’t all there is,” which is why labeling is the gold standard. Labeling gives the real truth, versus what is happening while the science is evolving.
Dr. Walson noted that labeling drives payment, insurance coverage, and quality care guidelines. A huge amount of data is coming from academics, but if the study is not done in a way that can result in labeling, it loses value and may even be immoral. The studies must have the involvement of the IND holder. Dr. Murphy said there are also moral issues around enrolling children in a trial that is not going to benefit them, so labeling plays a critical role in delivering public health care.

Dr. Danny Benjamin spoke about the paper mentioned by Dr. Murphy. He said it was not just that 60 percent of the studies were not published, but that with the remaining 40 percent, when there was a positive label change for the sponsor, the concordance between the article and the label was outstanding—even miraculously high. When there was a negative label change, there was substantial discordance; in those instances, what was in the article was different from what was in the label. He said that during the peer review process, scientists need to be careful about what they put their names on. The good news is that scientists (and all Americans) have access to the data through the BPCA, which is an incredibly important part of this program. He said he wants to get away from the questions of whether labeling should be the gold standard, because that is what the legislation calls for, so that is what is being pursued. He noted that the average WR cost is the total annual budget for this program, so scientists have to be very careful with these dollars. He said registries and electronic medical records are great, but asked who at the FDA will actually be making label changes from that. What is a rational plan for using registries?

Dr. Murphy said the FDA already knows there is a major problem with electronic medical records. As far as registries are concerned, there is no one at the FDA to give an answer, because they are still trying to determine what to do. This should not just be an NIH responsibility alone; the sponsor and the FDA own some responsibility as well. She said researchers need to get to a better point in the scientific discussion; someone needs to pilot registries, and registries should be a bigger priority. There needs to be a way of trapping the data that is not as expensive, and opportunistic data sampling is one idea. Researchers need to figure out how to find out what is happening to these children after being on drugs for a long time. Dr. Benjamin said he could never have dreamed 15 years ago that there would be the labeling changes, infrastructure, and FDA personnel to do this work. He said he is grateful to all the people in this room and that the group is headed in the right direction. Dr. Murphy encouraged attendees to keep involving young scientists who are interested in this area as a challenge.

Dr. Thomas Hultsch asked for advice about the process of getting the FDA’s pediatric team more involved in labeling discussions. He said his company, Genzyme, negotiates with FDA divisions and they have a tendency to defer pediatric studies until after phase 3 adult trials, whereas the sponsors may be interested in doing pediatric studies much earlier on. Dr. Murphy responded that the new legislation will help. The FDA is working on internal standard operating procedures and WR templates so divisions will have some internal guidance and know they have to consider these things at certain stages. There will also be processes developed.
Dr. Lynne Yao responded to Dr. Hultsch’s comment saying the guiding principle within the FDA’s Center for Drug Evaluation and Research (CDER) is that pediatric development is appropriate as soon as it can be done. Sometimes there are issues, so when it can be done is very disease-specific. However, CDER’s expertise is offered to anyone who requests it. With the new legislation, sponsors will have to start thinking about pediatric development plans earlier in the process. They work in conjunction with other laws and considerations to ensure safety, so if there is a new product that is indicated for a pediatric population, adequate safety studies can be required.

Dr. Patrick Reynolds responded to the earlier comment that it is immoral to do randomized studies without focusing on a label, noting that the Children’s Oncology Group (COG) and other groups have done hundreds of studies that improve care without the indication being clearly on label. Something is wrong with the process when it comes to dealing with life-threatening pediatric diseases. In some cases, to require a second randomized study for an agent that has been shown to save children’s lives is immoral. In one case, an agent has been shown through a 10-year follow-up study that it significantly increases life expectancy, but the drug still cannot get an FDA label. Dr. Murphy responded that the FDA understands it may not be possible to get to a phase 3 trial with pediatric oncology studies; there have been discussions about ways to have PPSRs for oncology submitted to the FDA so it can issue WRs. There is a problem with taking pediatric drug development to adult advisory committees, because the advisory committee needs to be augmented with more than one pediatrician. Dr. Murphy said she believes you cannot have a pediatric advisory committee that has only one pediatrician, and that anyone coming before a committee should ask that they have enough pediatric experts on the committee. Dr. Reynolds said there really needs to be a consensus group that addresses this issue for life-threatening and rare diseases in children. Dr. Murphy said a group about rare diseases is being formed.

Dr. Zajicek said after a pediatric subcommittee meeting about 13-cis-retinoic acid (Acutane) she wrote a PPSR that was released as a WR and then declined by the pharmaceutical companies, but they are working to back the data out of the COG database to support efficacy. There is a clinical trials agreement with a company to make a new formulation for use with neuroblastoma.

Dr. Yao noted that the FDA tries its best to make sense of the data available and minimize unnecessary studies in children and to get that data into labeling. Sometimes inconsistencies can be helped by the Pediatric and Maternal Health Staff (PMHS). In general, they are working hard to get this information into labeling and into the public arena so the label shows substantial evidence of safety and efficacy. In terms of rare diseases, they are working on an initiative that relates to pediatrics and rare diseases. In 2010 a product was approved based on a retrospective review of 17 years of data on 17 patients. She said they are trying to do the right thing. Dr. Zajicek reminded participants that there are always two sides to a story and there really may be reasons more studies are needed; other times, PMHS needs to get involved to move things forward.

**Integrating the Data Story: Opportunities and Activities**

*Steven Hirschfeld, M.D., Ph.D., Captain, U.S. Public Health Service, NICHD, NIH*
Dr. Hirschfeld shared ideas about how to accelerate and expand opportunities to move forward. He gave an example of the variety of definitions of “ages and stages of childhood” among different government agencies and organizations to stress the need for harmonization and agreement. He said the operative word is “interoperable,” meaning the tools and methods that conform to specifications that allow real-time exchange of information and alignment of process. The data are available, but one needs seemingly unlimited resources to convert, consolidate, analyze, and study them. There is a health care delivery system (although not everyone gets health care), but not many people live permanently in research space, so somehow researchers have to get people and subsequently their data into that space. The return on investment from an individual study is when data from that study can be pooled with other studies—called data sharing. This has been an active area for the NIH, but it has been inefficient. In practice, less than 10 percent of studies comply to the point where data can be readily shared. Another issue is how to get people who are already in the clinical research system to return to the health care delivery system and then back to the clinical research system on a schedule for long-term follow-up.

Dr. Hirschfeld noted that publications generally do not change practice. Studies show that unless one is in a research setting, it is harder to get people to change practice, and it can take decades, which is very inefficient and time consuming. Researchers have to think in new paradigms. Research data are an extension of the individual who volunteered, and these data need to be protected. Privacy and security are complementary aspects of protecting the individual and protecting data. Researchers need to elevate data and view data as a resource. The research process will be optimally functional with adoption of interoperable standards that are processes. There needs to be a culture where people work together.

Informatics trends can allow researchers to reach these goals, but more has to be done to institute the informatics. Other consortia are looking to achieve the same goals, but not all of them are allowed to share detailed information with each other due to proprietary issues. The paradigm for collaborative infrastructure is pediatric oncology, but it cannot absorb all the other specialties. Researchers need to consolidate platforms and make them interoperable, as the Clinical and Translations Science Awards Consortium Child Health Oversight Committee is planning to do. Another example of a harmonization initiative is the Global Research in Paediatrics (a 5-year project). In addition, the National Children’s Study (the Study) is looking for partners and would be a terrific way to conduct long-term follow-up studies. The Study is in partnership with other long-term birth cohort studies in the United Kingdom, France, Germany, China, and Japan, and the partners are harmonizing the data elements and methods. The Study wants to be able to leverage everyone’s investments.

The Study is making all its data structures conform to applicable international standards. It incorporates an informatics approach that is standards-based so other people will know how to use the data. For example, the Study staff work with the Department of Defense, which has 2 million military children in its system, to try to ask questions of mutual interest. The data can be used to describe the content of what is collected, along with operational data (once called paradata), which are the data about how operations are done. The Study has developed a catalog of 500 elements that is being used to learn and to monitor and maintain cost control and quality; this work has greatly reduced the need for auditing. In addition, all Study data will be tagged
with standardized metadata tags. The National Security Administration tags and digitalizes all its data, and the Study is trying to adapt that approach for clinical research; for example, Study personnel are determining how to develop instruments to ask study questions in a cost-effective way. One key project is trying to harmonize the terms and definitions that people/researchers use, because the existing nomenclatures are inconsistent. For example, SNOMED, ICD, MEDRA, and other systems all have a paucity in child health terms. To advance child health research, interoperable tools are needed to share and leverage the relatively scant resources and to work with others. In closing, Dr. Hirschfeld encouraged all participants to be open and expand and leveraging existing results.

Updates and Lessons Learned from the Pediatric Trials Network (PTN)
Michael Cohen-Wolkowiez, M.D., Ph.D., Assistant Professor, Division of Pediatric Infectious Diseases, Duke University

Dr. Cohen-Wolkowiez presented updates and lessons learned from the PTN. All trials and data are conducted under an IND application and apply to opportunistic studies conducted within the PTN. The PTN is an infrastructure for investigators to conduct trials that improve pediatric labeling and child health. The network is sponsored by the NICHD and studies formulations, safety, and efficacy for products used in children. Success for the PTN is determined by completing trials that improve dosing, safety, information, labeling, and ultimately child health.

Dr. Cohen-Wolkowiez showed a slide of the organizational structure of the PTN. At the center is Duke University, where the operations of the network sit; the sponsor (at the top) is NICHD; alongside the PTN is the Data Coordinating Center at the EMMES Corporation; and the five pillars are the Clinical Pharmacology Core, the Pharmacometrics Core, the Safety and Ethics Core, the Devices Core, and the Mentorship Core. The PTN started in 2010, and more than 200 investigators at 120 sites have expressed interest in participating. It is anticipated that about 60 sites will be actively enrolling in trials during 2012 and 2013. The PTN is growing the “rapid start network”—a pediatric clinical trial consortium affiliated with PTN—to about 100 sites. This means the sites have a general agreement with the PTN to do the studies, and much of the contract language has already been worked out. This allows studies to be started quicker.

PTN Studies. Dr. Cohen-Wolkowiez showed a map of sites currently participating in the PTN throughout the United States. He gave project updates, noting that the majority of the data are preliminary because the PTN is so young. However, some of the information has already been submitted to the FDA as a CSR and manuscripts are already being submitted. Many of the trials are enrolling neonates and premature infants.

Metronidazole. The metronidazole study was led by Dr. Cohen-Wolkowiez out of Duke University and looked at PK and safety of the drug for use in premature infants. This drug is used a lot and although it is a very old drug, the PK and metabolizing enzymes remain unknown. The study is being done to find out if the dose commonly given is the right one. Twenty-four infants were enrolled at less than 32 weeks gestational age. Infants were enrolled within 24 months and the CSR was submitted in June 2012. The study was conducted at three sites. The
researchers are now looking at other associated studies to learn more about the molecule. The study came out with a new postmenstrual-age-based regimen.

**Acyclovir.** The acyclovir study is led by Dr. Brian Smith at Duke University. This drug is used in neonates for herpes simplex infections, yet little PK data are available. Premature infants may require different dosing because the drug is primarily cleared renally, and renal function changes with neonatal developmental stages. Thirty-two infants were enrolled in this trial by June 2012, and the CSR is in draft form and will be submitted in the first quarter of 2013. So far results indicate that the dosing being recommended by commonly used sources is not appropriate for all infants. The dose used in the study achieved the target results. Many safety and efficacy questions remain unanswered.

**Hydroxyurea.** The hydroxyurea (HU) trial is led by Dr. Kathleen Neville at Children’s Mercy in Kansas City. This is a follow-up study to the Baby HUG study and is looking at the HU formulation to compare the exposure of a liquid formulation with the capsule form. The study population is 40 children, and preliminary analysis of 8 subjects has been done. Preliminary data show the liquid formula will work fine.

**Pediatric Opportunistic PK Study (POPS).** This study is also led by Dr. Cohen-Wolkowiez. It looks at the PK of drugs that are commonly used in children with “standard of care.” The study is inclusive of all ages and has no exclusion criteria. Enrollment is targeted based on certain ages, and an extensive gap analysis is done before drugs are added to this study. The goal is to enroll 1,000 children. There are currently about 15 active sites, and 15 more will soon be added. The first patient was enrolled in November of 2011, and 355 are now enrolled. Thus far, 12 BPCA-prioritized drugs are being studied. It is a very flexible mechanism.

**Lisinopril.** The lisinopril study, led by Dr. Howard Trachtman, looks at safety and PK of this drug in pediatric kidney transplant recipients. The study will also get pharmacodynamic (PD) data so a robust phase 2 trial can be conducted about safety and efficacy.

**TAPE.** The TAPE study is led by Dr. Susan Abdel-Rahman at Children’s Mercy in Kansas City. For this study, researchers developed a device that can be used to very simply estimate body weight in a child. The study enrolled 624 children in the United States and is conducting validation studies in other countries. The first patient was enrolled in January 2012. A CSR has already been drafted for submission. A picture of the TAPE device was shown in a slide and its use was described. The results are very accurate and effective. It will be a useful tool for estimating body weight in emergency settings and settings that lack resources to determine drug dosing and other issues.

**Ampicillin.** The ampicillin study of safety and PK in infants is led by Dr. Audrey Tremoulet at the University of California at San Diego. The study merges four to five data sources. This project will get PK data from 75 babies in the POPS study. The researchers have access to the Pediatrix data set, which includes about 800,000 babies. The study looks at safety and adverse events through a large epidemiological database. The first patient was enrolled in November 2011, and by June all 75 babies were enrolled. So far the preliminary models are showing that
clearance of the drug is related to postmenstrual age; similarly, there is an inverse relationship with serum creatinine.

**Obesity PK.** The obesity PK review is being led by Dr. Kevin Watt at Duke University. In collaboration with the National Library of Medicine, the researchers developed a search strategy, with Dr. Christian Baker doing the majority of the work. They looked at 1,700 abstracts and found 23 had PK data for 22 drugs. In 41 percent of cases, the drugs demonstrated clinically significant PK changes in obese children, and 81 percent were dosed by total body weight or unadjusted body surface size, which resulted in high or low drug exposures. There is a huge knowledge gap in obese child PK and optimal body size dosing measures.

**Other Trials.** Other trials in development include looking at the PK of three drugs under the same protocol, as they are used in the same populations and for the same indications, to help reduce the budget. The drugs being studied for safety and PK are anti-staph trio (clindamycin, rifampin, and ticarcillin), sildenafil, and clindamycin obesity.

Lessons learned thus far show the advantages of having a network. It shortens the time needed to get studies started and encourages young researchers to get involved. A slide showed a comparison of enrollment timelines for PTN trials compared with legacy trials. The PTN is planning a Phase 2 dose ranging study of diuretics to reduce risk of BPD in premature infants and a Phase 2 study of the safety of antibiotics in preterm infants with necrotizing enterocolitis. Also in the works is a study of pantoprazole PK in obese children and methadone PK in children.

In the POPS study, children receive drugs that are the standard of care and PK samples are collected. A variety of different things can then be done. For an off-patent therapeuetic, researchers can target specific age groups, by ethnicity, by condition, and so on. Even the data capture system can be changed. The study asks for consent to take blood at prespecified times based on dosing intervals. There are 15 or more therapeutics bundled into one protocol, which were all submitted to the FDA divisions as an IND. The researchers plan to use results as preliminary data to plan more traditional trials. The results give information about the quality of the data, enrollment, and so on. POPS provides a testing ground for sites and facilitates contracts and infrastructure.

Dr. Benjamin described PTN collaborations with other networks and training. The PTN is pilot testing collaboration with the Neonatal Research Network, which is sponsored by the NICHD and has 19 centers. The Neonatal Research Network does not necessarily want to do clinical pharmacological or early phase studies, whereas the PTN does. For the partnership, the PTN is looking at molecules in early stage for the Neonatal Research Network. If the clinical pharmacology is favorable, and if the dose ranging studies hint toward efficacy, the Neonatal Research Network will do the pivotal binding studies for the PTN. The PTN needs more partners that can do pivotal studies and registries.

The PTN is committed to data access on three levels. First is the current level of commitment on the pediatric trials. The PTN is on Task Order #20; of the 20 projects, 18 are led by a junior investigator who is either on a K23 or currently applying to be on one; an instructor or mentor; or
a T32-sponsored Fellow. The PTN is committed to having young investigators lead the work. Each young investigator is partnered with senior researchers. It is written into the PTN proposal that Dr. Benjamin, Dr. Greg Kearns, and Dr. Edward Capperelli cannot be the PIs or first authors for the primary studies in order to encourage young investigators’ participation. Second, the PTN wants to partner on secondary analyses with NICHD-funded T32 grant recipients and those who are applying for mid-career developmental awards. Third, when the PTN receives the prioritized drugs from other groups, the drugs are usually put into the opportunistic protocol to see how well they do. If they succeed in the first trial, they will be moved onto subsequent trials.

Dr. Benjamin thanked the PTN partners who were on the original grant submission for contributing to its success.

Dr. Zajicek asked about dried blood spots, and Dr. Cohen-Wolkowiez responded that they have been used for a long time in pediatrics through neonatal studies. It means whole blood is taken and put on blotting paper. Analyses can then be done from the sample. The advantages are being able to use a very small sample and that the spots can be left at room temperature to dry, put in a bag, and stored at room temperature. This allows researchers to take more samples with no risk to the patient. The PTN is also moving forward with validating use of dried plasma and urine spots.

**Meeting the Pharmacological Biodefense and Disaster Preparedness Needs of Children**

*David Siegel, M.D., Medical Officer, OPPTB, NICHD, NIH*

Dr. Siegel gave background information about the major federal effort that occurred after 9/11 to protect the United States from future potential threats. During the effort, it was found that the needs of the children in disaster scenarios were not met. The National Commission on Children and Disasters was formed to go through various aspects of disasters and find the gaps related to children. The Commission found serious deficiencies in each functional area, where children were more an afterthought than a priority. The Commission recommended that Congress, the Department of Health and Human Services, and the Department of Homeland Security (DHS)/Federal Emergency Management Services should ensure availability of and access to pediatric medical countermeasures at the federal, state, and local levels for chemical, biological, radiological, nuclear, and explosive threats.

The Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) was formed and is composed of subject matter experts from many government agencies. The DHS identifies risks and leaves it to this group and its subgroups to develop requirements to protect the population. Pediatric needs are now in requirement documents, and the PHEMCE personnel are going through the strategic national stockpile to ensure it has the right drugs and information to protect children.

**Difficulties.** Over the years, many challenges have discouraged the testing of drugs in pediatric populations, including:

- Lack of incentives for companies to study drugs in neonates, infants, and children
- Lack of necessary technology to monitor patients and assay very small amounts of blood
- Lack of biomarkers
- Lack of suitable infrastructure for conducting for conducting pediatric pharmacology drug trials.

Before 1998, pharmaceutical companies were not required to test drugs in infants or children, even if the drugs were commonly given to those populations. As a result, very little clinically derived evidence exists about the PK, safety, and effectiveness of most medications used in children. In the inpatient setting, 80 percent of drugs are used off label. In the ambulatory setting, it is between 50 to 75 percent. Chem Packs are forward deployed for disasters and contain countermeasures for nerve agent exposure. But drugs that are not labeled cannot be forward deployed. Thus, many autoinjecters have not been deployed for children.

Ethics is another area of difficulty. To involve a child in a study, one has to show a personal benefit, but for something like the anthrax vaccine, children have not been tested. So if there is a potential major threat, the question is whether children should be tested beforehand or not until the threat is active.

Cost is another difficulty related to biodefense for children, because manufacturers will not make a profit on biodefense drugs that are only used in the stockpile and only renewed every 5 to 7 years. Although in most instances it is necessary to fund biodefense-related adult research and development (R&D) initially, in many instances, the requisite pediatric R&D is never funded. Part of this is because much of the R&D is being done by the military, and the military does not focus on pediatric research.

Another difficulty is finding medical countermeasures that are appropriate for children and neonates and that have a long shelf life with reasonable costs. The difficulties associated with studies in children are accentuated in special pediatric populations such as premature infants and children with disabilities. There is also a shortage of researchers at all levels who are capable of performing pediatric biodefense-related studies.

**PTN.** Many drugs in the strategic national stockpile are generic and lack PK and safety information; these could be researched under the BPCA model. Although there is current legislation that provides a methodology for resolution of the critical need for scientific study of drugs that are commonly used in infants and children, a mechanism was needed to provide an infrastructure, as well as the requisite talent pool to perform pediatric clinical trials research. The PTN provides this infrastructure and talent pool. The PTN has a 7-year task order contract.

The PTN is not funded by Congress to do biodefense research, so the PTN focuses on dual use of drugs. Examples of dual use include:
- Opportunistic studies— for PK, select safety and select limited efficacy
- Doxycycline—for children under 8 (study sites include Israel and Singapore), hydroxocobalamin (cyanide antidote), acute care drugs (obesity-related dosing)
- Midazolam—for treatment of status epilepticus and nerve agent/organophosphate-induced seizures
- Neonatal/preemie studies
- Clindamycin—can be used for methicillin-resistant *Staphylococcus aureus* and anthrax
- Acyclovir—planning a prophylaxis follow-up study for acute radiation syndrome (ARS)
- Flagyl—for gastrointestinal syndrome
- Ampicillin—can be used for anthrax and other biodefense agents
- Fluconazole—used for ARS
- Mercy TAPE method—to ascertain accurate weight in the developing world or acute care setting
- Obesity database Web site
- Meropenem—a Duke study for meningitis caused by severe anthrax
- Protocol Task Order—prospective studies for which a national institutional review board will soon be opening.

Although the prime focus of the PTN is to support “regular” BPCA clinical study activities, the NICHD also anticipates the potential need to obtain much-needed biodefense/disaster-related pharmaceutical information for labeling or emergency-use authorization purposes. The PTN and NICHD, for biodefense and disaster related purposes, will take into account the prioritization process of the:

- OBPeds Integrated Program Team (IPT), PHEMCE
- Recommendations/requests of the FDA
- The BPCA’s working groups.

Developing medical countermeasures is a team approach with the NICHD representing just a small part. The biodefense-related research is funded by Congress. The chemical research is conducted by the National Institute of Neurological Disease and Stroke, and the National Institute of Allergy and Infectious Diseases conducts research about infectious diseases and radiation.

The NIH traditionally supports basic, translational, and early clinical R&D, but not always. The Assistant Secretary for Preparedness and Response traditionally supports advanced R&D (via the Biomedical Advanced Research and Development Authority). Dr. Siegel asked that people at the meeting with areas of interest in biodefense get in touch with him.

**Pediatric Hydroxyurea Phase III Clinical Trial**

*Jonathan Goldsmith, M.D., Deputy Branch Chief, Blood Diseases Branch, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute, NIH*

Dr. Goldsmith presented an update about the future developments of the Baby HUG trial. In 1996 a Special Emphasis Panel (SEP) met to review the Multicenter Study of Hydroxyurea (HU) (MSH) and the Baby HUG study of MSH use in children with sickle cell disease (5 to 15 years of age). The SEP recommended to the NHLBI that a randomized double-blind placebo-controlled trial be conducted in children recruited before 2 years of age to test the hypothesis that HU can prevent the onset of chronic end organ damage. Surrogate markers of end organ damage were suggested to evaluate pulmonary, renal, splenic, and brain function, as well as
developmental milestones. On September 1, 2000, contracts were awarded to conduct the recommended study.

**Landmarks of Baby HUG.** Contracts were modified in May 2008 to include the Statement of Work for Follow-Up Study I (September 2009 through December 2011). In January 2012, 5-year contracts were awarded to clinical sites and a data coordinating center to conduct a Follow-Up Study II. Both contracts are supported by the NHLBI and the NICHD.

**Phase III Clinical Trial.** The phase III clinical trial was conducted at 14 clinical sites. The first subject was randomized in October 2003, and the last was randomized in September 2007. Nearly 200 subjects were enrolled between 9 to 17 months of age (mean age was 13.6 months), and they received liquid HU preparation at a fixed dose of 20 mg/kg/day or placebo for 2 years. Of the subjects, 56 percent were female and 96 percent had hemoglobin SS. They were monitored every 2 to 4 weeks, and 167 subjects completed the study.

Safety was a major consideration for this study, as these were very young children and not as much was known about the drug as was hoped. Each site had an ombudsman and a primary endpoint person to monitor lab values and assist in clinical management. The safety pilot study was evaluated by the FDA after the first 40 subjects were enrolled to look at toxicity. Liquid HU and placebo formulations were developed for the study. Formal stability and sterility programs were established and conducted for each production lot. There was also identification and use of “child-safe” caps and light-transmission-reducing polyethylene terephthalate (PETE) brown bottles.

The interventional study had primary endpoints that were based on radionuclide scanning of spleen and renal function. These endpoints were not achieved. However, secondary endpoints demonstrated highly significant benefits of HU treatments, including markedly reduced episodes of vasoocclusive pain episodes such as pain requiring hospitalization, dactylitis, and acute chest syndrome. There were also improved hematologic results including higher hemoglobins, a rise in hemoglobin F, an increase in the size of the mean corpuscular volume, and lower reticulocytes. Results took about a half year to manifest. There were improved surrogate markers of spleen and renal function, even though the endpoints were not achieved. Safety endpoints showed cytopenias and reduced platelet count, but these had no clinical impacts.

**Toxicity.** Three tests are performed on these children: chromosomal Karyotype, illegitimate VDJ recombination events, and micronucleated reticulocyte formation. All three tests were done at the beginning, midpoint, and will be done at the end. Thus far there are no differences between the HU and placebo-treated subjects, but extended follow-up of subjects is needed.

**Results.** The benefits continue to accrue for subjects treated with HU at 2-year follow-up, including reduced emergency room visits for painful crisis, and reduced hospital admissions for acute chest syndrome and febrile illness. Slides were shown to demonstrate benefits to HU subjects.
Publications. Sixteen full-length, peer-reviewed articles have been published thus far about the study. The main article is authored by Win Wang and was published in *The Lancet* in 2012. Thirty-eight abstracts have been published about the study.

Follow-Up Study. The 5-year structured follow-up will look at consenting study subjects for the first decade of life. The average age when they come off study will be 10 years. The subjects will have enhanced neuropsychological, brain, cardiac, and pulmonary evaluations, as well as continuing renal and spleen/liver monitoring. The follow-up will end on December 31, 2016, at which point there will be characterization of clinical benefits, long-term toxicities, and so on. It is hoped the results will improve understanding of the natural history of sickle cell disease in young children and in the cohort who received HU.

Future. The goal is to achieve pediatric labeling for HU. It has been necessary to understand the elements of a regulatory setting and assemble the components for a filing. A WR for HU pediatric studies was issued by the FDA to Bristol-Myers Squibb (BMS), which is the innovator company for HU. In 2002, BMS was asked to submit the safety, efficacy, and PK studies across the pediatric age group, but it declined. In 2004, BMS was asked to supply open-label PK and safety studies of patients 2 to 5 years of age, and the company again declined. Thus, the WR was referred to the NIH to complete the studies.

Regulatory Filing and Pathway to Labeling. There are strong safety considerations and regulatory strengths of this study, including:

- Clinical site-specific ombudsman and primary endpoint person.
- A safety/feasibility pilot study in the first 40 subjects.
- Prompt and complete responses to the FDA queries.
- This is the only double-blind prospective pediatric trial to investigate the effect of HU in children with sickle cell disease.
- The patients in this study differ from those in other studies in that they were very young and were not selected for clinical severity.

In addition, the secondary endpoints are clinical benefits to subjects, which the FDA looks for. There have not been any major safety issues during the 2-year follow-up.

Thus far, there have been face-to-face meetings with the FDA, teleconferences, and filings to the IND. Ongoing issues include:

- Extemporaneous compounding
- A bioequivalence study performed by the PTN
- A food effects study.

The researchers hope at the end of the study to get an indication that says HU is indicated to reduce the frequency of painful crises, acute chest syndrome, and dactylitis in infants and children ≥ 9 months old with sickle cell disease, with or without clinical symptoms, and to reduce the need for blood transfusions and hospitalizations. This type of indication will make it easy to prescribe HU to very young children with sickle cell disease and radically improve their health.
Dr. Snyder presented a general discussion about the level of evidence the FDA is looking for in labeling for children. She gave background about pediatric legislation and how it has advanced pediatric drug development over the past 15 years.

Legislation has resulted in more than 400 labeling changes. Before the laws were enacted, more than 80 percent of pediatric drugs did not have labeling, and now about 50 percent have labeling. In 1997, the Food and Drug Administration Modernization Act (FDAMA) created a financial incentive for pharmaceutical companies to conduct pediatric studies to receive an additional 6 months of market exclusivity and created the WR process. The WR is a legal contract that outlines the studies that need to be done to get exclusivity or patent extension. In 1998, the Pediatric Rule, which was later replaced by the Pediatric Research Equity Act (PREA) in 2003, required pharmaceutical companies to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations. This reinforced the concept of extrapolation of efficacy introduced by the Pediatric Labeling Rule of 1994.

In 2002, the BPCA was enacted. It reauthorized FDAMA and provided a mechanism for study of off- and on-patent drugs. The NIH was also directed to establish a program for pediatric drug development through Section 409I (a) and (b) of the Public Health Service Act. In 2012, FDASIA made both the BPCA and PREA permanent.

Under the BPCA, a pediatric WR can be issued for on- and off-patent products. WRs are issued by the FDA and are sent to the holders of the drug application (drug companies) to let them know what studies are needed for exclusivity. These studies can be for an adult indication that also applies to pediatrics, or for a unique pediatric indication. For on-patent products there is usually one company involved, and it has incentive to do the studies. For off-patent (patent expired) products, the WR will likely be declined by the company. For off-patent products, the WR will go to generic companies as well. If a WR for a product is declined by all holders of an application, the FDA may refer the WR to the NIH for completion of studies.

**Goal of BPCA.** The goal of the BPCA is pediatric labeling. To label a drug for a specific indication, dosing, safety, and efficacy information for the drug are required. Many older drugs used in pediatrics were not initially studied for use in children and may be used off label. The focus of the BPCA/NIH initiative is to help provide pediatric labeling for off-patent drugs.

**Pediatric Labeling.** When a pediatric indication is granted, the information is spread throughout the label as appropriate. In the Use and Specific Population section of the label, information related to pediatric use is added. For drugs where there is a pediatric indication, cross references to other areas of the label would also be included. For drugs not indicated for pediatrics, information would be added in this section, but generally not in other areas of the label.
Considerations. Some considerations for pediatric drug development include:

- Is there a public health benefit?
- Is there nonclinical information to support drug development in children?
- Is there an appropriate formulation for use in pediatrics?
- Are there PK data to support dosing?
- Are there safety data to support that the dose is safe to use in the pediatric population?
- Is there efficacy information to support use in pediatrics?
- Are there any ethical issues related to the use of the drugs in pediatric patients?

For public health issues, the FDA looks at a couple of issues. First, is there substantial use in the pediatric age group? Generally, the FDA looks at whether there are 50,000 pediatric patients in the United States with the disease or condition. Second, is there a meaningful therapeutic benefit? Will there be significant improvement in the treatment, diagnosis, or prevention of disease compared with already approved drugs labeled for pediatric use?

For nonclinical studies, the FDA looks at the animal models that already exist to see if more juvenile animal studies need to be conducted before the drug is studied in pediatrics. The FDA may add a nonclinical study requirement to a WR if there is not sufficient animal data to support testing in children.

Formulation issues include whether an appropriate formulation exists for use in the pediatric population. The formulation must be appropriate for the pediatric patients expected to use the drug and should be developed as part of the study plan. The FDA may require bioequivalence studies, which are generally performed in adults.

PK studies in pediatrics may be needed to determine the appropriate dose in children, and sampling should be limited to reduce pain. Studies should be done in the pediatric population (indication) and age groups expected to use the drug, not in healthy children. Modeling and simulation may be useful for study design/dose selection, and population PK studies may be considered. This approach may not apply to locally active products such as topically applied creams and lotions, where PK may be needed to look at systemic absorption from a safety perspective, but evaluation of clinical activity at the site of action will be needed.

Safety. Safety data are collected for all studies. Once PK and safety data are collected to determine dosage, more safety data are needed to look for novel side effects in children, as compared with adults, and any other issues. Safety should be tested in the pediatric patient population (indication) expected to use the drug. Studies ideally would be large enough and of long enough duration to detect common and potentially infrequent, but not necessarily rare, adverse events. In some cases, existing data may be leveraged from published or historical data, but the data may be limited due to bias, changes in practice over time, lack of controls, and insufficient evidence about drug exposure.

Efficacy. The legal standard for determination of efficacy is defined by the Federal Food, Drug, and Cosmetic Act of 1962. Drug companies are required to provide “substantial evidence” that the drug is effective. This has generally been defined as having done at least two adequate and
well-controlled investigations or clinical trials. The FDA has been flexible within the statutory requirements, and guidance is available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf.

**Extrapolation.** Extrapolation is a hypothesis or an assumption that if a drug works in adults it is likely to work in children. In pediatrics, the law allows for extrapolation of efficacy from adult data or data in older children. This can be done in cases where the course of the disease and the effects of the drug are thought to be similar in children and adults, and adequate and well-controlled studies have been done in the adult population. The concept also applies across pediatric age ranges.

In cases where there is some doubt regarding the assumptions, the concept of partial extrapolation is introduced. In these cases, the FDA may allow one adequate, well-controlled study to suffice, or PK/PD exposure response information may be used to support efficacy. The article “Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs” published in *Pediatrics* offers a lot of information about this subject.

One outstanding question relates to what type and how many studies need to be done for a pediatric indication, particularly if there is no pediatric information for the drug but the drug is approved for that indication in adults. In general, the number and types of studies needed depend on whether efficacy may be extrapolated from adult data. This is generally determined on a case-by-case basis. For depression, two studies are needed, as there is often bias and placebo effect, and pediatric patients present differently than adults. Nonclinical studies may be needed if there is not enough information to support pediatric development, and a formulation may be needed if one does not exist. PK data are needed to support dosing, and safety data are needed to support the proposed dose to be used in the pediatric population. In some cases, one study may be sufficient.

Another question pertains to what the clinical development plan should be for a product that is seeking a new pediatric indication for which there are no pediatric data and for which there are no adult data for the indication sought, but there are data for a different approved adult indication. In these cases, efficacy cannot be extrapolated because the indication is not approved in adults, and generally two pediatric studies are needed. However, the appropriate clinical development program should be discussed with the FDA. Nonclinical studies may be needed, PK data are needed to support dosing, and safety data are needed to support the proposed dose to be used in the pediatric population. In this case, a full developmental program would be needed.

The third general question is about what type and how many studies need to be done if there is a current pediatric indication, but there is a potential interest in adding pediatric indications to labeling. The answer is that if the indications of interest exists in adults, then efficacy potentially could be extrapolated. If the indication does not exist in adults, then adequate and well-controlled trials are needed. The need for nonclinical studies would depend on what nonclinical data were collected for the original pediatric indication. A formulation may be needed if one does not exist for the age range considered for this indication. PK and safety data in pediatrics are needed to
support dosing in the indication. Safety data are needed to support the proposed dose to be used in the pediatric population. Existing safety data could potentially be leveraged from published or historical data, but this is looked at on a case-by-case basis. This is an example of when a full developmental program may be needed.

The last general question is whether labeling can provide specific information for neonates when the disease does not occur in adults. The answer is that if the intent is to add a specific indication for neonates, then a full developmental program needs to be done to add the indication to labeling. This would include PK, safety and efficacy information in neonates with the disease. Efficacy could not be extrapolated because the disease does not occur in adults. The indication, dosing, and clinical study data would be added to labeling if the clinical data were sufficient to establish safety and effectiveness for the specific indication in neonates.

Summary.
- The goal of BPCA-NIH initiative is to help provide pediatric labeling for off-patent drugs.
- Pediatric labeling requires information on dosing, safety, and efficacy for the proposed indication and population.
- PK and safety data must be collected in the population of intended use.
- Efficacy may be extrapolated to pediatrics from adult data or pediatric patients from different age groups in certain circumstances.

Academic Investigator Perspective: Population Based Studies of Tinea Capitis: How We Can (…and Why We Must) Use This Information to Guide the Design of Efficacy Trials

Susan Abdel-Rahman, Pharm.D., Professor of Pediatrics and Pharmacy, Division of Clinical Pharmacology and Medical Toxicology, Department of Pediatrics, University of Missouri-Kansas City School of Medicine, Children’s Mercy Hospitals and Clinics

Dr. Abdel-Rahman began by stating that if one does not have reliable background data on the natural course of a disease and does not understand the limitations of existing outcome measures, then clinical trials are set to fail. Tinea capitis is a great example of this, because the vast majority of therapeutic studies were conducted before these background data were available, and the studies do not reflect what is happening in clinical practice. Now that the disease knowledge is available, there is a need to redefine how to think about these clinical trials.

Tinea capitis is a very common infection that is generally a single pathogen. About 1 in 20 school-aged children have the active disease. The clinical consequences of the disease are mainly related to exclusion from school/social activities and psychosocial issues. Treatment requires oral therapy for many months, and the condition persists from months to years. The problem with treating this condition is that clinical response rates seen in well-controlled clinical trials do not match what is seen clinically. Trials found that the gold standard treatments should result in about 80 percent efficacy, but in real-life settings, the efficacy is 50 to 70 percent, at best. Thus, the doses and dosing durations have steadily increased over the last decade and now exceed the FDA label. The increased infection rates have outpaced knowledge of how to treat it.
Many times the response differences are blamed on poor adherence, which could be the case in some instances. Cost could contribute to the adherence piece, as could resistance, but evidence does not support this. The PK may be the culprit, but again, evidence does not support this.

Some researchers started looking at other possibilities for the difference in response. They looked at selected and nonselected populations and identified many children who carry the infection but remain asymptomatic. Over time, some remain culture positive, some become symptomatic, and others become culture negative. Thus, researchers started looking beyond cultures to genetics in order to get a “fingerprint” of the infection. Over time, they can then see how the child acquires, loses, or trades pathogens. They can also look at transmission within the population. They decided to look at a strain typing strategy, because this type of research cannot be done by phenotyping alone. To date, the researchers have identified more than 65 genetic variants. They found that by taking a different approach to expand knowledge of the disease, one can get more information.

The first step was to get an idea of the natural course of the disease. They identified a large, high-risk population that could be identified repeatedly. They selected one urban day care center and followed 446 children every month over 2 years. There was 100 percent participation. Infection rates were found to be 20 percent at the lowest and 50 percent at the highest, during any given month. The strain typing allowed a look at persistence of specific pathogens. Of the 446 children, 264 had one typeable strain and 173 had more than two. Of the 173 children who had more than two strains, 89 exclusively carried the same strain each time they were tested; 64 were predominant carriers of one strain; and 20 had a different strain each time. Ninety percent of the children carried the same strain over and over again, and time had no impact on persistence.

The burden was larger than originally thought, so a larger study was conducted in 44 urban elementary schools in Kansas City in grades K–5. In all, more than 10,000 children (99.8 of students) participated in the 4-month study. Data showed some schools’ infection rates approached 20 percent. In some, up to 30 percent of students in a grade level were infected. African Americans are at highest risk for this infection, and in this study the infection rate for this population was about 13 percent. For kindergarteners and first graders, infection rates were around 18–20 percent. Other studies across the country have shown similar infection rates.

The study found some children are at high risk for repeat infection, and other children never get it. In addition, rates of symptomatic disease in exclusive carriers are much higher than in those with transiently acquired pathogens. The day care center study was purely epidemiological, but the infected children were referred to the clinic physician, so their treatment outcomes were tracked. It was found that after one course of high-dose griseofulvin, 22.7 percent became culture negative, 6.8 acquired a different strain, and 70.5 percent remained positive with the same strain carried prior to treatment. The time for them to become culture positive again was about 2 to 3 months. After two courses of the drug, 46 percent became culture negative, and after 3 and 4 courses there was no change in outcome. Responders and nonresponders were both followed an average of 150–180 days before their first dose of the drug and were followed for about 200 days after treatment ended. Thus, there was no bias in relation to sampling time. In the general
population, clinicians are still seeing instances where the disease is not being effectively treated and children are remaining carriers.

There are host-pathogen interactions that researchers need to be aware of. Drug response in carriers and those who transiently acquire the pathogen should not look the same. The infection rates are lower and there probably will not be the same rates of response. But without getting some idea about the strain of pathogen, there is no way to understand whether the child was low or high risk, and likely to respond or not respond to treatment. In terms of epidemiology, in children less than age 6, environment may be a covariate. Researchers may need to look at strategies other than just treating index cases.

Current health department guidelines, diagnostic limitations, and standard of care practices need to be nested into the trial design. Researchers need to think about “intent to treat” analyses, because they cannot just enroll children and wait for a culture positive before starting treatment. Diagnostic limitations are that 30 percent of culture positive children are missed. This study helped show that the standard of care will change with high-burden diseases, and clinicians cannot look at label doses when they are far below standard of care.

**Study Success.** The relationship between the investigator and the community drive study participation. Studies can be successfully conducted in preschool- and school-aged children, as well as in disadvantaged populations. Community-based participatory approaches may be the best for these populations, as parents want a solution to their children’s health problems.

**Participant Questions**

A question was asked about whether noncompliance impacted the study, and Dr. Abdel-Rahman said it would not explain failure rates this high.

Dr. Mike Spigarelli asked whether, given how often pediatricians treat this condition, the symptomology could have nothing to do with the infection. Dr. Abdel-Rahman said they found that about 4 percent of the children have evidence of the disease without the pathogen. There are issues with being able to distinguish symptoms that are relatively nonspecific. Pressure is coming from clinicians, parents, and the community to treat the disease, and it is often overlooked.

Dr. Elaine Siegfried mentioned that not much is known about the efficacy of other treatments, and no data are available about those treatments either.

Dr. Janice Sullivan noted that many trials limit the children who can go into the study, so if they are on more than one medication they cannot participate. She asked what is being done to look at drug interactions. Dr. Snyder responded that design issues are often looked at by FDA divisions. Dr. Hari Sachs from the PMHS commented that sometimes safety and dosing information can be leveraged from existing studies to show differences in drug levels children are expected to receive when they are on monotherapy, as opposed to those taking than one drug.
Updates on BPCA Prioritization and Introduction of the 2012 BPCA Therapeutic Area Working Groups
Perdita Taylor-Zapata, M.D.

The BPCA initiative mandates that the NIH prioritize a list of drugs that need further study in children. The NIH has developed a prioritization process that includes input from the scientific and patient communities in determining this list. Dr. Taylor-Zapata discussed the role of the BPCA Working Groups (WGs), which are also a part of the prioritization process. The BPCA priority list is an outcome of the prioritization process and the goal of the prioritized list is that Pediatric Study Requests will be submitted to the FDA, Written Requests will be developed, and clinical studies will be performed that will inform the drug label. The focus is on off-patent drugs.

The WGs are part of the BPCA mandate to reach out to the community to determine their needs. Three therapeutic WGs are convened each year, and these WGs are asked to assist the NICHD in identifying gaps in knowledge in treatments of their respective disease areas by looking at available evidence, standards of care, and frequency of use. The Rheumatology and Dermatology WGs have come up with the requested information and formed subgroups. They have held conference calls throughout the year to narrow down areas of interest, and they developed paragraphs on those areas that will be presented today. Dr. Taylor-Zapata thanked all the WG leaders and participants and the logistics support team.

Rheumatology Therapeutic Area Working Group
Group Leaders: Mara Becker, M.D., M.S.C.E., Associate Professor of Pediatrics, Division of Clinical Pharmacology and Medical Toxicology, Division of Rheumatology, University of Missouri-Kansas City School of Medicine, Children’s Mercy Hospitals and Clinics
Laura Schanberg, M.D., Professor of Pediatrics, Department of Pediatrics, Co-Chief, Division of Pediatric Rheumatology, Duke University School of Medicine

Dr. Becker presented the work of the Rheumatology WG.

History of the Subspecialty. There has been a question about whether children really do get arthritis. Although there are reports of arthritis in children from more than 100 years ago, national professional organizations did not recognize pediatric rheumatology until the mid-1970s. In 1976, the American Rheumatology Association’s “Park City meeting” had 30 pediatric rheumatologists in attendance. The Pediatric Rheumatology Collaborative Study Group (PRCSG) was then formed to develop standard methodology for the design, conduct, and analysis of drug trials in children with rheumatic disease.

Barriers. Barriers to therapeutic development include:
- Diseases that are rare
- A small workforce (about 270 specialists in the United States), so there is a large clinical need and the research is naive
- Unknown pathophysiology and etiology
- Heterogeneous phenotypes
- Lack of validated outcome measures
- Barriers inherent to pediatric studies
  - Vulnerable population
  - Few biomarkers
  - Ethics/acceptability of placebo
  - Paternalism.

Some of the barriers have been overcome through the work of large organizations. The Pediatric Rheumatology Collaborative Study Group is involved in industry-related studies and collaborates with European colleagues such as The Paediatric Rheumatology InterNational Trials Organization. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) is a North American investigator-initiated network focused on facilitating high-quality collaborative clinical and translational research. The CARRA Registry has been developed over the past 2 years, and 60 pediatric sites and more than 8,000 children are enrolled. There have also been consensus treatment plans, where subgroups develop recommended guidelines for therapy that can be studied over time. The CARRA CoRe is an embellishment of the CARRA Registry that will fulfill Phase IV requirements. They are also interested in collaborating with the PTN.

The first pediatric Rheumatology WG meeting had several themes, including that the field uses a lot of “older” drugs with scant pediatric data to guide their use; formulation remains a major issue; and newer biologics lack indications for common usages.

The disease focuses for the WG subcommittees are:
- Idiopathic uveitis
- Juvenile idiopathic arthritis (JIA)
- Bone biology
- Pediatric systemic lupus erythematosus (SLE)
- Juvenile fibromyalgia.

**Idiopathic Inflammatory Uveitis**

Idiopathic noninfectious uveitis is inflammation of the uvea of the eye. A total of 10–15 percent of blindness in the United States is caused by uveitis and it is the leading cause of acquired blindness in childhood. It is present in 10–20 percent of patients with JIA.

The only FDA-approved treatments for adult and pediatric noninfectious uveitis are topical, oral, or intravitreal steroids, so people are questioning the role of immunosuppressive drugs in refractory or steroid dependent uveitis. It is poorly studied, so current treatment options are based on expert opinion, open-label studies, and anecdotal case series.

**Knowledge Gaps.** The use of methotrexate (MTX) is one of the knowledge gaps identified. It is considered a second-line agent for steroid-resistant uveitis. It is the most commonly used disease-modifying antirheumatic drug, and its safety and adverse effects are well studied in pediatric populations. However, the optimal dose or route for treatment of uveitis is unknown.
Biologics represent another knowledge gap. Cytokine blocking agents are used in MTX-resistant patients. Some data suggest small randomized controlled trials with etanercept are not effective, and open-label trials of infliximab and adalimumab have shown them to be effective in MTX-resistant patients and to minimize exposure to long-term steroids. Etanercept and adalimumab are approved for pediatric JIA, infliximab is approved for pediatric Crohn’s, and there are current trials of adalimumab with uveitis in JIA. The utility of other cytokine blocking agents is unknown, and the utility/indication for biologic use for treatment of uveitis, appropriate dosing, and long-term safety are all outstanding questions.

Subcommittee Recommendations. For MTX, the recommendation is to look at the indication and dosing guidelines in patients who are steroid resistant. These are patients with chronic uveitis who fail a minimum of 4-weeks’ trial of topical, subtenon, intravitreal or oral steroids. Suggestions are to randomize to treat with MTX doses with a step-up approach to dosing, or to have two separate arms (high- and low-dose MTX). It is recommended that outcomes be measured at 6 months and include anterior chamber cell density, intraocular pressure, flare, visual acuity, and ability to taper steroids.

For patients who do not respond to MTX, researchers need to know the indication, dosing guidelines, long-term safety, and the best time to withdraw therapy when using biologics. Anti-TNF-α agents are used most frequently after a failure with MTX. Doses of the agent are used every 4 weeks and the dosing range is enormous. The range goes from 5 to 20mg/kg/doses, and there is very little information about the high doses. If doses are to be studied, there must be some evidence of dose escalation to look at efficacy and safety. Outcome measures recommended are the same as with MTX. There is a question of whether long-term safety and efficacy can be studied using existing information, such as the CARRA Registry. Another question is whether there are any biomarkers for disease activity that can be used to determine when to withdraw therapy.

JIA

JIA is an immunoinflammatory disorder of unknown etiology. It affects approximately 300,000 children in United States alone and has a heterogeneous presentation. Morbidity over time is quite extensive and it has a great impact on the body over time. The 2011 American College of Rheumatology recommendations for treatment of JIA are based on scant strong evidence, utilizing available descriptive studies and expert consensus. CARRA has been working -o pilot different consensus treatment plans for a variety of diseases. The rheumatology community was polled to determine what treatment plans to test. There is a potential for biospecimen samples. Several recommended therapies for JIA do not currently have an indication for use in the disease, particularly anti-IL-1 therapy and infliximab. Long-term large scale safety studies are needed to detect rare adverse events.

Knowledge gaps identified for JIA include the use of Anakinra (anti-IL-1) in systemic JIA. Its optimal dosing remains unknown, and there are no pediatric PK data. Formulations are a huge issue. The injections are painful and difficult to titrate for weight-based dosing. It requires
transfer of drug from the original pre-filled syringes to accommodate for smaller doses, and there can be leftover medication. Data show that a subset of patients are not responsive or lose response over time, but it is not known how to identify these patients.

Another knowledge gap is with infliximab (anti-TNF-α). The trial design used to study this drug could have been better, but it is still used a lot. The optimal dosing remains a question. There have been differences in weight-normalized clearance and volume in children less than 7 years of age, and this could be due to differences in resting energy expenditure. There is a question about when to give it, early versus late. There is variability in response, as up to 40 percent of patients do not respond or lose response over time. Antibodies to the drug are created, raising the question of whether there are ways to predict who will develop them. Long-term safety is still a major concern, including the onset of late cancer development.

The third knowledge gap is long-term, large-scale safety studies, which are important to understand risk versus benefits. Traditional single-product phase IV registries are difficult. Most of these children are on multiple agents serially over time, making it difficult to prove causality. Researchers need to consider the contribution of the underlying disease, so a registry with large numbers of patients with varied medication exposures is needed.

**Recommendations.** The WG recommends studying the following drugs:

- **Anakinra**, which has little PK data. Administering the drug and the right dose are difficult. Efficacy studies are needed for systemic JIA (sJIA), and targeted biomarker studies are needed to determine which sJIA subjects will respond to anti IL-1 versus anti IL-6 therapy. Long-term safety studies using the CARRA Registry and CARRA CoRe will be instrumental.

- **Infliximab**, which is FDA approved for inflammatory bowel disease at this time, but not for JIA. It is used extensively for JIA, and investigating developmentally targeted PK studies to determine if higher doses required in younger children (for example, tocilizumab) would be interesting. Studies are also needed to investigate variability in response to individualized therapeutic decisions, as are long-term safety studies using the CARRA registry and CARRA CoRe. Formal support for these registries from the BPCA members would be appreciated.

**Bone Biology**

Bone metabolism is of concern due to risk factors for osteopenia/osteoporosis. Rheumatic diseases are inflammatory in nature, so they have inflammatory cytokines, which impact bone biology. Also, long-term steroid use has an impact on bones. Bone loss in childhood also increases risks of morbidity in adulthood. Bisphosphonates are FDA approved for treatment or prevention of glucocorticoid-induced osteoporosis, but not in children.

Children with rheumatic disease have decreased bone mineral density and potentially lowered peak bone mass. This is important because during adolescence it is critical to be laying down bone mass. There are challenges in diagnosing osteopenia and osteoporosis in children because there are just recently released pediatric-based references for dual x-ray absorptiometry (DXA), but radiologists may be using adult references.
Bone biology knowledge gaps include bone density assessments and the possibility of misinterpretation of results due to adult norms. The best modality to use for assessment is still unknown. DXA is the gold standard, but what is the role of ultrasound and quantitative computed tomography (QCT)? There are also questions about frequency of monitoring in relation to safety and cost effectiveness.

There are knowledge gaps related to treatment for osteoporosis. Some evidence suggests long-term safety and efficacy of bisphosphonates in children. There have been some pediatric PK studies of zoledronic acid and osteogenesis imperfecta, and studies specific to steroid use in children with rheumatic disease showed sustained increase in bone mineral density (BMD). However, binding to bone and prolonged renal excretion over years still raise long-term safety concerns.

Other knowledge gaps are how to prevent osteoporosis and the role of bisphosphonates in conjunction with glucocorticoids to prevent bone loss. Can researchers better characterize the impact of disease activity with glucocorticoids on BMD?

**Bone Biology Recommendations.** The WG recommends a randomized clinical trial administering a single dose of bisphosphonate in patients started on long-term steroids with DXA monitoring at 3, 9, 15, and 24 months. QCT and ultrasound should also be incorporated to look at the effect of bisphosphonates on bone loss, safety, and appropriate frequency of BMD monitoring and to compare imaging modalities.

**SLE**

Dr. Schanberg said that 15–20 percent of all cases start in childhood and the disease is worse in children. They have higher disease severity and more organ involvement, especially renal and perhaps neuropsychological. They have a much longer burden of disease, and noncompliance is especially acute in the teenage years. These children are given potentially dangerous drugs before their immune system has matured, which could have long-term consequences. Other issues of interest to researchers are that SLE in children has a stronger genetic component, and there are growth and body image issues, particularly for teenagers.

There is very wide variability in treatment and few studies to guide that treatment. CARRA has a consensus treatment plan for nephritis induction therapy and a pilot study is being done for cyclophosphamide versus mycophenolate with three different steroid regimens. There is a high rate of complications, short and long term, with current therapies. Cyclophosphamide is more commonly used in the pediatric age group, probably because of severity of disease in children.

The clinical need is great, as there are no clinical trials in primary pediatric SLE (pSLE) treatment, no drugs specifically indicated for pSLE, and no outcome measures designed specifically for pSLE. A major goal is to reduce lifetime exposure to corticosteroids and cyclophosphamide.
Some of the knowledge gaps include the lowest effective cyclophosphamide dose that can be used, the optimal use of steroids, and the pediatric dose, effectiveness, and safety of hydroxychloroquine use in children.

To minimize the cyclophosphamide load, the WG recommends a clinical trial comparing the efficacy of the Euro-Lupus protocol (low dose) versus the NIH protocol (high dose) for pediatric proliferative nephritis induction. The Euro-Lupus protocol uses a lower dose that is given less frequently. A study could show whether the lower dose is as effective and give information about the effect of high doses. A current pediatric dosing level needs to be established.

**Corticosteroids.** For corticosteroids, the current clinical trial compares the safety and efficacy of intravenous methylprednisolone with cyclophosphamide, mycophenolate, and rituximab. Comparative analyses, PK, and interferon signature and other biomarker studies are needed.

**Hydroxychloroquine.** This drug is used off label for several pediatric rheumatic diseases, such as pSLE, primary Sjogren’s, drug-induced SLE, and JIA. The CARRA Registry currently has more than 1,500 children on this drug and longer-term safety and PK studies could be done to develop age-appropriate dosing. There is a need to develop a liquid formulation and/or smaller tablets to facilitate weight-based dosing.

It would be desirable to develop pSLE specific disease activity measure using data collected from the CARRA Registry.

**Juvenile Fibromyalgia**

Chronic pain is common in pediatrics. Twenty-five percent of new patients seen by pediatric rheumatologists have headaches, musculoskeletal pain, and abdominal pain, and 25–40 percent of children with chronic pain meet the criteria for fibromyalgia. The prevalence varies from 1 to 6 percent, depending on the study, and studies suggest long-term pain problems.

In 2005, the American Pain Society put out consensus management guidelines with modifications based on the children’s age, developmental level, and social environment (for example, less medication than for adults). Age-appropriate outcome measures exist, including pain, quality of life, anxiety, functional disability, and others. It has been difficult to identify patients for studies, as these children often see many specialists rather than just rheumatologists.

The subcommittee decided not to address purely analgesic drugs, but based recommendations for study of drugs based on proposed mechanism of action relative to proposed pathophysiology, drug availability and cost, coverage by Medicaid and third-party payers, lack of pediatric labeling, and the unlikelihood of industry development.

The clinical needs are that no medications are labeled for use in juvenile fibromyalgia, there are no studies looking at drug treatment, and drugs are commonly used off label in children and adolescents with fibromyalgia, particularly amitriptyline and venlafaxine.
**Knowledge Gaps.** Knowledge gaps for juvenile fibromyalgia focus on amitriptyline and venlafaxine. There are no data on efficacy of either agent in juvenile fibromyalgia, no good PK/PD/pharmacogenetic data for either agent in pediatrics, and no data looking at the concentration of the active moiety of the parent plus the active metabolite in pediatric patients. The drugs are used off label for pediatric headache and abdominal pain.

**Recommendations.** The subcommittee recommends clinical trials testing the efficacy of amitriptyline and venlafaxine in pediatric fibromyalgia, incorporating PK and PD studies to identify core metabolizers and extensive metabolizers.

**Summary.** The WG’s conclusions are that there are multiple therapeutic needs in rheumatology and a major lack of evidence-based knowledge. Clinical pharmacology input and collaboration will be instrumental in this work.

**Participant Questions**

Dr. Nielsen asked how a pediatric patient is defined. Dr. Becker responded that it is defined as children younger than 16 years of age, according to the definition of JIA. Dr. Schanberg noted that lupus uses age 18 as the cutoff. Dr. Nielsen asked whether it is important to understand pharmacology based on something other than an arbitrary age limit. Dr. Becker agreed and said it might be better to look at hormones, puberty influence, and the entire continuum of childhood. Dr. Schanberg said a trial was done on pediatric patients with lupus and found that the only differences were when the group was broken down by Tanner stages.

Dr. Gordon Klein noted that the proposed bisphosphonate study would give the single dose intravenously rather than orally.

**Dermatology Therapeutic Area Working Group**

*Elaine Siegfried, M.D., Professor and Division Director, Department of Pediatrics and Dermatology, Saint Louis University Medical School*

Dr. Siegfried first gave an overview of pediatric dermatology. It is a small specialty that has a large demand, accounting for 30 percent of pediatric primary care visits. It is ambulatory based and does not generate much hospital revenue. The work is more medical than procedural. There is limited evidence basis for treatment, and few FDA-approved treatments are available. Pediatric dermatologists treat children with very serious, life-threatening diseases and chronic conditions.

Internationally, the biggest society for dermatology is the American Society of Pediatric Dermatology, with 1,000 members in 45 states and 37 countries. The subspecialty earned certification in 2004 by the American Board of Dermatology (ABD). The certification exam is done every other year, and 232 pediatric dermatologists have been ABD-certified.

Some of the challenges associated with management of children with skin diseases include: limited opportunities to provide training to primary care providers, a high proportion of Medicaid
patients (with increased numbers of patients with limited socioeconomic resources and language barriers), limited formularies, and few medications with labeled indications.

The WG had a large number of members. Four unmet needs were identified during a series of conference calls: atopic dermatitis, hemangioma of infancy, epidermolysis bullosa and other genodermatoses, and pediatric dermatology drug development.

**Atopic Dermatitis (AD)**

**Clinical Features.** AD is a chronic, recurrent, inflammatory skin disease characterized by widespread redness, edema, scaling, and crusting. The major morbidity is severe itch, often interrupting sleep for the patient and multiple family members. The patients have a lifelong tendency toward dry skin, occupational skin disease, skin infections, eye problems, disrupted family and social relationships, and work/school absenteeism.

**Pathogenesis.** AD is a phenotype, representing a group of conditions caused by genetic and environmental factors responsible for skin barrier defects; increased susceptibility to bacterial, viral, and fungal skin infections; and immune dysfunction.

**Epidemiology.** The typical onset is younger than 2 years (in 80 percent). Most children with the disease have mild AD, which usually improves over 10 to 15 years. About 40 percent have moderate to severe AD, which is life altering. There has been a 300 percent rise in prevalence over the past 30 years. It has a strong genetic link with other allergic conditions.

An increasing number of non-allergic comorbidities have been identified, including: sleep deprivation, neuropsychiatric disorders (ADHD, anxiety, depression, autism), poor growth, osteopenia, and cataracts.

**Therapeutic Issues.** One of the biggest therapeutic issues is that early intervention and disease control may favorably impact progression and comorbidities. This disease is treatable, but poor adherence is a common cause of treatment failure. Commonly prescribed topical treatment for AD is time-consuming, complex, and difficult to master. The obstacles to adherence are difficult treatment regimens, no well-defined standard of care, conflicting recommendations from doctors, medication phobias, and drug labeling/access restrictions.

**Principles of First-Line Treatment.** Patients are given skin care education about avoiding complex topical products, bathing, and using emollient; ways to control itch and skin infection; and topical medications that can be used (corticosteroids and calcineurin inhibitors).

There are many topical corticosteroids that have FDA labeling, but safety/efficacy data are limited. The two FDA-approved topical calcineurin inhibitors (TCIs) are labeled as second-line therapy “for short-term and non-continuous chronic treatment of AD in nonimmunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for AD.” However, this is not how the medication is generally
used in practice. These drugs are most often used as a steroid-sparing adjunct to augment treatment with topical corticosteroids in children who require daily medication. A first-line use is for facial and skin fold dermatitis.

**TCI Labeling Change.** In 2003, sales of TCIs rose, due to an unmet need for a corticosteroid-sparing agent and a desire to avoid topical steroids. In January 2006, a boxed warning came out based on a theoretical risk of malignancy. This resulted in a firestorm of confusion and drug phobia, followed by third-party payor restrictions, creating a significant dilemma for prescribing dermatologists. Subsequent studies involving large numbers of patients have not identified a significant risk, and mandated post-marketing surveillance studies are in process.

The WG’s recommendation for mild to moderate AD is to reevaluate the evidence of TCI use. There is a hope that labeling may be revised to reflect safety and efficacy of pimecrolimus cream in infants ≥ 3 months.

**Severe AD.** There is no FDA-approved systemic therapy for severe AD, a chronic and relatively common disease that is a therapeutic challenge. The current standard of care is with off-label, level 3 evidence-based drugs: immunosuppressive (cyclosporine, azathioprine, mycophenolate mofetil) and cytostatic agents (methotrexate), or immunomodulators (IVIG, IFN-gamma). Few new chemical entities are being evaluated in early-phase, adult-only trials.

**Existing Resources.** There is an international core outcomes consortium called the Harmonizing Outcome Measures for Eczema (HOME) and a U.S.-based multicenter research network called the Pediatric Dermatology Research Alliance (PeDRA), which is currently conducting an Inflammatory Skin Diseases Group unfunded comparative study of cyclosporine, azathioprine, mycophenolate mofetil, and methotrexate.

**Committee Recommendations:**
- Provide funding to expand clinical trials of systemic therapies for severe AD initiated by PeDRA
- Encourage drug comparison efficacy studies, rather than placebo-controlled trials
- Include children as young as age 2 with severe AD in trials involving systemic immunosuppressant medications and new chemical entities
- Develop and validate standardized outcomes measures for pediatric AD across the age spectrum.

**Genodermatoses.** Epidermolysis bullosa (EB), a subset of genodermatoses, is a rare, inherited condition of skin fragility and blistering, with significant early morbidity and mortality. It is thought of in three terms: junctional, dystrophic, and simplex. They are all crippling and often fatal diseases with many comorbidities. The costs of managing EB are high and optimal care is via tertiary centers that support a coordinated team. There are no FDA-approved therapeutic agents available for any subtype or age group.
There have been advances in research and 15 genes have been identified to cause various forms of EB. Recent therapeutic strides applicable to patients with severe forms of EB include new methodology for gene replacement, protein replacement, and biologic therapy.

**WG Committee Recommendations:**

- Provide funding to expand the EB Clinical Research Consortium National registry/database
- Centralize genetic testing results
- Identify potential subjects for clinical trials
- Registry expansion should occur in parallel with clinical studies to allow maximum progress
- Support studies to test and validate outcome measures
- Initiate therapeutic trials in adults
- Define inclusion criteria for children with severe EB subtypes to enable early enrollment in the same trials
- Develop parameters to maximize safety for the youngest age groups
- Encourage fast-track FDA approval for EB drugs.

**Hemangioma of Infancy**

This is the most common tumor of childhood and impacts about 80,000 infants per year in the United States. Most do not need treatment, but about 12 percent have severe tumors that require intervention. Complications necessitating treatment include disfigurement, ulceration/pain, visual impairment, airway obstruction, and congestive heart failure. There are no FDA-approved treatments, but there is one industry-sponsored, phase II/III international multicenter, placebo-controlled double-blind trial that is scheduled for FDA presentation in January 2013. There is also an existing research network, the Hemangioma Investigator Group (HIG), which has been prolific.

**Treatment Options.** Off-label oral and topical beta blockers have rapidly been adopted as first-line therapy, including propranolol suspension. There were 30,000 more prescriptions for this drug in 2011 than in 2007. Timolol ophthalmic is another non-selective beta blocker available as gel solution now commonly prescribed for topical application by a variety of clinicians as a presumed safer alternative. However, it is more potent than propranolol, and adverse events have been reported, such as bradycardia, hypoglycemia, and wheezing. It is anticipated that off-label use of these drugs will continue to increase.

**Oral Beta-blocker Clinical Needs.** Additional safety/efficacy information is needed for oral beta-blockers, as is validation for consensus-derived guidelines. Other needs include information about monitoring, dose escalation, age initiation, use in preterm infants, use in PHACE/LUMBAR syndrome, duration of treatment, and guidelines for discontinuation of use.

**Topical Beta-blocker Clinical Needs.** Clinical needs for topical beta-blockers include safety/efficacy/PK data, oral/topical comparative data, dosing guidelines, indications for use, safety and efficacy for the treatment of ulceration and periorbital lesions, and use in premature infants, especially those <2 months old.
Existing Resources. PeDRA is a U.S.-based multicenter research network that includes HIG, which has been responsible for the majority of recent studies related to pathophysiology and epidemiology of this condition.

Committee Recommendations:
- If the Pierre Fabre oral propranolol formulation receives FDA approval, there remains a desperate need for additional studies to evaluate safety/efficacy of oral propranolol for complicated cases, including PHACE/LUMBAR syndrome and affected premature infants <3 months old.
- Utilize expertise within the PTN, NICHD, HIG, and industry to design and perform these studies.
- Standardized safety reporting protocol to track likely adverse events for infants enrolled in beta-blocker studies.
- Phase I/II studies of percutaneous application of timolol maleate ophthalmic solution.

Pediatric Dermatology Drug Development Issues

Many skin-related conditions in children are common and costly in economic terms. Many are chronic, cause significant morbidity, carry substantial comorbidity risks, generate emotional distress, and markedly impair quality of life for the affected child and family. The unmet need is high for safe/effective treatments for children with chronic and severe pediatric dermatologic diseases.

Major obstacles hinder new drug development for pediatric skin diseases, including:
- Product labeling that overemphasizes theoretical risks of new treatments compared to well-established risks of poorly controlled, chronic disease
- Underappreciated risks of adverse events from widespread off-label use of drugs that lack evidence-based treatments
- No well-defined risk parameters or guidelines for development of new drugs in children with non-lethal, but life-altering disorders.

Goals:
- To state the need for well-defined regulatory clinical development pathways to inform, facilitate, and incentivize new treatments for severe and chronic pediatric skin diseases
- To generate an official request to seek input from experts in order to draft a guidance document for FDA review and modification per the Current Good Guidance Document Practices
- To offer initial suggestions for inclusion into a Level 1 Guidance Document for New Drug Development in Pediatric Dermatology.

Guidance Document Suggestions:
- Develop optimal packaging to assist in delivery of appropriate amounts of topical medication
- Determine optimal topical dosing quantities
- Do not postpone early phase drug trials in infants and children until after efficacy is determined in adults.
- Do not exclude drugs that have not achieved proven efficacy in adults as presumably ineffective in children.
- Do not place higher priority on theoretical risks of new drugs than on established morbidity and impact on quality of life for pediatric skin disease
- Determine age limits for initial trials based on the drug and the disease:
  - Include premature infants with a newly detected hemangioma of infancy in trials of a topical beta-blocker
  - Include children as young as age 2 with severe AD in trials involving systemic immunosuppressant medications
- Apply adverse event data for drugs that have been studied for other pediatric indications to further study of skin disease in children.

Dr. Siegfried asked that attendees be attuned to the Harmonizing Outcome Measures for Eczema (HOME) project (http://www.homeforeczema.org). HOME is a group of experts working together to agree on a core set of outcome measures for use in all AD clinical trials. HOME III will be held in April 2013 in San Diego, CA. Representatives from the European Medicines Agency will be participating, and similar FDA participation would be optimal.

The WG recommends incorporating input from parents of affected children in clinical trials protocol design through surveys seeking parental opinion on tolerable washout periods, acceptable duration for placebo exposure, achievable frequency of study visits, tolerable number of phlebotomies and skin biopsies, and what they consider to be worthwhile outcomes. They also suggest requiring use of microtainer technology for routine hematology and chemistry assays.

Attendees were asked to support PeDRA, a currently unfunded network to facilitate design and conduct of clinical trials, share resources, and garner sufficient cohorts to study pediatric skin diseases.

**Final Committee Recommendations:**
- Recognize new drug development as a significant unmet need for children with severe and chronic skin disease
- Appreciate the importance of an FDA-issued guidance document relevant to new drug development for children with severe and chronic, but non-life threatening skin diseases.

The committee is aware that 21CFR10.115 specifically encourages submission of subjects and drafts to the FDA for consideration and modification towards creating guidance documents. It is hoped that this background information provided can be applied toward developing a level 1 guidance document for new drug development for the top three identified areas of need: hemangioma of infancy, epidermolysis bullosa, and atopic dermatitis as a first priority.

Dr. Siegfried said she hopes there will be additional support to convene a working group of experts to create an initial draft for review and modification by the FDA. The ideal working group would include participants with expertise in clinical care of children with skin disease, drug development for skin disease, pediatric drug development, and guidance document design.
Questions and Answers

Dr. Murphy said she is delighted to see a dermatology group involved. But she noted that the black box warning for TCIs was not just a theoretical risk. It was developed by an FDA safety committee that looked at clinical cases in children and adults. The concern was there, and the FDA would rather be safe than sorry. The FDA needed additional safety data, which they are now getting. If more information is gathered, the warning can be revisited. She also noted that the risk with comparison-only studies is that they need a larger effect size and delta impact, or efficacy cannot be demonstrated. She suggested thinking about other types of studies. Dr. Siegfried said she is glad to hear the door is not closed.

Dr. Richard Gorman said he heartily endorse the recommendation for grade I guidance documents, as they are enormously helpful. What amazes him is what has not been approved for pediatrics (for example, analgesics). He asked about systemic AD and what they will begin studying. Dr. Siegfried said immunosuppressants are currently the standard of care. Antihistamines do not help with AD. Systemic corticosteroids give short-term relief, but they get rebound and can contribute to the disease. There are not enough data currently available.

Dr. Michael Reed asked about efficacy of the beta 1 specific drug. Dr. Siegfried said there is only anecdotal evidence at the present, but the door is now wide open because of the efficacy of propranolol.

Wrap Up/Discussions

Perdita Taylor-Zapata, M.D.

Dr. Taylor-Zapata thanked all the presenters and discussed where the group goes from here.

The initial legacy studies are all completed and the CSRs are being submitted. The PTN studies will continue and will look at moving forward with recommendations, and prioritization will continue based on this meeting’s recommendations. The working groups will now receive a formal response from the NIH and FDA about their recommendations, starting in early spring 2013. The new working groups will also begin in early 2013. In summary, the BPCA is committed to moving forward.

Dr. Taylor-Zapata thanked everyone for their time and dismissed the meeting.

Participants

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