Eunice Kennedy Shriver
National Institute of Child Health and Human Development (NICHD)
National Institutes of Health (NIH)

2022 Best Pharmaceuticals for Children Act (BPCA) Stakeholders Meeting

December 8-9, 2022

Meeting Summary

Purpose: The purpose of this meeting was (1) to provide updates on the Best Pharmaceuticals for Children Act (BPCA) Clinical Program at the National Institutes of Health (NIH) and (2) discuss the current state and future needs for pediatric drug development.

Day 1: Thursday, December 8, 2022

Welcome, Introductions, and Overview of Meeting Goals

Perdita Taylor-Zapata, M.D.
Medical Officer
Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB), NICHD, NIH

Dr. Taylor-Zapata welcomed participants to the 2022 BPCA Stakeholders Meeting. Over time, and especially post-COVID, researchers have reflected on the possibility of a paradigm shift in pediatric drug development, which has historically followed behind adult drug development.

The Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) have had a dramatic impact on pediatric drug development. The BPCA has two main components: the FDA's work with pharmaceutical companies and drug companies to conduct pediatric trials with mostly on-patent drugs; and the NIH's work with an off-patent drug development program under Section 409i of BPCA. The NIH BPCA program has evolved over the years, to include the addition of the Pediatric Trials Network (PTN) in 2010, as well as all of the broadening of the program's key responsibilities that include prioritization and dissemination, clinical trials, pharmacology training, and translational research. Dr. Taylor-Zapata outlined the meeting agenda and noted that the purpose of the meeting was for NIH to provide updates and collect participants' feedback about the NIH BPCA program and to have an open dialogue about the current status and future direction of pediatric drug development more broadly.

NICHD Updates and Perspective

Aaron Pawlyk, Ph.D.
Chief, OPPTB
NICHD, NIH

Dr. Pawlyk noted that this was his third BPCA meeting, and a lot has happened in those three years. He shared several achievements of the Pediatric Trials Network (PTN) and noted that NICHD has also developed the BPCA Pediatric Drug Development Framework, led by Dr. Taylor-Zapata, which will continue to evolve over time.

In addition to the important work funded by BPCA, there are several other NICHD-supported initiatives that focus on medications for pediatric and maternal health:

- The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) was established as part of the 21st Century Cures Act to advise the Secretary of Health and Human Services (HHS) regarding gaps in knowledge and research on safe and effective therapies for pregnant and lactating women.
- A new institutional career development (K12) program has been developed as part of the BPCA's training mandate. This program will provide support to institutions that mentor clinical fellows and scientists and help them become independent research investigators.
- The Maternal and Pediatric Precision in Therapeutics Hub (MPRINT), supported by both BPCA and PRGLAC recommendations, collates data and generates new tools to support drug development for pediatric and maternal pharmacology.

Under the leadership of Dr. Lesly Samedy Bates, the NICHD is exploring ways to support pediatric pharmacology training and career development across a cohesive pipeline, such as through the addition of a K12 component. The Institute is also reassessing how it conducts training and career development activities to make sure that researchers establish themselves in careers and ensure a diverse workforce. NICHD is in discussions with the Foundation for the NIH to consider how to work in the drug development space for pediatric and maternal populations more broadly. There are also increasing NICHD interactions with the National Academy of Sciences related to inclusion of pediatric and maternal populations in drug discovery and development.

As COVID has changed society in radical ways over the last three years, more researchers have learned about the need to include pediatric and maternal patients earlier in studies and the challenges to doing so. Dr. Pawlyk noted that as the pandemic recedes, there is an opportunity to reflect on lessons learned from COVID and apply them to the future of pediatric drug development.

Advancing Pediatric Therapeutics: Regulatory Perspective

Prabha Viswanathan, M.D.
Deputy Director
Office of Pediatric Therapeutics, FDA

Dr. Viswanathan began her presentation by listing general principles of pediatric drug development and presented a timeline of historical milestones and legislation in pediatrics. She noted that it was not until the 1990s that incentives and requirements were developed to have medical products evaluated in children, which were formalized under BPCA and PREA. She also noted the inclusion of orphan drug designations, which helped to incentivize development of medical products to treat diseases that impact only a small number of patients. She clarified that products with orphan designation are generally exempt from PREA requirements under the current regulations, with the exception of some cancer drugs. Dr. Viswanathan noted that the Research to Accelerate Cures and Equity (RACE) for Children Act of 2017 requires Sponsors to consider pediatric investigations for adult cancer drugs that act on a molecular target that is substantially relevant to pediatric cancers, irrespective of whether that product has orphan drug designation.

Dr. Viswanathan presented a schematic of the new drug and biologics development process for the U.S. and the European Union (EU). She noted that there is a desire to align global development programs to improve the feasibility of conducting pediatric clinical trials and generating data that can support regulatory action. The EU asks for a pediatric investigational plan (PIP) fairly early in drug development, while FDA requests an initial pediatric study plan (iPSP) a little later in the development process. When products receive marketing authorization in the U.S., the pediatric trials that were previously proposed in the iPSP are revisited, and the necessary pediatric trials are requested as PREA post-marketing requirements (PMRs). Sponsors are held accountable to complete these pediatric studies within a pre-specified time frame. In the U.S., Sponsors can ask FDA to issue a Pediatric Written Request in parallel with the process of establishing and revising the iPSP and issuing PREA PMRs. Authorities under BPCA allow FDA to provide marketing exclusivity when Sponsors complete the studies outlined in the Pediatric

Written Request, which often overlap with studies requested under PREA, but may also address other potential pediatric indications.

As of September 2022, there have been more than 1,000 pediatric labeling changes for drugs and biologics, including five labeling changes for two COVID-19 products. From 1998 to 2021 there has been a steady increase in the number of pediatric labeling changes completed each year. Dr. Viswanathan noted that these changes are not evenly distributed among therapeutic areas; the fields with the greatest number of pediatric labeling changes include infectious diseases, dermatology, and psychiatry. Through the 409i program there have been 17 off-patent labeling changes for 10 active drugs. These changes provided pediatric dosing and safety information that providers greatly needed and addressed important gaps in pediatric labeling, including dosing for neonates and obese children.

The FDA is involved in several programs and initiatives to optimize pediatric development. Dr. Viswanathan outlined several FDA Guidance documents that have been published in the past year which address diverse topics impacting drug development for children across the age range, including neonates. She also highlighted the aforementioned RACE for Children Act, which became effective in August 2020, and requires Sponsors to investigate the potential utility of adult oncology products that might be beneficial for the treatment of pediatric cancers. The FDA also has a Rare Pediatric Disease Priority Review Voucher Program to incentivize development for rare pediatric diseases, which is a challenging area for many reasons, including smaller patient populations and market share. As of 2021, FDA has granted over 480 rare pediatric disease designations for over 220 unique pediatric diseases. They have also awarded 32 vouchers at the time of marketing authorization, and 25 of those 32 products were the first approved therapy for the indicated disease.

Dr. Viswanathan addressed several ongoing challenges for the FDA and other key stakeholders in pediatric drug development. She noted the PREA exemption for orphan drugs, which continues to be a challenge for rare diseases. Delays in pediatric labeling continue to be an issue due to factors such as staggered pediatric enrollment by age groups, delays in age-appropriate formulation development, and recruitment and enrollment challenges. Also, neonates continue to be an underrepresented population in clinical trials, and as a consequence, there are persistent gaps in product labeling for neonates and preterm infants.

Looking forward, the FDA intends to use past success as a model for future development, recognize the challenges they continue to face in supporting pediatric clinical research, and work collaboratively to improve efficiency, feasibility, and timeliness of pediatric clinical trials.

NIH BPCA Reflections: In the Air & On the Ground in the Pediatric Drug Development Space

Perdita Taylor-Zapata, M.D.

Dr. Taylor-Zapata presented an update on the BPCA Program at the NIH, its progress and challenges, and future steps. The program's goals are prioritization, the clinical program, which includes the PTN, and dissemination. The first BPCA priority list was published in 2003, with the program's first clinical trial initiated in 2004. The PTN was launched in 2012 and awarded to Duke Clinical Research Institute (also including the data management and statistical infrastructure provided by the data coordinating center, EMMES since 2009) to provide an infrastructure for effective research. FDA submissions of trial results started in 2009 and Label changes began in 2012 and continue through the present. The program began submitting data to the Data and Specimen Hub (DASH) since 2016. As the science of research evolved, the clinical program introduced master protocol designs around 2017 which serves to provide a continuing pipeline of drugs to be studied in children. More recently, the BPCA Framework resource was developed in 2021 as a one-stop resource of articles and guidelines available in pediatric drug development.

Dr. Taylor-Zapata outlined the BPCA Program's work in each of their three primary goal areas. In order to prioritize research needs, the program considers emerging safety concerns, public input, and research gaps and determines whether those prioritized studies can feasibly be conducted within the program's infrastructure. The program has developed this prioritization process over many years, and they are currently reviewing the process itself and the stakeholders who are involved. This involves focused outcomes, approaches, and expectations.

For the PTN and clinical program, success is defined by improving dosing, safety information, labeling, and ultimately child health. Of the label changes submitted to the FDA thus far, the majority have come in the past five years, largely as a result of master protocol and opportunistic design models that collect pharmacokinetic (PK) data for modeling. Dr. Taylor-Zapata summarized one of these label changes, which came from a study of acyclovir in preterm and term neonates. She also shared two study examples: the Pediatric Opportunistic PK Study (POPS), where understudied drugs are administered to children per standard of care;

and Pharmacokinetics and Safety of Commonly Used Drugs in Lactating Women and Breastfed Infants (CUDDLE), which studies dosing of drugs given to lactating mothers and transfer of the drugs into breast milk.

In the area of dissemination, the program's submissions to the DASH have generated data sets that are available to researchers and had resulted in secondary publications. The BPCA program is involved in innovative partnerships with organizations such as the International Children's Advisory Network (iCAN) to discover how to reach the pediatric population and engage them earlier in the trial design process. The BPCA Framework provides articles and guidelines related to pediatric drug development, and the program is working towards making this a web-based resource. In terms of next steps, NICHD is redefining and establishing the program's goals; promoting the value of the program through toolkits and trainings; creating an environment and platform for innovative research paths, collaborators and resources; and expanding engagement with researcher, provider, and patient communities.

Off-Label, but On-Evidence? From Problem to Solution

Saskia N. de Wildt, M.D., Ph.D.
Radboud University Medical Center

Dr. de Wildt gave a presentation on some of her team's work with off-label pediatric prescribing in the Netherlands. All practitioners in the Netherlands use the Dutch Pediatric Formulary, which was developed 15 years ago as clinicians were attempting to harmonize doses of drugs given to children, supported by evidence from scientific studies and practice. The Formulary is an online resource that provides drug doses, and these are determined by a team of pharmacists who summarize the literature around the drug in a draft monograph and risk analysis. This is then presented to a multidisciplinary editorial board, including pediatricians, clinical pharmacologists, and hospital pharmacists, which reviews the information, reports a decision and publishes a monograph. When Dr. de Wildt became the Director of the Formulary in 2015, she made it her goal to expand the Formulary beyond the Netherlands, and as of 2022 four countries share the information in the Formulary.

Dr. de Wildt noted that regulators demand proof of efficacy and safety, but just because a drug has not been researched does not mean that it is ineffective or unsafe. The Formulary's position is that it is not unethical to base decisions about drugs on limited information, as long as the decision is based on a careful evaluation of risks and benefits. They became involved in crafting several guidelines for off-label prescribing, including those initiated by the European Brain

Council and a more pediatric-specific statement from the European Academy of Paediatrics and the European Society for Developmental Perinatal and Paediatric Pharmacology.

Dr. de Wildt and her team also developed a benefit-risk assessment to support decision-making for off-label drug use in children. This assessment is systematic and considers the right dose and what is known about efficacy and safety. While they have published the framework, they do not yet have the resources to test its effectiveness and the time it takes to complete.

In order to find evidence to support off-label use, Dr. de Wildt and her team were able to use the more than 800 drugs in the Dutch Pediatric Formulary, 90% of which are prescribed to children across the world. For each of these 800 drugs, there were on average two indications and five age groups. During COVID, they enlisted medical students to read through the evidence documents and score drug indication age groups for the highest level of evidence available. They found that for approximately 250 drugs, with two indications and more than one age group, there was a low level of evidence. Studies show that more adverse events occur when off-label drug use is not supported by evidence, but conducting new studies for each of the 250 drugs with low evidence is not feasible. In order to solve this problem, several steps are necessary: creating a new decision tree for evidence generation; reaching international consensus on how to prioritize which drugs to study; constructing a research agenda broken down by subspecialties; then generating new evidence and implementing it in practice.

Dr. de Wildt noted that the traditional drug development paradigm has a heavier focus on Phase 2 and Phase 3 trials, extrapolates from adults to children, and assumes that necessary studies are done prospectively. She suggested that researchers should look to other data sources to support evidence generation, such as physiologically-based PK modeling (PBPK) and existing population pharmacokinetics (popPK) data. Dr. de Wildt presented work that she and her team had done in each of these areas. One of their papers included a decision framework for clinical implementation, which takes into account factors such as: the certainty of target concentrations; the clinical risk of over or under dosing; the certainty of model output; adequate target exposure of the current dose; which dose results in a significantly better target exposure; whether the proposed dose is practical; and whether the population in the published PK model was comparable to the target population.

Dr. de Wildt emphasized the potential of using and collating published data and developing innovative methodologies to use real world data. Bringing published data from evidence generation to the label is an ongoing discussion of the European Network of Paediatric

Research at the European Medicines Agency (Enpr-EMA). She summarized three examples of off-label use with published evidence done by Enpr-EMA's off-label working group members with dexmedetomidine, estradiol, and tocilizumab. Her team is working with this group on a proposal to include more pediatric data in the medicine label, through a consistent guideline and benefit-risk assessment procedure by the regulators, financial incentive for academic groups to prepare data packages, and support from all stakeholders. Dr. de Wildt also shared some factors to consider when prioritizing drugs to study: disease burden; epidemiology; risk and cost of therapy failure; risk and cost of toxicity; existing evidence; the need for an appropriate formulation; and other available alternatives. She concluded her presentation by sharing her goal that by 2035, every child will receive effective and safe medicine.

Status of Pediatric Drug Development

Moderators:

Phil Walson, M.D.
University Medical Center Goettingen, Germany

Katie Vance, Ph.D.
Program Officer, OPPTB, NICHD, NIH

Panelists:

John Alexander, M.D., M.P.H.
Deputy Director
Division of Pediatrics and Maternal Health, FDA

Danny Benjamin, M.D., Ph.D.
Faculty Associate Director
Duke Clinical Research Institute

James Feinstein, M.D.
Clinical Research Director
Children's Hospital of Colorado

Mark Turner, M.D., Ph.D.
Professor of Neonatology and Research Delivery
University of Liverpool

Jian Wang, Ph.D.
Head of Translational, Oncology Regulatory Science, Strategy & Excellence
AstraZeneca

Shetarra Walker, M.D.
Clinical Team Leader
Office of Rare Disease, Pediatrics, Urologic, FDA

Kevin Watt, M.D., Ph.D.
Chair, Clinical Pharmacology
University of Utah

Leanne West
President
The International Children's Advisory Network Inc. (iCAN)

Dr. Vance introduced the panelists and invited participants to place questions in the chat. **Dr. Walson** presented the first question for panelists: How well is the FDA's support for pediatric drug development integrated with the European Medicines Agency (EMA) and other international bodies?

Dr. Walker noted that the FDA is involved in international collaborative discussions, including pediatric-focused discussions, with health regulatory agencies. Their Office of Pediatric Therapeutics hosts monthly Pediatric Cluster teleconferences with the EMA, Japan's PMDA, Health Canada, and Australia's Therapeutics Goods Administration, during which participants discuss ethical, scientific, safety and regulatory issues affecting global pediatric product development programs. FDA's Common Commentaries communicate informal, non-binding comments to sponsors. **Dr. Turner** said that the Clusters do work well and deliver useful advice to companies, but there are increasing calls for more to be done. Global drug development is needed for underserved populations and rare diseases, and this must include all stakeholders from the beginning. Ideally sponsors would have a single global development plan that could bring stakeholders together in a systematic way, but the scope is currently limited by resources and policy decisions.

Dr. Walson asked what the United Kingdom's current position was in the EMA post-Brexit. Dr. Turner said that the UK does not have a position in the EMA, but regulators do borrow

information from each other and data can cross borders, with oversight from the World Health Organization. Dr. Walson presented a question from Bob Ward in the chat: are adverse outcomes cited as a reason not to change a label to include pediatric patients in Europe, as they are in the U.S.? Dr. Turner said that in his work across 20 countries he had never heard this as a reason to avoid label changes. Finance and reimbursement were more likely to cause issues. Dr. Walson said that there were good models for how regulatory agencies could work together, but there are many legal barriers to implementing them.

Dr. Walson presented the next question: How are public-private partnerships or other similar business models being used to advance pediatric drug development? Dr. Walker gave the example of the Centers of Excellence in Regulatory Science and Innovation (CERSI), a public-private partnership that fosters collaboration with external stakeholders through research, lectures, workshops, and fellowships to encourage innovation in regulatory science. The Division of Pediatrics and Maternal Health has leveraged the CERSI tool to hold workshops that focus on strategies to advance pediatric therapeutic product development. **Dr. Wang** said that public-private partnerships are valuable in identifying priority areas to address unmet needs, sharing data, and collaborating to develop new tools and methods to facilitate innovations and optimize development. They also offer an opportunity to include the patient voice and perspective, which is crucial for drug development.

Dr. Turner added that the European approach to public-private partnerships is extremely institutionalized; for example, the Innovative Health Initiative is funded by the European Commission and pharma, device and medical technology companies, and it addresses specific issues in product development. Transatlantic and global collaboration could be very helpful in this area. **Ms. West** gave an overview of iCAN's work. She noted that iCAN works with industry to assist in their drug development processes in many ways, such as improving recruitment in clinical trials by identifying elements that make them more appealing to the youth population.

Dr. Walson noted that more work needs to be done to establish global collaborative funding. He asked the panelists how emerging clinical trial designs, such as platform or master protocols, were being leveraged to accelerate pediatric drug development. **Dr. Watt** said that the PTN has pioneered several opportunistic studies and master protocols that have helped enroll and study drugs in children, including the POPS and the CUDDLE studies. Both studies have been successful and enrolled many participants, and the resulting data has been used either to directly change labels or to combine with dedicated studies of particular drugs. **Dr. Benjamin** said that opportunistic studies and master protocols help to solve problems of startup and

enrollment, as well as participant and family preferences. He added that many novel study designs are easier talked about than conducted, and he was glad to see that master protocols from the studies that Dr. Watt mentioned had been used to submit label changes and emergency use authorizations.

Dr. Walson asked whether panelists had seen a trend for more active engagement among children and adolescents and not simply their parents, and what the outcome of that approach has been. Ms. West said that there is a trend in that direction and that talking to the patients can have huge impacts on trial designs. Children are the experts on living with the conditions, drugs, and treatments being studied, and they want to be engaged in the process. **Dr. Feinstein** agreed and said the trend toward active engagement was particularly prominent during the COVID vaccine development and rollout, where many youth and young adults participated in initial trials and post-marketing voluntary reporting programs. Incorporating patient and family voices into the stages of pediatric research helps overcome barriers to participation, and the more involved children are in the process, the more researchers can tailor their studies to fit patient and family needs. Technology has also been an important tool to engage youth in research activities, by allowing participation in study-related activities through virtual communication and clinical data collection through digital health technologies.

Dr. Walson asked panelists to comment on the current pathways to approval and timelines for pediatric drug development, including pediatric-only diseases, and how they could be improved. Dr. Alexander said that the main path to approval, which is based on PREA's requirements, starts with drugs that are used on adults and then applies those to children who have similar conditions. The associated timelines do not work when trying to figure out how to get new drugs approved that address needs specific to children. When a condition occurs mainly in children and there is no interest in developing an associated drug for adults, researchers need to figure out how to conduct the needed studies in the pediatric population to advance the pediatric drug development timeline.

Dr. Watt said that when applying for label changes, the PTN has had success partnering with the FDA's pediatric group to help review divisions understand the nuances of pediatric studies. He agreed with Dr. de Wildt that they should look at using the aggregate of published data to inform the label and noted that the work on ampicillin involved modeling and simulations with existing data to show the correct dose. Dr. Alexander said that this had also been used for some of the labeling changes under 409i, but more work is needed for conditions that only occur in pediatric populations, and this process still falls within the paradigm of figuring out how to

apply drugs that are effective in adults to pediatric patients. Dr. Walson added that there were several comments in the chat about respect for pediatric patients in the pre-IND process and the need to involve nurse practitioners, pediatric nurses, and pediatric pharmacists in designing drug trials.

Dr. Walson asked how having multiple sponsors impacts the label change of a generic drug, and what can be done to improve that process. Dr. Alexander said that it was a difficult process to convey label changes, especially when there are multiple generic manufacturers who may not have the research staff to ensure that their labeling reflects new information.

Dr. Walson asked about challenges that are unique to pediatric clinical trials and what can be done to overcome them. Dr. Benjamin listed several challenges: the number of people involved, including participants, study coordinators, PIs, and experts from pharmaceutical companies and divisions at the federal level; differences in expertise in central IRBs; low numbers of participants, which can cause a study to fail; and a lack of financial incentives for pediatric drug development, especially compared to adult drug development. He noted that faster communication via digital technology, high-functioning networks funded by the NIH, and master protocol pathways and increased pediatric expertise at FDA have made pediatric clinical trials easier in his experience. Ms. West said that talking to children at the beginning of the process when developing the protocol can help with the problem of low participation, as well as adapting trial times to avoid kids' school and extracurricular activities and asking children what they would like to see as the outcome of the trial. Dr. Walson added that a participant in the chat mentioned electronic footprints in rural areas, the use of ePRO and eConsent, and the use of dried blood spots to make trial participation more convenient.

Dr. Walson asked how COVID had impacted pediatric drug development infrastructure. Dr. Turner said that in the UK, the existing research infrastructure quickly shifted to focus on COVID, which hindered progress in non-COVID spaces. Dr. Watt agreed and added that COVID hurt pediatric research in many ways; clinical studies saw a huge decrease in enrollment and universities were shutting research down. It has remained challenging even as COVID wanes, and even though studies have resumed and begun enrolling participants again, many have lost staff and coordinators. Dr. Alexander predicted that in the future they would see long delays in timelines related to the COVID period. Dr. Walson referenced a comment in the chat calling for greater funding for start-up studies, as well as suggesting that trials provide babysitting, parking, et cetera to make participation easier for parents. He said that IRBs sometimes do not

allow this, but drug companies are often willing to provide anything that will increase trial recruitment.

Dr. Walson asked participants about key changes needed to advance pediatric drug development. Dr. Feinstein said that improved collaboration between and within stakeholder groups was necessary, along with leveraging new models of research, using available technologies to enhance participation, and continuing to improve public awareness of the importance of pediatric rare disease research and drug development. Dr. Benjamin said that they should focus on more direct to family trials, centrally as well as within institutions. Most children receive care in the outpatient setting, and these sites tend to be open during school hours when it is inconvenient for children and families to access them. Ms. West added that children will participate in clinical research for very altruistic reasons; even though the results of research may not benefit them, they want to help other children and families. If they know that they are making a difference, they are more likely to participate, and they are also able to take back some control over their own lives. Dr. Walson added that academia needs to make it easier for people who devote their lives to pediatric clinical trials to achieve promotions, and there should be more discussion about how to involve more non-Western countries.

Dr. Walson asked each participant to reflect on their main priority for pediatric drug development. Ms. West said that her priority would be involving patients. Dr. Turner said that his would be monetizing the benefits of pediatric drug development. Dr. Feinstein said that his priority would be training, Dr. Walker said that hers would be leveraging existing data to hasten the labeling of older products, and Dr. Alexander said that collaboration was his priority. Dr. Benjamin said that he would prioritize funding that reflects the fact that pediatric patients are 20% of the population and 100% of our future, and Dr. Watt said that decentralized research trials were his priority.

Day One Summary

Perdita Taylor-Zapata, M.D.

Dr. Taylor-Zapata thanked the panelists for their discussion and insights and noted that the following day would focus more on the future of pediatric drug development.

Day 2: Friday, December 9, 2022

Welcome, Introductions, and Overview of Meeting Goals

Perdita Taylor-Zapata, M.D.

Dr. Taylor-Zapata welcomed participants to Day 2 of the meeting, summarized remarks from the previous day, and outlined the agenda.

Updates from the Pediatric Trials Network

Rachel G. Greenberg, M.D., M.B., M.H.S.
Duke Clinical Research Institute

Dr. Greenberg began her presentation by noting that children are not just smaller adults, and they do not respond to drugs according to scale. Because only a small percentage of drugs and devices are approved by the FDA and labeled for pediatric use, clinicians are forced to use many drugs off-label. The PTN was created to be an infrastructure for investigators to conduct trials that improve pediatric labeling and child health. The PTN works with the FDA to develop study plans and submits their data and plans under IND. Much of their work is in the Phase 1 and Phase 2 space, and they work with FDA after the studies are completed to submit data, make changes and reanalyze data according to review division requests. The PTN has worked with more than 222 sites in 44 states and 4 countries. They have enrolled over 11,000 participants in studies conducted across 18 therapeutic areas, resulting in 100 publications, 44 studies, more than 26 products submitted to the FDA, and 17 label changes obtained. Dr. Greenberg highlighted the two most recent label changes for diazepam and clindamycin. The data for the diazepam label change came from a reanalysis of clinical trial data to better define PK parameters for pediatric patients between ages three months and 18 years. Data from four PTN studies contributed to the revision of the label for clindamycin; the studies found that the doses necessary to achieve therapeutic exposure were greater as premature infants became older.

The PTN studies many drugs in addition to those that have achieved label changes. They have developed methods to study drug concentrations in plasma and dried blood spots, breast milk, cerebrospinal fluid (CSF), and urine. In addition to performing studies, the PTN works to advance the science of pediatric drug development. They use specialized techniques such as advanced PK modeling, blood sampling methods, and leftover samples, and innovative trial

designs including dose-escalating safety trials, master protocols, registries, and incorporation of real world data.

PTN's recently completed studies include studies on furosemide and digoxin, and they are conducting ongoing studies on sildenafil, anesthetics and analgesics, a registry study on antipsychotics in children, the Pediatric Opportunistic Pharmacokinetics Study (POPS), and a study evaluating exposure of infants to medications in breast milk (CUDDLE). In the near future they will be starting studies on terbutaline and methadone in adult populations in order to gather additional data before moving forward with pediatric studies. They will also be conducting a device study of Positron and a study of the drug guanfacine in children with Down syndrome. This last study is a collaboration with the INCLUDE Project, which is an NIH initiative to address health and quality of life needs for individuals with Down syndrome.

In addition to their clinical studies, PTN has undertaken initiatives to understand what drives site enrollment in order to increase their efficiency and productivity. They examined existing data about site enrollment and spoke with PIs to see how high enrolling sites differed from low enrolling sites, and they have found that sites that enrolled more participants tended to have faster startup times. The PTN intends to continue their analysis to determine how they can help sites to be as efficient as possible in a time of many resource constraints. They have also been exploring ways to engage participants. Current engagement efforts include posting Results At-A-Glance on the PTN website and sending thank-you notes to study participants. They also work with iCAN in many ways, including engaging participant advocates to review PTN study materials and participate in discussions of study design. The PTN Steering Committee also partnered with iCAN to better understand and increase diversity in PTN's study enrollment. Dr. Greenberg shared a video that was created as part of this initiative, which included several pediatric study participants sharing their perspectives on diversity in pediatric studies. The full presentation was shared with participating PTN site investigators and study staff, and PTN is working on an action plan to promote continued and improved diversity in enrollment.

Future of Pediatric Drug Development

Moderators:
Abi Tepede, Pharm.D.
Health Science Administrator
NICHD, NIH

Katie Vance, Ph.D.
Program Officer
OPPTB, NICHD, NIH

Panelists:
Lily Mulugeta, Pharm.D.
Associate Director
Division of Pediatrics and Maternal Health, FDA

Sue Rahman, Pharm.D.
Chair, Missouri Medicaid Drug Utilization Review Board
Missouri Department of Social Services

Mark Turner, M.D., Ph.D.
Professor of Neonatology and Research Delivery
University of Liverpool

Robert M. Ward, M.D.
Pediatric Pharmacology Program
University of Utah School of Medicine

Kevin Watt, M.D., Ph.D.
Chief, Division of Pediatric Clinical Pharmacology
University of Utah

Kanecia Zimmerman, M.D., M.P.H.
Associate Professor
Duke Clinical Research Institute

Dr. Tepede noted that on December 8, 2022 the FDA amended the emergency use authorization of the updated bivalent Moderna and Pfizer vaccines, to include use in children down to the age of six months. She asked panelists what changes in the U.S. and international regulations for approval or policies were most needed to drive the pediatric drug development transformation. **Dr. Mulugeta** noted that existing regulations allowed for rapid development and approval of the COVID vaccines for adults and children. In the case of COVID there was unmatched collaboration between scientists, developers, and government, as well as available

resources and funding and high numbers of volunteers for studies. **Dr. Turner** agreed and added that in Europe, development of the vaccines for adolescents and younger people was held back by a narrow focus on biological harm, whereas the U.S. took a more preemptive and holistic view that accounted for schooling and social harm. **Dr. Ward** said that when consulting with sponsors conducting international trials, they often hear that the regulations for study timelines vary across countries. He asked other panelists if they had heard conversations internationally about the need for children to be studied on a more consistent timeline. Dr. Turner said that he had heard conversations on this topic and it seemed that everyone wanted to have the same program, though there are cultural and legal issues and differences in scientific practice between countries. It will not happen quickly, but forums like this meeting build the trust that is needed to establish that collaboration.

In the chat, **Dr. Walson** asked Dr. Ward to elaborate on the Critical Path Institute (C-Path) and its role in pediatric drug development. Dr. Ward explained that C-Path is an organization that sponsors the International Neonatal Consortium and the Institute for Advanced Clinical Trials for Children (I-ACT). C-Path is currently coordinating real-world data collection to capture the electronic health records of up to 1 million newborns from Japan, Canada, the U.S., and Europe. I-ACT is a nonprofit group that is attempting to facilitate sponsored studies to achieve labeling in children, with a focus on study design. Dr. Walson suggested that the next BPCA Stakeholders Meeting could feature a presentation from C-Path. Dr. Ward added that C-Path holds meetings with the FDA about basic, non-proprietary issues that may impede the completion of clinical trials.

Dr. Tepede noted an additional question in the chat asking about the role of the American Academy of Pediatrics and similar international groups, as well as pediatric hospitals, in providing up-to-date admission, morbidity, mortality, and cost data as well as impact on pediatric preventative care. Dr. Turner said that there was talk of developing a European health data space that would contribute those measures. The European Academy of Paediatrics, which is comprised of 44 national pediatric associations, is lobbying for children to be included in that data. Europe is behind the U.S. in the electronic health record space, and outside of high-income countries there are large parts of the world that do not reliably use electronic health records. Dr. Ward said that in the U.S., issues of funding and costs of healthcare are important and diverse and proprietary interests emerge when trying to elicit data for trials.

Dr. Tepede asked how roles in academic, public-private partnerships, pharma, and federal government need to change to advance pediatric drug development research. **Dr. Rahman** said

that it is increasingly the case that medicines administered to children receive accelerated approval despite limited data on meaningful outcomes, and public and private insurers are now able to enter into value-based purchasing agreements with drug developers. In order to leverage real-world data to impact drug development and labeling in children, several things need to happen: clinical experts and patient group experts will need to define the criteria for what "works"; EHR vendors will need to refine applications to support the collection of relevant data; and payers will need to collaborate and move past proprietary restrictions to share data in a way that regulatory agencies will accept to inform labeling changes. Under the healthcare utility model, not-for-profit social welfare companies deliver products and services in the healthcare space and these are capitalized by healthcare systems and philanthropic organizations. This model has entered the pharmaceutical space and similar models for pediatric formulation development could be possible. **Dr. Zimmerman** added that the level of collaboration that occurred with COVID needs to happen for every single drug. Dr. Mulugeta said that it was important to find ways for drug developers to collaborate to allow innovative and efficient trial designs, and to educate and engage healthcare professionals, patients and patient organizations.

Dr. Tepede asked for panelists' thoughts on the role of training and best practices for the next generation of pediatric drug development researchers. **Dr. Watt** noted that there are a number of hubs around the U.S. that are doing good work on this issue, many of which are centered on NIH's T32 clinical pharmacology training grants. Many of these hubs are affiliated with networks such as the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub, the Cancer Prevention and Control Research Network (CPCRN), and the Pediatric Emergency Care Applied Research Network (PECARN), which provide infrastructure for appropriate mentorship. Two important questions for the future are how to bring in people who are not affiliated with these hubs and how to get researchers more experience in regulatory and industry spaces. Dr. Watt gave examples of two models that currently focus on these areas. One is an NICHD-sponsored pediatric critical care program that invites scholars from around the country to submit grants and network at an annual meeting, then convenes a national advisory committee to distribute the awards. He also shared his experience working at the FDA through the Intergovernmental Personnel Act (IPA), which allowed him to understand more about the regulatory side of pediatric drug development. Dr. Ward added that it is important for trainees to train at centers that are accredited by the American Board of Clinical Pharmacology.

Dr. Zimmerman agreed that it is important to expose researchers to career paths much earlier, especially when thinking about diversity. Rich knowledge can be passed down through multiple

channels, including study coordinators and operational staff. As academia, industry, and regulatory scientists learn to collaborate, there should be spaces where training opportunities can happen. Dr. Tepede noted that Dr. de Wildt left a note in the chat about providing funding to train internationally. Dr. Mulugeta said that this year, her division at FDA established the first regulatory pharmaceutical fellowship in the Office of New Drugs, in collaboration with Rutgers University and Sanofi, to expose postdoctoral fellows to drug development and regulatory science. The FDA also recruited their second fellow under the FDA/Children's National Hospital collaboration.

Dr. Tepede shared her experience with the Massachusetts College of Pharmacy running clinical trials as a fellow, which allowed her to take a nontraditional route for a PharmD. She noted that she had also attended the FDA Clinical Investigator Course earlier in the week, and one of the takeaways was draft guidance around the race and diversity plan. She asked participants how they could build trust and sustain relationships through active community engagement. Dr. Zimmerman highlighted the importance of asking the community what they want and what will affect their lives, following through on those things to build relationships of trust, and remaining engaged after the study is done. Engaging communities at the very beginning of the process is crucial. Dr. Rahman added that studies must be viewed as a true partnership between researchers and communities. Researchers must consider the value-add for the community and think about what they can do to maintain a relationship by investing in the community over time so that they feel that they are part of the solution. Dr. Ward noted that in a survey by the International Neonatal Consortium one of the main messages from parents was that they wanted to be involved in the studies and then have the results provided to them, and too few investigators do both of those things.

Dr. Tepede asked if investigators should be giving deliverables to community engagement boards. Dr. Rahman said that rather than bringing the community to investigators, investigators should be going into the community. Community boards are often a small subset of individuals who cannot necessarily represent the entire community effectively. Investigators need to engage as many community members as possible, and when they are invested, they will help to define the deliverables. Dr. Zimmerman added that if investigators are giving deliverables to the community at the end of the process, then they have failed, because that is not the nature of a true partnership. Dr. Turner said that meaningful engagement requires meaningful resources, which are often missing. When sponsors and academic leaders do not devote the required time, effort and people, it becomes a tokenistic exercise. Investigators also need to be prepared

for the unexpected, such as the community not wanting to do the study that a regulatory agency has designed.

Dr. Tepede pointed out some questions and comments in the chat. Ms. Simone asked how to approach communities when studies are already planned, versus partnering with particular disease or indication groups. Small research groups do not have the funding to do a broad tutorial of clinical research. Dr. Walson suggested asking communities to give deliverables to investigators. Dr. Ward suggested that storing information in online locations would not require as many resources for the community or for small startup companies.

Dr. Tepede asked what trial designs or other methodologies would be transformational for pediatric drug development. Dr. Turner said that for him the elements that will be transformational are the values, such as the moral values of community engagement and increasing the value of medicine for children so that researchers can expect their careers in pediatric medicine to develop in a certain way. Dr. Mulugeta added several transformational factors: adaptive study designs that could be modified as more data is collected; enrichment approaches to define narrower patient populations; quantitative modeling of disease progression to identify potential biomarkers and surrogate endpoints; and various extrapolation approaches to leverage existing adult and pediatric data and minimize the burden of pediatric trials. Dr. Ward said that he would like to see increased emphasis on the planning of pediatric studies during the development process, to reduce the current delay for pediatric labels to be created after approval. He also said that he would like to see increased utilization of platform trials.

Dr. Zimmerman reiterated the importance of taking research to the communities and the data safety measures that will be required to do so. She added that researchers learned a lot about adaptive trial designs from COVID. Dr. Watt emphasized the importance of finding innovative ways to engage participants outside of the traditional clinic environment. In the chat, Dr. Anand suggested capturing data directly from EHRs and utilizing remote data capture technology to reduce the burden on families.

Dr. Tepede asked panelists how artificial intelligence (AI) tools could enhance pediatric research. Dr. Rahman suggested looking beyond the sphere of clinical pharmacology. She noted that the commercial sector has successfully discovered how to incentivize people to collect, leverage, and monetize data. Dr. Zimmerman said that training and collaboration between industries will be important in bringing together clinical pharmacology and machine learning.

Dr. Rahman suggested that collaboration between experts in those two fields might be more effective than training people to be skilled in both. Dr. Turner suggested a need for caution as well as validation and qualification when working with machine learning and AI. In the chat, Dr. Anand noted that AI and machine learning can be used for remote assessments, but validation of the tools and FDA acceptance of digital biomarkers can be time-consuming and costly. Dr. Walson suggested starting with simple but necessary data collection and analysis.

Dr. Tepede asked panelists what they thought needed to be done on the science and programmatic sides of precision medicine to get children engaged in clinical trials. Dr. Ward said that as the world and trials become more connected, ethnic differences in pharmacogenetics may influence the outcome of studies. Those data should be collected, but that is a sensitive issue for some ethnic groups. He also said that there has been discussion around how similar adolescents are to young adults, and suggested incorporating those two groups in the same studies. Dr. Turner said that, similar to AI and machine learning, precision medicine needs its own validation and people sometimes underestimate how difficult that can be. Dr. Watt said that researchers are exploring ways of using modeling and simulation to identify key parameters that could be helpful, but there are still many challenges to be solved. Interesting work is being conducted with subcutaneous and transcutaneous devices that can measure drug concentrations in real time, and if this can be achieved, it would move the field much closer to personalized medicine.

Dr. Tepede mentioned a recent FDA discussion paper focused on point of care and distributed manufacturing. She asked the panelists how compounding and 3D printing would be impacted in the development of pediatric research. Dr. Ward said that point of care testing had the potential to make pediatric drug trials more convenient. Dr. Tepede added that having more established guidance from regulators around precision medicine could help researchers feel more confident in deploying those technologies.

Dr. Tepede asked panelists what the future priorities should be for pediatric drug development. Dr. Watt said that his two priorities were moving towards precision medicine and training to develop the next generation of clinical pharmacologists. Dr. Mulugeta listed challenges with trial design, recruitment, and completion; orphan diseases; and non-proprietary registries and quality natural history studies as her priorities. Dr. Ward said that he would prioritize neonatal studies of drugs that are used in the NICU and clear evidence related to acceptance or denial of extrapolation to facilitate conducting those studies. Dr. Rahman emphasized the importance of EHR reform to make sure that the FDA gets valuable real-world data to support labeling

changes. Dr. Zimmerman said that cross-collaboration is the key to achieving many of the priorities listed by other participants. Dr. Turner said that feasibility, adaptive design, and community engagement will all change what researchers do, and validated feedback should be prioritized so that they can make rational choices as the process is still ongoing. Dr. Tepede summarized the day's discussion and added that leveraging extensive resources is another key priority.

Wrap-Up Discussion/Thank You

Dr. Taylor-Zapata thanked the participants and noted that the conversations from both days provided insight into what needs to happen to continue to move pediatric drug development forward. She noted that in the online poll where participants could identify their priorities for pediatric drug development, the words “collaboration” and “innovation” were common answers. She summarized the wins, challenges, and priorities that were discussed on Day 1:

- Wins:
    - Increase in labels, over 1,000 at FDA and 17 from the PTN
    - Focused legislations such as RACE
    - Pediatric-focused guidelines
    - Evidence generation for off-label use
- Challenges:
    - Special populations, including neonates and orphan designations
    - Limitations in patient and staffing numbers, the pipeline of experts, and IRB approvals
    - Incentives for kids are less optimal because of limited market
- Priorities:
    - Monetizing the benefits of research in kids
    - Training the next generation
    - Leveraging existing data
    - Maximizing the inclusion of kids in the discussion and design of research
    - Collaboration

She also summarized the key takeaways from Day 2:

- There will be more challenges
    - When thinking ahead, investigators should learn from the past and consider kids holistically

    - Health is biological, social, mental, and more
- Find the common ground
    - Non-competitive spaces for interests and collaborations, including public-private partnerships, payers, CMS, and healthcare professionals
- Improve the pipeline
    - Training programs that are multi-dimensional including hubs affiliated with NIH networks, industry, FDA fellowships, STEM programs in schools, international exchange programs
- Inclusion is not just moral, it's scientific
    - What is important to the community?
    - Include from the beginning and report back, research is a partnership
    - Meaningful engagement requires meaningful resources
- Forward movement
    - Requires context and value added
    - Minimize the burden of trials
    - Improve data safety
    - Bioinformatics in the health care model, new models are needed but investigators must be cautious about quality and validation
- Priorities
    - Precision medicine approaches
    - Training the next generation
    - Non-proprietary registries and data access
    - Studies in orphan diseases
    - Drug studies in the NICU
    - EHR reform for real-world data (RWD)/real-world evidence (RWE) to FDA
    - Cross-pollinate, cross-collaborate
    - Validated feedback on deliverables and outcomes

Research in kids requires innovation and investment, and researchers need to foster a spectrum of research, examine the role of big data, implementation and dissemination, and the patient and community voice. Research with children can be more expensive, with high risks as well as high rewards. It requires prioritizing investments in science and the workforce, leveraging existing resources, creating funding streams and new business models, and communicating what does and does not work. Pediatric drug development needs multifaceted inclusion models at all points in research and trials, multidimensional models and sponsors, and continuous communication and collaborations.

Dr. Taylor-Zapata thanked all of the participants for their discussion and their help in making the meeting a success.