Job number 9840421 – FDA – Interested Parties - 09.15.25
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Interested Parties Meeting: Implementation of the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)

September 15, 2025

(Please stand by for captions)

Welcome and Opening Remarks: Dionna Green, MD

U.S. Food and Drug Administration (FDA)

Good morning. I would like to welcome you to the FDA Interested Parties meeting on the implementation of BPCA and PREA. And welcome everyone in the room and those online. My name is Dionna Green, Director of the Office of Pediatric Therapeutics. I will serve as the MC for today's meeting. I want to thank all of the FDA staff who helped to organize and execute today's meeting. Also, all the Interested Parties' speakers who will be participating today. To start the day, I will provide a brief overview of BPCA and PREA and their role in advancing medicines for children. I'm

going to be sharing a few reflections of the last 20 years since the passage of these laws, an overview of the laws themselves, successes, opportunities for improvement, and I will also end my remarks with select aspects of FDA's work to address feedback we received from the 2019 Interested Parties meeting that was previously held. I will also provide an overview of the day's agenda, as we transition into the listening session portion of today's meeting.

This slide depicts some of the historical milestones that have occurred and that have brought us forward to where we are today. Many of you in the room are familiar with these important opportunities and milestones that have occurred. Over the last decades, FDA and other interested parties have worked to address the problem of inadequate testing of drug and biological products in children, and the critical lack of pediatric information in product labeling. Since 1994, there have been a series of rules, regulations and legislations that have come forth to encourage and also to require drug manufacturers to perform pediatric studies. In 2002 and 2003, BPCA and PREA were enacted by Congress.

In 2012, under the FDA Safety and Innovation Act, both BPCA and PREA were made permanent. The laws have been successful drivers of pediatric product development in the United States. Inclusion of children and clinical research is essential if children are to share fully in the benefits of medical advancements and also to assure that children have access to products that have been deemed safe and effective for pediatric use. And so there are a few general tenets when we think about this area and we consider these our guiding principles. Pediatric patients should have timely access to products that have been appropriately evaluated. Product

development programs should include studies in children when pediatric use is anticipated. It is paramount to encourage and engage in early and thoughtful planning for pediatric development programs and pediatric trials should be designed to yield interpretable data. Further, obtaining that data and obtaining knowledge of the effects of medicinal products should be done without compromising the well-being of pediatric patients enrolled in clinical studies. With the laws in place and with these guiding principles in mind, a tremendous amount of progress has occurred over the last 20 years since the paradigm has shifted from one of excluding children from clinical research to now protecting pediatric patients through their inclusion in the clinical research enterprise.

About two years ago, FDA announced that an important milestone had been reached, with over 1,000 medicines now including evidence-based pediatric information in the product labeling. This means that for those products, healthcare providers, patients and their families have the critical information that they need to make important therapeutic decisions. This accomplishment reflects the collective efforts of so many, including all of the interested parties who played a role in developing the current approach to developing medicines for children. Importantly, it reflects the contributions of the thousands of children, along with their caregivers, who have participated in clinical trials. Without their enrollment and participation, and without the integration into the drug development process of their lived experience and with their own condition and disease, countless medical breakthroughs and advancements would be impossible.

Again, it's been 20 years since BPCA and PREA were enacted. When these laws were originally conceived, they were designed, and still are designed, to work

together to address the therapeutic needs of children. This slide depicts some similarities and differences between the laws - and before we get to that, I'm just going to explain a little bit about what these laws are about. Under BPCA, as we know, FDA can request that sponsors voluntarily conduct pediatric studies and these pediatric studies are for areas in which FDA feels there's a therapeutic need that can be beneficial to children. Under the same program, there are provisions that allow for partnership between FDA and NIH in order to be able to help develop and inform the data for off-label products that are no longer on patent but are being used in pediatric patients.

Whereas for PREA, the studies under PREA are required, PREA gives FDA the authority to require sponsors to assess safety and effectiveness of products in certain pediatric populations for certain products. Products, for example, NDAs, BLAs and supplements, that are associated with a new indication, a new dosage form, a new dosing regimen, and a new formulation and a new route of administration would all be required to have studies under PREA. Here are some of the similarities and differences. As you can see, both BPCA and PREA apply to drugs and biologic products. As I mentioned, studies under PREA are required and therefore sponsors are required to submit to the agency pediatric study plans. It's important to note that under PREA, the indication that is studied and approved in adults dictates the studies in pediatrics. It's also important to note that products with orphan drug designation are exempt from the requirements for PREA, except for those products with a new active ingredient that's intended to treat an adult cancer that is directed at a molecular target that may be relevant to pediatric cancers.

In the case of BPCA, FDA can issue written requests to sponsors to voluntarily conduct studies for pediatric patients and once adequately conducted, this can qualify sponsors for a financial reward. For BPCA, the requested studies relate to the entire moiety of the product and so it allows FDA to request studies that cannot be required under PREA, and it also allows FDA to expand the indications beyond those that are studied in adults. Unlike PREA, BPCA studies can be requested for products that have orphan drug designation and in the case of both of these laws, any pediatric studies that are conducted must be described in labeling regardless of whether the studies are positive, negative or inconclusive.

In terms of examples of success, as shown in this graph, BPCA and PREA have led to a significant increase in the number of pediatric labeling changes that have occurred over the last couple of decades since the laws went into effect. When taking a closer look at the labeling changes that have been achieved, they have occurred across a wide array of therapeutic areas and some areas, like infectious disease, have seen a higher number of labeling changes compared to others. In some cases, these labeling changes reflect the first product to be indicated for use in pediatrics for a specific indication, or new mechanisms of action or new formulations of products that are now unavailable for use in the pediatric armamentarium. Or the communication of important safety data or lack of efficacy findings recommending against the use of certain products in pediatric patients. Also, when taking a closer look at the labeling changes that have been achieved, you can see as shown in the dark gray in this pie chart that the majority of pediatric labeling changes that have occurred have been pursuant to PREA. So, in other words, it is the FDA's authority to require pediatric studies under

PREA that is driving pediatric drug development to a much greater extent than the incentive program.

Historically, under PREA the requirements to conduct pediatric studies of cancer drugs were often waived because of the low incidence of adult cancers or adult type cancers in children. However, an important shift in the regulatory landscape for pediatric cancer drugs occurred with the implementation of the FDA reauthorization act. Which through the RACE for children act, amended PREA by requiring sponsors to submit reports to FDA on pediatric investigations for certain new drugs. Specifically, this is pertaining to new drugs that are directed at a molecular target determined to be substantially relevant to the growth or progression of one or more pediatric cancers. Regardless of whether the drug is for an indication for which orphan drug designation has been granted. And so this change eliminated the orphan exemption for pediatric studies for cancer products under PREA and it made the requirement for pediatric investigations based on mechanism of action, as opposed to clinical indication. As a result of this change and since its implementation in August 2020, there has been an increase in the development of targeted therapies in pediatric patients, an increase in the number of agreed iPSPs, and also an increase in the number of post marketing requirements for pediatric studies for oncology products. In the second column in this table in the slide you can see that the total number of planned pediatric studies under the RACE Act in the last five years is 73. Compared to the last column in the table, which shows that the total number of planned pediatric studies that could have been required pre-RACE Act is only 14. And so you can appreciate the substantial difference

and I think clearly this demonstrates another example of success do to pediatric legislation.

But despite these important successes, there are still challenges that remain, and actually those convey opportunities for improvement. A few of these areas are shown on this slide, and likely to those of you who are involved in pediatric clinical research you know these all too well. Opportunities for improvement, such as: making pediatric product development more efficient, building enduring trial infrastructure, use of innovative trial designs quantitative tools, as well as digital health technologies, addressing understudied population and long term safety assessments, as well as further integrating real-world data and patient voice into the process, are just a few of the examples that will continue to help advance and optimize product development for children under BPCA and PREA.

So Section 508 of the 2012 FDA Safety and Innovation Act requires FDA to report on the implementation of BPCA and PREA. The first report was required to be submitted to Congress in 2016, and then every five years thereafter. These reports contain detailed information on pediatric studies, labeling, successes, as well as suggestions for improvement, to ensure that the objectives underlying BPCA and PREA are effectively and efficiently implemented. As part of the process for preparing for the report, Section 508 specifies that the agency solicit input from interested parties and summarize that input into the report. So FDA is presently preparing the next report to Congress, which has a reporting period of July 1st, 2020, to June 30th, 2025, and is due to be submitted to Congress in the summer of 2026.

Ahead of the last report on BPCA and PREA that was submitted to Congress, FDA held a public Interested Parties meeting in 2019, to obtain input on any recommendations or information relevant to the report, similar to what we are doing here today. From that meeting, several key themes emerged from the interested parties' feedback that was received and I'm going to highlight a couple of these themes over the next few slides. One theme that emerged from the feedback was interested parties generally noted that the FDA needed to issue more guidance documents on key pediatric issues, as well as, update or finalize existing guidances. FDA guidance documents as many of you know, address a range of topics and are an important means to convey the Agency's interpretation of regulatory issues to the regulated industry, FDA staff, and the public. The FDA's external webpage contains a search engine that provides a convenient way to search for these documents using keywords. A list of pediatric-related guidances can be yielded by entering in the search term 'pediatric product development'.

There are over 80 FDA guidances that discuss pediatric product development to varying degrees. As can be seen from the graph on this slide, the issuance of pediatric guidance has continued to increase over time. During the current reporting period for the upcoming Report to Congress, FDA has issued a range of pediatric focused or pediatric relevant guidances, some of which are listed on this slide and on the next slide. There are guidances, such as: the 'Scientific and Regulatory Considerations for Complying with PREA and Qualifying for Exclusivity under BPCA'; 'Considerations for Investigations and Finalization of Existing Guidances', including E11A guidance on 'Pediatric Extrapolation as an Internationally Harmonized Guidance', the first on this

topic; ‘The Guidance and Considerations for Long-Term Neurodevelopmental Neonatal Safety Studies and Product Development for Rare Diseases’. A final guidance was also issued on iPSPs, as well as guidances for ‘Clinical Pharmacology Considerations for Pediatric and Neonatal Studies’. There were also several oncology related guidances that were issued, including on topics such as master protocols, the ‘FDARA Implementation for Molecularly Targeted Oncology Drugs’ and a guidance pertaining to minimum age considerations for cancer trials.

Another theme that emerged from past interested parties’ feedback was the importance of international alignment on pediatric studies. Interested Parties encouraged the FDA to continue to work with EMA, and other global regulators, to harmonize pediatric testing requirements. FDA continues to routinely engage with global regulators through a variety of means, -- one example is the monthly pediatric cluster teleconferences that include EMA, PMDA, Health Canada, the Australian TGA and Swissmedic as participants. During the cluster discussions, there are product specific and general pediatric topic discussions that are held in these forums, as well as common commentary documents, that outline the discussions that can be issued to sponsors. These in-depth discussions, held at this critical forum, facilitate regular exchange of information between regulators, and also help to avoid exposing children to unnecessary or duplicative trials and they aim to achieve global pediatric development that in line with the pediatric legislation and regulations in the EU and US.

Product development for neonates continues to be a theme that Interested Parties raised. While BPCA and PREA play important roles in increasing the overall numbers of pediatric clinical trials in general and also have served to promote ethically

timely and scientifically sound product development and medicines for children, there are still subgroups that remain understudied and unaddressed in product labeling, including for example neonates. A majority of medicines are used off-label and there are very few new therapies being developed to address some of the unique diseases and conditions impacting the pre-term and term neonates. Advancing product development for this population is an important priority for the FDA. The Office of Pediatric Therapeutics Neonatology Program is available for consultation across the agency and provides expert recommendations and advice on neonatal clinical trials and product development programs. The number of consultation requests, as can be seen in this graph on this slide, has continued to increase for this program over the years. In the last few years, the FDA has published guidances that are relevant to neonatal drug development, hosted multiple workshops on topics such as BPD, preterm birth, as well as efficacy endpoints for neonatal clinical trials. The FDA also continues to actively engage in public-private partnerships, such as the one with the Critical Paths International Neonatal Consortium to advance safe and effective therapies for neonates.

The last theme that I'll touch upon is regulatory science and forums for scientific exchange. This is another theme that Interested Parties have raised to help advance the science and improve our knowledge of understanding of how best to develop products for children. The FDA does create opportunities and public forums for stakeholders to meet to discuss challenging scientific issues related to pediatric product development and regulatory science. An example of this is 'The Advancing the Development of Pediatric Therapeutics' ADEPT Workshop series, which has covered a range of topics over the last several years which you can see here listed on this slide.

FDA soon will be announcing its ‘ADEPT 10’ so 10 years of ADEPT which is an amazing workshop topic later this year. Please stay tuned for that.

Let's shift the focus to today's meeting. As outlined from the prompts included in the Federal Register Notice announcing this meeting, the purpose of today is to hear from Interested Parties about the public health impact that pediatric legislation has had. Some of the areas for which we are seeking input include, but are not limited to, treatment advances for children, areas of continued unmet need, balance of incentives and requirements for pediatric product development, the barriers or the resources that are preventing conduct or timely completion of pediatric clinical trials under PREA and BPCA. Issues related to clinical trial infrastructure and enrollment and input on the successes and challenges experienced when leveraging scientific advances, such as: pediatric extrapolation, real-world data, modeling and simulation and so on and in what ways have these advancements helped or not helped facilitate more timely evidence generation for pediatric populations.

That is the context and scope for today's meeting. We have a full agenda today of speakers so we will not be able to entertain discussion on topics outside of this scope. We do look forward to having a very productive meeting. We have a number of speakers that represent various interested parties impacted by the BPCA and PREA legislation. The day will be divided into five sessions during which we will hear from a number of Interested Parties. The sessions have not been ordered in any particular manner. Each speaker will have 10 minutes to share their prepared remarks and to ensure we stay on schedule, there will be a timer and at the one-minute remaining

mark, the lights on the podium will turn yellow and when the time has expired the lights will turn red. We do ask that everyone adhere to their allotted time.

The meeting is convened in a listening session format with no clarifying questions between the various speakers. There are breaks built into the agenda and lunch is at 12:15 PM Eastern. There will be an open public comment period from 3:15 to 4:15 PM Eastern, during which we will hear from individuals that requested in advance to provide remarks at today's meeting. Please keep in mind there is a public docket opened for this meeting, which will remain open until September 30th, and is open for submitting comments. We are scheduled to conclude our day at 4:30 PM Eastern. Now that I covered the logistics for today's meeting, we will proceed to session 1 and begin to hear from the Interested Parties. The first speaker this morning is Dr. Anjali Deshmukh from the American Academy of Pediatrics.

Session One: Interested Parties Comments

American Academy of Pediatrics (AAP): Anjali Deshmukh, MD

>> Thank you for the opportunity to participate in this important discussion on the implementation of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. My name is Anjali Deshmukh. I am a board-certified pediatrician and Associate Professor of Law at Seton Hall University, School of Law specializing in pharmaceutical law. I have to start by saying you have no idea how excited I am to be here. It's a true privilege to speak at the FDA on behalf of the American Academy of Pediatrics. The AAP is a nonprofit professional organization of 67,000 primary care pediatricians, pediatric medical subspecialists and pediatric surgical specialists.

Dedicated to the health, safety and well-being of infants, children and adolescents and young adults. Please note, my comments are on behalf of the AAP and my own, and do not reflect the position of my employer.

I know everyone in this room shares a common goal, and everyone works tirelessly to ensure children get timely access to safe and effective medicines. I have personally relied on the pediatric guidance and labeling that you produce at the FDA. So I have to start by saying thank you for all of your hard work and for being a partner to the AAP in pursuit of that shared endeavor. BPCA and PREA have revolutionized medicines for children in the last 28 years. Before drugs were seldom studied in children, but we all know children are not just little adults. Drugs work differently in children because of their unique biology and because diseases often present differently in children compared to adults and without actually studying drugs specifically in children, healthcare providers are left without trustworthy vetted information. Like whether the drugs are safe for children, what are the appropriate pediatric doses, and even if those drugs work. With more than 1,335 label changes from BPCA and PREA today, I celebrate the excellent work from FDA to rewrite that narrative. Today children's pharmaceuticals are no longer ignored, but there is still work to be done.

I will address three issues today. PREA compliance, the orphan drug exception and funding of NIH's BPCA program. -- PREA studies are required by law, but too many drug companies complete their pediatric studies late, seek repeated deferrals or ignore their PREA obligations altogether. PREA is a premarket requirement, but due dates for studies are typically, and at times appropriately, deferred at FDA until a date after adult approval. The different pediatric studies effectively become post-market requirements,

but FDA lacks enforcement tools to ensure that the studies get completed in a timely manner. Progress -- Congress had previously tried to address this problem with drug companies not completing required PREA studies, like in 2012, with legislation that created a new process to extend PREA deadlines when good cause exists and issue non-compliance letters when FDA finds there is not good cause for delay. Unfortunately, the changes have not created the accountability necessary to ensure studies get done.

My team's forthcoming research, analyzing all publicly nonrelated letters issued by FDA under PREA between 2015 and 2023, found that nearly half of the post-marketing requirements referenced in non-compliance letters remain delayed. Nine companies never responded to FDA's non-compliance letter. The results raise important concerns about the effectiveness of current enforcement mechanisms and underscore the need for stronger FDA authority and systematic solutions to address persistent barriers in pediatric drug development. The PREA requirement ensures pediatric studies are built into development plans, but adequate enforcement mechanisms are missing. As a result, too many PREA studies are significantly delayed or never completed. Without timely data, children are left waiting years for labeling updates, even as those drugs are widely used off-label in pediatric populations.

We recognize the importance of balancing between incentives and requirements in pediatric drug development. The AAP continues to support congressional efforts to allow FDA to issue civil monetary penalties for PREA non-compliance. FDA would retain the ability to extend PREA deadlines when there is good cause to do so. Companies acting in good faith to get their studies completed would not be subject to

fines. I also ask that FDA reconsider its public facing data tracking mechanisms. Right now, tracking the current status of PREA requirements is not an easy task. FDA archives data on PMRs that are fulfilled, released, or terminated periodically throughout the year when it updates the public website, making it exceptionally difficult to understand the full picture of PREA mandates. We know FDA itself faces challenges in tracking PMRs. It highlights the crucial need for an updated, easy to use, comprehensive software to track and manage required drug studies at FDA.

The second issue I would like to address is another gap in PREA mandates, the orphan drug exception. The AAP urges FDA to act to ensure that drugs are approved with orphan drug designation are studied under PREA. In 2024, 52% of novel drug approvals were designated as orphan drugs. That means FDA cannot require these drugs to be studied in children under PREA, despite the fact 50 to 75% of orphan diseases occur in children. We understand that many orphan drugs are studied, approved and labeled for use in children. Sponsors do so voluntarily, meaning they are excused from section 505B of the Federal Food, Drug, and Cosmetic Act. When they choose to study these drugs in children, sponsors are not required to submit an initial pediatric study plan and have an agreed initial pediatric study plan, have any interaction with FDA's internal pediatric review committee and any labeling changes are not generally considered by FDA's Pediatric Advisory Committee. And if a company decides not to study an orphan drug in children, FDA cannot require it, even if children need it. That creates gaps. FDA's reported that as many as 36% of drugs intended for rare diseases affecting children are approved without comprehensive pediatric information. This is a result of being exempt from PREA. Simply put, FDA cannot

require the sponsor to conduct studies in other pediatric subpopulations, most often younger age groups that are also affected by the disease. Section 505B(k) gives FDA the authority to apply PREA to orphan drugs through regulation. We urge FDA to initiate such rulemaking as soon as possible. While we understand the challenges associated with drug development and orphan diseases, those challenges can be overcome, as evidenced by the increasing number of orphan drug designations and orphan drug approvals. PREA also gives FDA extensive authority to waive and defer pediatric studies when such studies would not be feasible or advisable. With close to 700 rare diseases without a treatment, and a majority of orphan diseases affecting children, PREA must be used as a vital tool for ensuring that orphan drug diseases are studied and labeled for use in children.

Last but not least, I would like to discuss the BPCA that authorizes a program at NIH to study older off-patent generic drugs in children that the BPCA exclusivity incentive and the subsequent PREA requirements were unable to reach. By funding the Pediatric Trial Network to do pediatric studies on these drugs that have been used in children for decades without sufficient data, the BPCA NIH program fills an essential gap in pediatric drug research. The program has resulted in 23 drug and two device label changes with important new pediatric information. There are even more studies submitted or near submission. All told, the BPCA and NIH program has studied, or is currently studying, over 100 different drugs in children. It has studied over 20 drugs in breast milk to determine infant drug exposure and the BPCA NIH program also funds training in pediatric pharmacology so that there are sufficient experts to conduct drug studies in children. But the BPCA NIH program has been flat-funded at 25 million since

its original authorization in 2022. While, the current statute authorizes 25 million in appropriations for the program, the program has never been appropriated dedicated dollars. Rather NIH funds the program by asking its Institutes and Centers to contribute money to it each year. Drug studies are expensive. While the program is highly efficient at using its scarce resources, the 25 million funding level is insufficient to meet the current need. While accounting for biomedical research inflation, the purchasing power in 2022 was only half of what it was in 2002.

The low level of funding also restricts the types of studies that can be conducted through this program. To date, the BPCA program has only been able to fund less expensive phase I and phase II studies to evaluate safety and pharmacokinetics. It currently lacks the funding to do phase 3 studies that can show drug efficacy in children, when efficacy cannot be extrapolated from adult studies. In many instances the NIH BPCA program was unable to pursue the needed phase 3 studies given the funding limitations. The AAP urges HHS, FDA and NIH to work together to increase funding for this research to 50 million in order to make the funding for the program more commensurate with the need.

Now I want to conclude where I started. By saying thank you. The conversation we are having today is only possible because of the tremendous hard work, dedication and advocacy for change by FDA staff that has occurred over the past two decades. Children are getting more and more of FDA's wanted standard of excellence in drug evaluation and the AAP values our strong partnership with FDA. I can say with pride that the AAP is committed to continue to work together to improve pediatric drug development to ensure that it meets the needs for all pediatric populations. Thank you

for your leadership and for your attention and for including pediatric providers and patients in this important conversation.

Session One: Interested Parties Comments

International Children's Advisory Network (iCAN): Leanne West, MS

>> Hi, I'm Leanne West, and I am the President of the International Children's Advisory Network, and I would like to talk a little bit today about what iCAN is and what we do. Our members are children and families. And what iCAN does is really to give them the opportunity to talk about what it's like to be them living with a condition, device or drug. We are a nonprofit with 46 member organizations around the world. We want to make sure that kids are heard in healthcare by clinicians, by drug developers, device developers, whoever it might be in the healthcare system. We have a program of raising the next generation of healthcare professionals to know that kids are the center of their healthcare journey and they are the experts.

So everything I'm going to talk about today, you will see a lot of quotes, these are directly from our kids and our parents about why it's important to include children in drug studies and why the drug studies are important instead of just using things off-label. Having better dosage study for kids, where the standard of care is established, the parent quote is very similar. Making sure that the drug works for children and is safe for children because it has been tested on children and with children.

I will go through these quickly with the limited time. But we will have this slide presentation up on our website after the event. I know you will get the recording through the FDA. What do our kids think about off-label drug use? You can see the

quote ‘I would like the patient to be listened to more and to be involved more directly in the process rather than thinking of the product first and patients second’. We really want to make sure that children and their families are included from the very beginning. That's really important because it's important to know what's important to the child and the parent about the drug or how medicine is practiced.

How would you feel if more safe and effective medications were developed for young people? Overwhelmingly, our kids say yes that would be great. ‘If drug testing for pediatric patients was actually done on pediatric patients, rather than on adults, and then scaled down, then the effects can be different for different ages, I would feel better about the situation’. That's from one of our youth. They really want to make sure that what they are taking is safe and effective, for them and not just guesstimated by clinicians by scaling down the drug.

Do you have any hopes or suggestions for improving future treatment options for children? ‘I hope the big Pharma companies can see past the fact that kids can be a less profitable demographic than adults and still dedicate resources towards them for better medication and treatment’. The problem is often pediatric drugs and devices are not a market typically that gets as invested in and kids want to make sure just because maybe they are a smaller population they are still really important to take into account.

At iCAN one of the things that we do, is we have a sale of approval program. What we do is we talk to industry partners, in this case Pharma, and talk to them about different things they are developing. It could be the assent or consent to make sure that kids and families understand what they are getting into with a clinical trial so you have less dropout. We also do things like look at the protocol. Are you even asking the right

questions? Are you making sure that your goals for the clinical trial are the same as the patients' goals for the clinical trial? Additionally, we look at things like are there things in the protocol with the clinical trial that are showstoppers? Or things that are okay that maybe you were worried that would be not acceptable by families? Working together we can create clinical trials that families are going to participate in and they are going to be asking the right questions. So if you go through this program with us it's an iterative process. But you can get a seal of approval for your products before you put them out there just to show that you cared enough to ask kids and families what they thought before putting them out there.

We have a young professional group, that was the group that I mentioned in the very beginning where we are training the next generation of healthcare professionals. This group is open to anyone college age and up, considering a career in healthcare of any type. We also have some of our kids that come to our original program that want to remain active and share what it's like to be them. So our youth, on learning that some of the Pharma companies were getting rid of their pediatric Centers of Excellence, came up with a public comment for the FDA. You can use the QR code to go directly to the paper, the comments, to see everything they said.

Here are some things I've highlighted that I want to share. By partnering with pharmaceutical companies to host direct engagements with pediatric patients and caregivers, iCAN provides a platform for these companies to directly hear from young people and truly understand the challenges they face. This direct insight allows companies to design clinical trials that are genuinely patient specific. By fostering open communication and demonstrating a genuine commitment to addressing patient needs,

we can significantly improve enrollment and retention and ultimately make the research processes more efficient and cost-effective.

So this is a great conclusion I think. We respectfully recommend the FDA include a formal requirement or incentive for incorporating pediatric patient groups during feasibility assessments in all pediatric trials. I think it's really important to what we are speaking about today and the youth recognize how important it is. Here is another document, it is a position paper the our youth wrote at our latest in-person Summit. We have 11 countries represented and the QR code can take you to this document. The document is all about how kids want to be included and how to include them and when to include them in research.

You can't read this it was so small. But I just want to highlight something. Our kids really recommend replacing impersonal questionnaires and surveys with things that directly engage them, like interviews or storytelling. They want to be included in all steps throughout the process, and we think it's very helpful to industry partners to understand what it's like to be them and what's important to them.

Just some final thoughts. This can all be very positive, our kids really benefit and -- we believe that our Pharma partners in this case also really benefit from the direct interaction. You can't develop anything for pediatrics in a silo. It is really through a partnership with patient organizations like iCAN and the FDA and industry altogether making sure the youth voice is heard and taken into consideration. Patient partnerships should be supported through every step of the clinical research process. Include them in every step. Later in today's call you're going to see three of our youth that are going to be telling their own stories, so stay tuned and make sure you know this is what you

learn when you talk to kids and include them throughout the process. Thank you very much for listening and having me today. I appreciate it and if you ever need anything please reach out and go to our website, iCAN.health.

>> Thank you Ms. West. Next will be Dr. Aaron Pawlyk from the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Session One: Interested Parties Comments

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD): Aaron Pawlyk, PhD

>> Hello, everyone. While I have the honor and privilege to give this presentation, I really want to acknowledge the tremendous amount of work that a lot people have put into this over a few decades to get here. That is really what I am presenting today. What I will talk about today is specifically what is very specifically on the right-side panel of the slide, the NIH 409I provisions of BPCA legislation, which directs the NIH under the oversight of the NICHD to prioritize medications for study in pediatric populations of different age groups, settings of care; prepare for and conduct clinical trials to support label changes; and really to build up the workforce around this training career development, which is a very important component of that. This slide really highlights why we need to understand the systemic differences in pediatric physiology and pathophysiology across various age groups and design clinical trials that address drug response efficacy within those specific age groups and populations.

I'm going to break down the program a little bit in terms of different goals for the NIH 409I program and how we've tackled that and I'm going to dive into a bit on the NIH

perspective here. The two things in bold I think are what are most germane to the conversation today, discussing label changes themselves. We do prioritization, prepare for and conduct the trials for label changes. Additionally, as part of preparing for this, we have supported pediatric clinical pharmacology research in a variety of different mechanisms over time because we need to make sure we are incorporating the newest science, the newest tools as we conduct this, sharpening the tools we use in clinical trials.

Training and career development - pediatric clinical pharmacology is a very small community so we have been working to build that up. And very importantly also dissemination of the information to public health. We need to get the information to caregivers, patients, as well as providers. The NIH has funded this work through three different buckets. If I try to map it – it would look like spaghetti on the slide, so I just have it off to the side. We have contracts that support the clinical program, we have a logistical contract that supports a variety of different activities, the training prioritization process and we've used grant mechanisms in different ways over time to support the training and career development and research activities.

Really, the take away I want for the slide is to emphasize that NICHD and OBPTB have evolved over time, innovating the programs we supported. It's really never been static. We change with the changing environment and go forward with that. Another important thing that I want to point out is in the top bar for pediatric drug trials - there are actually a lot of efforts that occurred before the BPCA legislation. The NICHD was supporting this research even back then, and worked very closely with the FDA, as well as the American Academy of Pediatrics, in the inception of the BPCA legislation.

I want to give a snapshot now of where these programs are this year, starting from the bottom. We've long supported a clinical pharmacology training program. Currently, we support this through institutional fellowship awards, T-32s and institutional career development K-12 awards. We have the virtual network, which is enabled by our logistics contract. It's an important alumni and trainee and Junior Faculty Network that I think gives a tremendous amount of value to the program. Individual trainee and career development awardees have chosen to join this network because of the benefit that they see.

Additionally, using our logistic contract, we have been able to support a lecture series, which is incredibly well attended across the globe and from various sectors, including pharmaceutical representatives. This is a way where we get a lot of information out there to groups to conduct the research. In terms of how we support fundamental pediatric clinical pharmacology, the current iteration that NICHD is taking is actually to combine this with separate efforts in maternal and lactation pharmacology in something that we refer to as the Maternal and Pediatric Precision Therapeutics Hub, which you can click on the QR code and take a look at everything they do.

I'm going to focus in on the label changing efforts, the current iteration being the Pediatric Trials Network and you will hear a lot more specifics on that from Drs. Greenberg and Benjamin later today. I'm going to give you the NIH perspective. I would really say I think the NIH has enabled the creation of what is the best in science network and capability to update off- patent drug labels because we need to ensure that drug use in children is safe and effective and that the drugs are only used when they're

necessary and when we know they're efficacious. We have to consider that in a variety of different age ranges, as we focus in on improving child health.

To drill down, we often refer to the BPCA clinical program structure as the way we support the clinical networks. This is composed of a contract to Duke to conduct the actual research, trial enabling studies, etc. The DCC is supported by a contract through Emmes. Our logistical contract provides a lot a different support for training, lecture series virtual network and of course oversight from NICHD and NIH staff with overseeing the program. The successes we have had - the program has been very successful and what it is meant to accomplish – 26 label updates so far, 11 on deck. Equally important, if not more, we have demonstrated that we can build the infrastructure to conduct the trials in the academic environment, which is a nontrivial thing to accomplish. However, there's a lot more that we need to do in terms of child health in the United States and there have been various reports and meetings ongoing and publications that point to that, including medication use in children. One thing I need to mention is in this fiscal year, in FY 2025, due to the way NIH is utilizing contract as a funding mechanism, we had to cap the amount we can spend on these contracts from 18 million to 11 million in the fiscal year and that has impacted the programs, and aspects of the program which are shown in red.

To me, this is just a reason to continue the evolution that I talked about earlier. We have to think in different ways and be more innovative in how we do certain things. I think there's a tremendous opportunity to collaborate more and work with various networks in new ways. For example, with the Unified Pediatric Research Consortium concept approved at NICHD's Council on September 9th. We need to prepare our

workforce for the future that will involve a lot more use of real-world data, new approach methodologies are alternative methods, and AI and machine learning tools. I also think, as we focus in on how we impact child health, thinking about partnerships, as we all know both medications and devices are used off- label if we don't have appropriate information early on, which often happens. If we have a pediatric medical device partnership that we are working on, could we expand that into the drug partnership space in some way with different networks and pharmaceutical industry? Are there ways that we can work in public and private partnerships as the public and private sector help each other in this area? Could we help with PREA requirements? Could we find ways to leverage that for the BPCA 409I program because we all have the same goal with improving child health?

There is a lot of different directions that we could go with this, and I don't have time to describe these all today. In terms of future trajectories, we could walk together, but there are three that I would like to highlight. One is an emphasis on understanding the origins of long-term child health that occur during pregnancy and early life nutrition, including medication exposure during these time periods. Real-world data will be increasingly important, and I think there are ways we can leverage that through post-marketing pregnancy registration, electronic health record mining, with linkage between mother and baby, as well as looking at long-term longitudinal outcomes for children for quite some time. And I also talked about the partnering. I think it's very important that we consider public-private partnerships and how they can be utilized in this space to drive towards improved child health.

I look forward to talking with a lot of you in different venues about the different ways we can go, and of course we have to think about there's a lot on the menu of what we can accomplish with the resources and that are authorized and within the five-year reauthorization for the 409I program. So with that and on behalf of a lot of people I want to thank you for your time.

>> The next speaker is Ms. Pamela Gavin who is joining us from the National Organization for Rare Disorders.

Session One: Interested Parties Comments

National Organization for Rare Disorders (NORD): Pamela Gavin, MBA

>> I can't do this without these (glasses). Good morning. My name is Pamela Gavin, and I'm the CEO of the National Organization for Rare Disorders. I want to begin my remarks with my gratitude and thank you to the FDA for the opportunity to share our thoughts with all of you on this very important topic.

NORD is an independent nonpartisan nonprofit founded 40 years ago by a coalition of patient advocacy groups that were instrumental in passing the Orphan Drug Act. NORD remains a long-standing advocacy organization dedicated to helping people with rare diseases and assisting the organizations that serve them, including more than 355 NORD member organizations. Over more than 30 million people in the United States are living with a rare disease and over half of them are children. Approximately 30% of these children will not live to see their first birthday. Before the passage of the Orphan Drug Act, less than 40 treatments were on the market for rare diseases. Today, 882 of those designations have resulted in at least one FDA approved therapy for use

and 392 rare conditions. Despite the progress, the discovery of diseases has really outpaced the discovery and development of treatments, leaving 95% of the known 10,000 or more rare conditions still lacking an FDA approved therapy.

Even when and where approved orphan products are available, pediatric labeling is often missing. Without proper labeling for pediatric patients, medical providers are left without adequate information regarding the safety, proper dosage and effectiveness of the product. When providers need to prescribe a therapy without proper pediatric labeling, they frequently must extrapolate the appropriate dosage for the patient and advise parents that a therapy has not yet deemed to be safe for children. This creates potential safety and effectiveness challenges, and it risks undermining the families' trust in the therapy. Pediatric studies therefore remain vital for our community.

The Pediatric Research Equity Act, or PREA, and the -- Best Pharmaceuticals for Children Act, BPCA, have helped build on the success of the Orphan Drug Act. These complementary landmark pieces of legislation are designed to improve information about how to use therapeutics safely and effectively in children, while recognizing the unique challenges of orphan product development. PREA and BPCA together provide incentives, flexibility and accountability for the development of pediatric therapies. As a result of over 1,200 labeling changes to include pediatric information, today more drugs, including several key orphan products, are marketed for use in pediatric patients with proper labeling, dosage and safety information.

BPCA requirements for enhanced adverse event reporting has also greatly expanded the availability of real-world safety data for pediatric patients and their families. Notably, orphan indications are exempt from PREA study requirements;

however, in order to incentivize the conduct of rare pediatric studies, written requests may be issued for orphan indications under BPCA. While both PREA and BPCA have supported greater study of pediatric patients, significant gaps remain in pediatric trials for rare conditions. PREA established requirements to study adult product indications in children when children can benefit from pediatric studies; however, far too many required pediatric studies have never been completed. If a company fails to complete an adult post-market study, FDA can penalize the company by imposing a fine. The agency is prohibited from applying these penalties to pediatric post-marketing- studies under PREA. Additionally, in most cases, FDA cannot require orphan products to be studied in children under PREA. While the incentives and requirements under BPCA and PREA are effective in spurring the study of newer therapies in children, they are insufficient for encouraging studies of older therapies. Congress authorized NIH's BPCA program to fund studies of off-patent products used in children with children that companies are not incentivized or required to conduct.

However, the program has been flat funded at 25 million since the original authorization in 2002, as you heard from the previous speaker. When accounting for biomedical research inflation, that purchasing power of that program 20 years ago is about 56% of its original capacity due to the increased cost in conducting therapeutic studies. When PREA was permanently reauthorized in the FDA Reauthorization Act of 2017, the orphan product exemption was maintained. At that time, Congress required FDA to report on the lack of information labeling of products for indications with orphan designations with respect to the use of such products in pediatric populations.

According to FDA's August 2019 report titled ‘Pediatric Labeling of Orphan Drugs’, almost 40% of orphan indications approved from January 1999 to August 2018 that warranted pediatric labeling was incompletely labeled. About 64% of that group of those products have no pediatric information and about 36% or just over one third was missing some pediatric information. These gaps weren't addressing the requirements of the existing requirements and incentives to conduct pediatric rare disease studies. When PREA was first passed in 2003, orphan therapies made up a small minority of annual approvals. Today, the majority of therapies approved are orphan products; therefore, the majority of newly approved therapies are exempt from pediatric study requirements. Refinements to existing pediatric study requirements and incentives are needed to ensure pediatric patients with rare diseases and their families are not left behind, as the science of rare disease treatment accelerates. Developing therapies for rare diseases is uniquely challenging. Pediatric studies can be significantly more complex to plan and implement than for other diseases. Certainly, certain regulatory requirements that are appropriate for more common diseases must be adapted to the rare disease context.

For some orphan products, temporary or permanent exemptions from study requirements, including in some cases certain pediatric studies, may be needed to adequately support continued therapeutic development efforts. NORD appreciated the FDA's release of the 2023 draft guidance that was in a slide that set the stage for this morning's talk. It's titled ‘Pediatric Drug Development: Regulatory Considerations complying with the Pediatric Research Equity Act and qualified for pediatric exclusivity under the Best Pharmaceuticals for Children Act’. However, we were concerned that

the document stated that upon finalization “FDA does not expect to issue written requests solely for studies or planned studies that are required under PREA”. This strong departure from previous practice may be warranted in many cases. However, the unique challenges of orphan therapeutic development continue to make pediatric studies in rare diseases more complex.

NORD encourages FDA to reconsider this policy change for those select orphan products that are subject to PREA requirements, as they should remain BPCA eligible given the significant challenges in this arena. FDA should consider tools, pilot programs and additional guidance that the agency can provide sponsors to further de- risk therapeutic development in rare diseases and reduce the burden associated with pediatric studies for rare diseases in particular. For example, FDA could consider how best to leverage real-world evidence, natural history studies, and the RDIA pilot program to help bring more safe and effective therapies to market for rare disease patients. Pediatric patients. Refinements pursued through legislation can also help strengthen enforcement or requirements, as well as increase opportunities to accelerate incentives designed to spur more pediatric studies. I want to close by thanking FDA for convening the public and for its commitment to partnering with rare disease patients through the therapeutic development process. Much progress has been made, and I can certainly tell from the alignment of comments already this morning that we are on the right path to achieve more. NORS stands ready to collaborate with the agency, industry leaders and other stakeholders to advance pediatric rare disease development. Thank you.

>> Thank you Ms. Gavin. The next speakers are Dr. Petrea Cober and Dr. Rachel Meyers from the Pediatric Pharmacy Association. Dr. Meyers is joining us here at the podium and Dr. Cober will be joining us virtually.

Session One: Interested Parties Comments

Pediatric Pharmacy Association (PPA): M. Petrea Cober, PharmD and Rachel Meyers, PharmD

>> I will let my colleague begin and I will advance the slides.

Thank you Dr. Meyers. My name is Patricia Cober, and I'm the immediate past president of the Pediatric Pharmacy Association, and Dr. Meyers and I would like to talk to you a little bit about the struggles that we have as pediatric pharmacists. Who is the Pediatric Pharmacy Association? We are a national nonprofit organization that represents pediatric pharmacists. Currently we have over 1,700 members in our organization and our mission is really to advance pediatric pharmacy practice, support the health and well-being of children and promote safe and effective medication use in children through collaboration, advocacy, research and education. What do we like about these two very important laws? They have provided earlier labeling for drugs in pediatrics. As pediatric pharmacists, we actually have better information than just case reports. I was a neonatal pharmacist for 20 years and it's not uncommon for us to have to use very limited information in order to take care of our patients. With this information, we are more confident in using these newer drugs in children.

I will take over now, I am Rachel Myers, and I am a pediatric ICU pharmacist and a general pediatric pharmacist and I'm a clinical professor at Rutgers University. We will

talk about what we are missing here. We wanted to highlight one of our core projects that we have at the Pediatric Pharmacy Association and that's called the KIDs List. We first developed the KIDs List in 2020, and it's somewhat equivalent to what the BEERS Criteria is for geriatric patients. The BEERS Criteria came out in about the mid-90s and lists the medications that are what we consider inappropriate for geriatric patients. We try to take that same approach for pediatric patients. These are again potentially inappropriate medications, which of course, there may always be clinical situations where they are appropriate. First published in 2020, and we just updated it in 2025, and just came out in July of this year.

What we found in the KIDs List that I wanted to highlight here is in the 2025 edition, there were 39 drugs and drug classes and 10 excipients that we consider potentially inappropriate. Of those, 69% had a low or very low quality of evidence. So we're going based on a couple of case reports and the best evidence we can find. It really highlights the need for more research for medication safety in children. There are other things out there. Ethanol is on our list of excipients that we are concerned about and right now the only guidance on ethanol is in over-the-counter products. So we would love to see more guidance on ethanol, particularly in prescription products because it continues to be an excipient we have to battle and navigate around in our practices. Emerging evidence helps to clarify some of our risks. We know there's been a lot out on Montelukast in the last few years, for example. Daptomycin is another example that was on our original list and we took that off the list in our most recent edition because we have more evidence now about its safety in neonates. As has been highlighted, old drugs need attention too, and we are very grateful for all the NIH

funding and drugs that are getting more and more labeling. We have a few still that have other needs out there. We have metronidazole, we still need more data on, especially in the way we use it in practice now. Doxycycline we could use some more information on.

The other thing that I want to highlight, which I think maybe gets missed sometimes, is what is actually in the package insert that comes out. Sometimes we get package inserts, even for some of the newer approved drugs, and this information is not helpful, and it runs contrary to other requirements. For example, daptomycin, the diluent volume that they tell the pharmacist to mix it in is based on the age of the child and we are not allowed to mix that way anymore and haven't been allowed to mix that way in 15 years. We are required to have a standard concentration, and we can't do a different concentration for every child. We can't build an electronic medical record that way or run an infusion pump safely that way. What is in the label runs contrary to how we are supposed to be practicing. Chlorothiazide suspension, the dose is listed per pound and we don't like that anymore in medicine and the volume is listed in ml and in teaspoonfuls, which we don't like using teaspoonfuls either. I know the American Academy of Pediatrics has come out very strongly opposed to teaspoons. We, as pediatric pharmacists, completely agree with that, we want to use volumetric measurements for measuring.

Liquid concentrations for a lot of our medications are still listed for 5 ml's. This adds another calculation – in pediatric pharmacy we do a lot of math - we would love one less step and also contributes to medication errors. And that is not the way we dose

medicines anymore -- we don’t dose based on teaspoon. The way information is presented runs contrary to how we practice.

We have more examples, newer drugs with unhelpful information. Rivaroxaban – this happened to me recently with a patient. I had a patient who needed a 5 mg dose and the package insert says you may not use 2.5 mg tablets, even though the child can swallow tablets. The requirement is to use the liquid. We don't have the liquid on formulary at my hospital. All we have is the 2.5 mg tablets so that is what we we’re going to give. Some things come out and don't really make sense.

Combination antibiotics continue to be a big sticking point, particularly in hospitals, but also in the outpatient setting. The information coming in labels lists dosing and concentrations and mixing preparation in both total dose of the different products and then also in individual components. So it’s almost too much information and everyone is doing it different and it leads to medication errors, both on the inpatient and outpatient sides. We would love to see guidance from the FDA about doing it the same way for different combination antibiotics.

Finally, we wouldn’t be pharmacists if we didn't bring up costs. Cost - it's always a concern for us and for our patients. We always have trouble with reimbursements sending patients home on medications that may still be off label for pediatrics. Maybe it’s been approved in adults already and we don't have the labeling for kids yet. And especially with some of the biosimilars that we have children coming in for infusions and we run into a lot of issues with insurance coverage. The price of some of these newer pediatric products, and we love having them and we’re grateful to have them, but

sometimes the price can be prohibitive for some of our pediatric patients. Now I'm going to transition back to Petrea.

>> Thank you. Again, as I mentioned, the Pediatric Pharmacy Association is very big with advocacy. Sometimes, as a pediatric pharmacist, unfortunately our hands are tied with some legal obligations that we have and it's shocking for many people to realize that prescriptions do not have to have a weight on them, and everything is dosed in milligrams per kilogram for these patients. How am I, as a pharmacist, supposed to be able to check that dose for that patient if I don't have things such as their weight, and even more importantly, some things are dosed in body surface area, so I also have to have their height. These are definitely issues that we struggle with every single day and I just want to point out our most recent position paper on patient weight being included on all medical prescriptions and advocating for that more.

In summary, Dr, Meyers and I and the entire Pediatric Pharmacy Association, we love what the FDA is doing and we love having more data, more labeling for our newer medications, newer drugs, even some of our classics that we have. But we need to keep on looking at older medications, having data on pediatric dosing, updating the labeling for safety, really focusing more, moving away from providing doses in teaspoons, providing doses per 5 ml, which really is not indicated at this time. And then in a more practical user-friendly information and labeling, often times we find the labeling is very hard for parents and caregivers on how to administer the medication to their children. So often times the pediatric pharmacist has to serve that role in translating the information to these vital caregivers of our patients. I want to thank you

for all that you do for children and help us to continue to help the patients that we love so dearly. Thank you.

>> Thank you very much Dr. Cober and Dr. Meyers. That concludes Session 1. I would like to thank all the Session 1 speakers one more time. And we are now going to take a brief break and we will return at 10:40 AM Eastern for Session 2.

(Break until 10:40 AM)

>> Welcome back. We will go ahead and open Session 2. Our next speaker is Dr. Cathy Gelotte from the Consumer Healthcare Products Association who has shared a video of her remarks for us today.

Session Two: Interested Parties Comments

Consumer Healthcare Products Association (CHPA): Cathy K. Gelotte, PhD

>> Good afternoon, I'm Cathy Gelotte, a clinical consultant representing the Consumer Healthcare Products Association. Previously, I was employed by J&J Consumer for about 25 years. During my time there, I was a member of CHPA's Pediatric Research Task Group and conducted pharmacokinetic and efficacy studies with OTC medicines. Our goal today is to provide perspective on challenges with conducting pediatric research on OTC medicines and to suggest potential solutions for FDA's committee to consumers. From our collective experiences, pediatric research of OTC medicines has unique challenges and barriers compared with prescription drugs. Regarding potential solutions, the CHPA Task Group supports the extrapolation of efficacy and/or safety from adults to children, including extrapolation among pediatric age groups. We also

advocate the development of alternative clinical research methods and sources of evidence to support the efficacy and safety of pediatric OTC medicines.

Let's start with some challenges. First, many OTC medicines are intended to provide temporary relief of symptoms associated with acute conditions, such as headaches and colds, rather than to resolve the underlying disease state. These acute conditions are generally mild and self-limiting, which makes demonstrating efficacy challenging, even in adults. For example, symptom improvement scores are often limited to the low end of a four-point scale near mild to moderate severity. To evaluate cold symptoms, there's only a short 2 to 3 day window after a cold begins when they are severe enough to detect strong effects. Also, these clinical trials have a high placebo response due to the rapid improvement in daily variation of acute symptoms, making it difficult to discern treatment effects. Adding to this is the higher placebo response by children for self-reporting symptom relief compared to adults.

Another challenge is recruiting children for treatments for transient minor ailments, typically managed by parents with available OTC medicines. Finally, demonstrating efficacy, of a single ingredient that relieves only one symptom of the common cold, for example, is more difficult than demonstrating efficacy of combination products that relieve multiple symptoms. Specifically, the lack of improvement and other symptoms can cast a negative halo effect on subjective scoring of the target symptoms being studied. Although recruiting children for clinical studies is generally challenging, a few enrollment barriers unique to OTC medicines were identified in our pediatric efficacy trials. The most impactful, is that parents don't take children to the doctor for most colds.

Instead, parents treat the symptoms at home, after selecting products readily available over the counter.

So there is a limited opportunity for a parent to interact with an investigator site. In fact, it took over four years to involve children ages 6 to 11 years in each of two cold studies. Enrollment was especially difficult for the cough suppression studies where only 128 children got enrolled before the study was terminated. Another barrier was there is only one of multiple cold symptoms was addressed in each study. Most children experienced multiple cold symptoms to provide relief of only one may not be desirable.

Lastly, the study requirements may have outweighed the potential benefit for a mild condition. These included missing school and participating in a clinic visit for up to six hours, wearing a cough counting device for 24 hours, completing self-assessments over several days, and disrupting parent schedules with return visits. Other barriers were identified by our web-based symptom surveillance study of cold symptoms, which often surveyed the willingness of parents to participate in clinical trials of OTC medicines. We learned that 46% of parents were not willing to go to the clinic site within one day of symptoms, which is the key timeframe to have symptoms severe enough to measure. 88% of parents were not willing to permit their children to remain out of school to participate in the study. 71% of parents were not willing to dose their child or administer a symptom scoring tool at school. Often cold medicines are dosed every 4 to 6 hours, thus making efficacy assessments challenging. Regarding children ages 2 to 5 years, use of self-reporting tools to evaluate symptom relief is beyond their comprehension. Now Let's address some potential solutions to the challenges and barriers.

The CHPA Task Group strongly supports the implementation of extrapolation to confirm the efficacy of OTC medicines in children. The approach limits the burden on children, such as time away from school, especially when the ailment is mild and addressable by parents. It leverages modeling simulations to support pediatric doses, disease progression similarity, and bridging of pharmacodynamics and efficacy among pediatric age groups and adults. We also support techniques, such as model-based meta-analyses of summary level data in adults to support extrapolation. Another solution we recommend, when additional pediatric efficacy data are needed, is to design studies that align with the pharmacology of the active ingredients and label indications. Use objective and surrogate biomarkers, where possible, and have endpoints that support the temporary symptom of relief over one or a couple doses. We also propose modifying study protocols to permit the evaluation of combination products that relieve multiple symptoms, rather than study each ingredient individually. There may be opportunities to loosen burdensome inclusion criteria because OTC medicines are generally well-understood and commonly used by parents. Another modification would be to collect only safety data for a younger age group in the same study with older children or adults to support efficacy extrapolation.

Another potential approach is to adapt study designs to accommodate the OTC environment. We could reimagine study designs for OTC pediatric products at the first point of contact with the healthcare professional where a parent manages their child's ailment. This may include open-label use studies to obtain safety data when needed to support efficacy extrapolation or double-blind placebo-controlled studies. For example, a study may be set up at pharmacy clinics, which represents a real-world scenario.

Qualified pharmacists or nurse practitioners would be enlisted as investigators. Tools, such as FDA's 'My Study app' would enable electronic data collection by smart phones at home. And a 24-hour call center would be available to answer questions and address any safety concerns that may arise.

Here are examples of other alternative approaches to consider when it makes sense for researching pediatric OTC medicines. One is to implement a master protocol that might be helpful when recruiting children for a multi-symptom condition. The advantage is that the trial has a single infrastructure and trial design but evaluates multiple ingredients and products simultaneously in more than one sub-study. Investigational supplies can be simplified by evaluating blinded commercial products because most OTC medicines are already commercially available. Besides pharmacy, clinics as mentioned previously, consider other nontraditional investigational sites in the OTC environment. These may be similar to actual OTC sites where contract research organizations set up investigational sites in empty store space at malls when conducting Rx OTC switching studies in adults.

In summary, several challenges and barriers that are unique to studying pediatric OTC medicines have been identified. CHPA Member companies advocate extrapolation, where appropriate, to support pediatric efficacy or safety of OTC medicines. When needed to confirm efficacy or safety, we also advocate that alternative approaches to conduct pediatric research in the OTC environment should be adopted. Thank you for your consideration.

>> Thank you very much, Dr. Gelotte. So our next speaker is Dr. Florence Bourgeois…OK a little technical issue there. Our next speaker is Dr. Florence Bourgeois from the Harvard MIT Center for regulatory science, who actually also has shared a video of her remarks this morning.

Session Two: Interested Parties Comments

Harvard-MIT Center for Regulatory Science: Florence Bourgeois, MD, MPH

>> Hello, my name is Florence Bourgeois, and I am a pediatrician and Associate Professor of Pediatrics at Boston Children's Hospital and Harvard Medical School. I'm also the Director of the Harvard MIT Center for Regulatory Science. I'm delighted to be here today to contribute to this important session and will be speaking to you on pediatric labeling additions that result from PREA studies.

In considering topics for this talk today, I looked at the last report submitted by the FDA to U.S. Congress back in 2021 and focused on some of the findings and statements around the timelines to study completion. Specifically, the FDA at that time looked at a three-year period and stated that the average length of time between approval of an application and the inclusion of any pediatric use information in the product's labeling was approximately six years. They also stated that these data suggest that there remains a substantial lag between original approval of a drug and the inclusion of specific pediatric use information in the drug's labeling. The FDA also noted that requirements may have changed as a result some of the implementations of the Food and Drug Administration Safety and Innovation Act which went into effect in 2012 and some of those might have a positive effect on these timelines. Specifically, there

were new requirements put in place to submit initial pediatric study plans no later than 60 days after end of phase 2 meetings.

To examine this issue further, I looked at a cohort of drugs approved over a six-year period from 2014 through 2019. This period was chosen to allow for the full implementation of any new changes after the last legislation in 2012, and also to allow for a minimum five-year follow-up through the end of 2024. During this time period there was a total 261 drugs that were approved, of which 77 or 30% (almost one third) had PREA study requirements and there were a total of 172 PREA study requirements associated with these 77 drugs. Looking at the study types, the majority were efficacy studies. So, 46% of these PREA study requirements were efficacy studies followed by 40% safety studies and then 14% were PK/PD studies. It is also interesting to look at the breakdown across the age groups-neonates through adolescence. As you can see, the smallest number of studies are issued for neonates at about 23%, and there is an increasing percentage with the older age groups. This would be consistent with what we know of how pediatric studies are conducted with progressive inclusion of progressively younger age groups.

When the studies are issued, there is a detailed study plan that has been agreed upon between the FDA and the sponsor which includes a planned study duration and a report due date. For the 77 drugs that I examined, the mean planned study duration was 5.4 years with a range of six weeks to 14 years. To put this into context, the FDA can also issue post marketing requirements for adult studies under separate authorities and for these, the average duration has been estimated in separate studies to be about 2 to 3 and a half years. This is of course not to say that we would expect the pediatric

studies to have these types of shorter durations, but it is useful as a reference perhaps, but also for comparison as we consider conduct and completion of pediatric studies. Looking at the mean durations by study type, you can see that efficacy studies are planned as the longest studies at about 6.4 years whereas PK/PD studies are anticipated to be the shortest at 2.7.

Across the age groups there were no particular differences with all of them being between 5 and 5.4 years for each of the five age groups. Once this study is underway, for a number of reasons, the plan durations can change. In particular, sponsors can request extensions to the due date which need to be reviewed and then approved by the FDA. Studies can also be modified, in which case they may be replaced and this replacement or new version of the study can then include a modified and extended later due date. It turns out that this does happen with some frequency and in this cohort of studies, overall, there were about 38% studies with at least one extension, 21% that were replaced with a modified so extended due date, and in all, this comprised 56% of studies. So, 56% had a modification and extension to their original due date and the mean change in the due date was to 2.5 years. This is not insubstantial if you consider that the original planned duration of the studies was about 5.4 years.

How does this translate into the observed timelines and completion of pediatric studies? Well, take a look now, at just the 134 studies in that cohort that had due dates by the end of 2024. For all of these, we would expect them to be completed. And what you see are just over half, 54% were completed and 1/4 were completed by the original due date. There were some variation by study type with efficacy studies showing the lowest percentage of on-time completion at 16% and safety studies the highest at 33%.

There was also some variation with the age groups. Neonates had the lowest percentage of on time completion at 16%, the others were all higher, although there was no particular or noticeable trend with the increasing age groups.

Another way to examine completion rates is to compare the expected and observed times to completion using Kaplan-Meier analysis which allows us to see what study completion actually looks like, over time. Here in the red line, we have the percentage of studies expected to be completed over time since the drug approval and the blue line depicts the actual completion rate. What you will notice is that there is an increasing divergence over time. So, at five years, we have 47% of studies that are expected to be completed whereas 26% are actually observed, to be completed, and by 10 years, while 93% of studies were expected to be completed, we found that just under two thirds, so 64%, were actually completed.

Now let's take a look, at what these timelines mean for the addition of pediatric labeling information, which is the primary objective. As you recall, we have been looking at a total of 77 drugs with PREA study requirements. And among these, over the study period, I found that there was almost half, so 49%, that had some type of pediatric labeling information added. Most of these additions were the addition of pediatric approval at 82%, another 21% involved expansion of approved pediatric age ranges- usually due to lower age ranges and then 3% (so small number in this group) had information added regarding lack of safety or effectiveness in pediatric patients. In terms of the time to labeling additions, prescribing information was added after a mean of 5.2 years with some variation based on the type of information being added. So, about 5.4 years for the addition of pediatric approval, about 3.5 years for the expansion

of age groups and 8.7 years, so much longer, for the addition of information indicating lack of safety or effectiveness. In all this looks fairly positive if you'll recall that the planned mean duration for the PREA studies was 5.4 years. But there are a few important considerations with interpreting these numbers.

First, since many studies are not completed on time, this represents just a small sample of studies, which might not be representative of the full cohort. Indeed, if we look at the expected duration for just this group of studies with labeling changes, it was somewhat shorter at just 4.2 years. In addition, what these mean durations don't capture, are the large number of drugs that still have no pediatric labeling information. Here again, looking at Kaplan-Meier analysis is useful to more fully understand the timelines for these labeling activities. The red line here are the expected completion dates for all studies associated with a drug. This is not necessarily the same date when labeling changes will be expected but we will be using that as a proxy. And the blue line depicts time to labeling addition. Again, there is a divergence over time between the expected completion of studies and observed labeling activities. At five years, you have 28% of drugs that are expected to have all PREA studies completed, whereas 14% have labeling additions. By 10 years, while 90% of drugs are expected to have all studies completed, just 50% have labeling changes. So, this is one important take away here: that over a follow-up period of 10 years among all drugs with PREA study requirements, half have pediatric labeling information added at the 10-year mark.

In the way of conclusions, PREA studies are issued for a large number of drugs, (almost one-third), so they play an important part of the pediatric prescribing information that becomes available. Over half of these studies have revisions to the original due

date with extensions of about 2.5 years, and about 1/4 of the PREA studies are eventually completed by the original due date. Importantly, what this means is that at 10 years since drug approval, about 50% of drugs have pediatric labeling additions, although 90% of drugs were expected to have all PREA studies completed. What this really indicates is that while the FDA already has a number of activities that they engage in with close monitoring of study planning and conduct, these timelines do indicate that other approaches may be needed to increase timely labeling additions and this could include additional enforcement mechanisms, incentive structures for sponsors and perhaps, also, prioritization of studies deemed to be most feasible or to have the greatest clinical value for pediatric patients. Thank you very much, please feel free to reach out at this email with any questions and again, many thanks for including me in today's program.

>> We want to thank Dr. Bourgeois for those comments. So we have our next speaker who is coming up to the podium, Dr. Danny Benjamin, who is speaking on behalf of the Multiregional Clinical Trials Center of Brigham and Women's Hospital and Harvard.

Session Two: Interested Parties Comments

Multi-Regional Clinical Trials (MRCT) Center of Brigham and Women's Hospital and Harvard: Danny Benjamin, MD, PhD

>> Thanks so much, I'm Danny Benjamin, distinguished Professor of Pediatrics at Duke University. I happen to be the Chair of the Pediatric Trials Network, the efforts of the Pediatric Trials Network will be covered by Rachel Greenberg, who co-chairs that effort together. And this is based on a partnership on platform trials with the Multiregional

Clinical Trials group. I am up here because typically when people talk to you about trial design or platform trials, they've read about it, they have a slide deck and they attempt to educate you about it. But they've actually never done a platform trial themselves. Or if they have done a platform trial, they have done one. They are like the medical student in rounds who says, "In my experience..." Anyway, in partnering with MRCT, and you can see their updates there in the middle bullet on tuberculosis major depressive disorder and oncology, I want to give you two slides on experience so that I'm not like the medical student who says, "I've done two trials so "time and again, I've seen this in patients" or, three patients, "Time after time after time." I'm going to give you some experience that is based on 15 master or platform trials, 15 different platform trials, 10 of them have been through the Best Pharmaceuticals for Children Act.

Just a quick summary. These are varied, these are five different trials. The first two are kind of focused on PK and pharmacology and dosing. You're basically getting the drug per standard of care , and the consent form is, "You are getting the drug per, standard of care as your physician has ordered it, just please give us a little bit of blood, a little bit of baby's blood, some breastmilk or a little bit of your child's blood and we will figure out the dosing later." We have done that to study dozens of molecules with FDA and with NICHD/BPCA. The two trials, SCAMP and LAPs, those are areas where we really are randomizing or doing the study for safety information. And we also get dosing information. For example, forthe antipsychotics, the drugs are labeled for 48 weeks. But of course, anyone who has had a child on one of these molecules knows, your child is going to be taking those for five, or 10 or25 years, which is a little bit longer than 48

weeks as it relates to safety. It is really only amenable to a platform trial can you really make sense of doing that study affordably.

ACTIV-1 was a trial that during the pandemic, the NIH and the Foundation for NIH f asked us to lead. It was in adults. I am not licensed to practice in adults, but I am licensed to do trials in adults, and that is because of our experience with so many platform trials, that they asked us to do that pivotal randomized blinded study for efficacy in nearly 2000 adults during the SARS-CoV-2 pandemic. These are the other trials that have been done just between 2018 and 2024 through the Best Pharmaceuticals for Children Act. There are 10 of those. Those are, the molecules on the right, are not for you to read, although they are publicly available. But we've got some experience with doing some platform trials so I'd like to give you some lessons learned. The first is, on the front side, you are going to be doing a ton more work with getting your key stake holder input. It is really important for all trials, but you can multiply that by several fold if you are going to be doing a platform trial because with each molecule or each question you bring into the trial, brings its own set of interested stakeholders.

So, while the big advantage is that your sites have real infrastructure that they can develop, that comes with it and co-travels with it, a lot of different stakeholders and a lot of different needs. And the economics for these trials really break down in the low single digits with respect to your molecules. You want to be able to need two hands or more, really to count your molecules or questions if you are going to be doing these types of trials. Now, a big advantage of platform trials is they are incredibly flexible. For example, you decide, "oh my gosh," right in the middle of it, "let's include renal

replacement therapy," or, "oh my gosh, we've got all of this dosing and exposure variability in antiepileptics," you can make changes during the trial. The thing is, not only do you know how flexible they are, but all of your partners know that too. So, there is a never ending push to, "Oh, we've got flexibility, let's make this change because it's a living document, a living trial," and we've gotten into some of these platform trials that have been running five, 10, 15 years, and all of sudden Rachel and I will look at each other and are like, "oh my gosh, this is an out-of-control octopus that is on steroids and illegal drugs."

Now, this is related. The platform trials you are able to pivot- so we saw this during the SARS-CoV-2 pandemic, where people were using all sorts of stuff in adults and children of like, "Oh my gosh, remember in 2020 when hydroxychloroquine or Ivermectin or all sorts of other really interesting products to be used in children." Well, what we were able to do with the platform trials was we were able to actually study some of those projects and time to addition of product to first child enrolled during the pandemic was six weeks. That's incredibly powerful. But, again, when you get into these trials, you are going to realize that just like some people are more popular than others, I was rather unpopular in middle school, some drugs are more popular than others. If you are in industry, this can be a real bummer if you are like me and don't get to sit at the cool lunch table and you're sitting in a platform trial with a lot of other cooler drugs, your drugs can really languish.

For NIH this means going really beyond traditional major medical centers and to smaller centers. I wanted to mention just a couple of facts and take some lessons learned looking forward. So BPCA is really uniquely positioned to innovative clinical

trials and these lessons learned can be applied not just to molecules but to other clinical care questions as well. So, what we put into our application for the competitive renewal, we said “ok, we would like to take guidelines that are put out by the AAP or other professional associations and reverse engineer them so that all the molecules that are in there and a lot of other standard of care questions will address all of those where there is considerable equipoise or where there is low-quality evidence.” And the vast majority of guidelines, whether it is in adults or children, the vast majority of recommendations, especially if it is in children, there is considerable equipoise as to whether or not we should be doing what is outlined in the guidelines. So, what we propose is, “Ok, we will first randomize at the site because we definitely don't want the trial to fail. And then we will randomize subsequent questions at the individual level with different time points so that the outcomes don't compete with each other.” So, if you get into a traumatic brain injury, what should you set the intracerebral monitoring pressure for? And then if your ICP goes up, what drugs do you use to bring it down, how far should you bring it down? What should you go to as your second line therapy? All of These are all different questions that can be answered within the same protocol as well as all the various molecules that are being used. The long-term goal is to answer dozens of questions with each trial. This is what I think is the really next step for us in platform trials is to be addressing both standard of care, molecules, are they safe? Do they work? But also, do we even have the right trial design? So, with migraines and major depressive episodes, where the trials are failing, can we really extrapolate? Do we have any business doing that? And within the platform trial is a unique environment for us to accomplish all those things.

Now unfortunately, as has been mentioned, we are not able to execute on that because the Peds Trials Network budget for fiscal year 2025 was cut by over 60%. I know because I am the award recipient. Even though that information isn't publicly available, I know that it happened because I was there. What that meant was we are not able to do any new trials, to get any new trials off the ground. It also means that the four trials we had, that were in startup, we had to stop those trials. And the progress that we are making for child health is considerably disrupted. Together, we are in a group of people who can achieve amazing things. When I look out across my colleagues over the past 25 years, together we have done some really awesome things about which we can be extremely proud to help better the lives of children worldwide. We've done that, and our mission is to continue to do so. Thank you for asking me to speak.

>> Thank you, Dr. Benjamin. So, next we are privileged to be able to hear from patient representatives from iCAN, the International Children's Advisory Network. This morning, we have Anvita, Inaaya and Meghan who will be joining us. Anvita and Inaaya will be joining us virtually and then Meghan has shared a video of her remarks this morning. I will go ahead and invite Anvita to please go ahead and come on camera and share your audio.

Session Two: Interested Parties Comments

Pediatric Patient Representatives (iCAN)

>> Hi. My name is Anvita Anbarticar and I am a member of iCAN. Thank you so much for having me here today to share my perspectives. So, I am 17 years old and a few

years ago, I was diagnosed with silent small bowel Crohn's disease. And since being diagnosed, I have been treated with Humira, which is a biologic. And, having access to a medication like this has really been a game changer. It's been so impactful. Before Humira and other biologics were approved for pediatric use, treatment options were really limited to things like steroids which have a lot of side effects, and hospital IV infusions, which are really inconvenient for both pediatric patients and their families. And so, medications that were off label didn't have clear dosing or safety information for kids. And so, when biologics like Humira were approved for pediatric Crohn's disease under the BPCA, this made a huge difference and it's been able to impact so many kids like me who are able to get that treatment where there is reliable information on how to dose the medication by age and weight, which was really important, especially for someone like me who was always on the smaller side, didn't weigh as much as, you know, kids my age. And so, having that appropriate dosage and the convenience of being able to do the treatment at home meant that I could avoid the side effects and the trips to the hospital to get infusions and it made managing my disease so much easier and sustainable for both me and my family and my community in general.

This is just one example of how policies like the BPCA can directly improve patients' lives like mine. And so by encouraging pediatric studies under this ACT, I think that kids are not left behind and we get treatments that are safe and effective and really tailored to what we need. And so, I kind of just want to end off by saying as more drugs and more treatments like biosimilars do come to market, I really hope that the same kind of focus does remain on children, with labeling and dosing information and safety monitoring to make sure that all kids have access to the same kind of benefits that I

have been able to receive and it's been absolutely amazing. So again, just thank you so much for having us here and allowing patients to share their voice in this conversation.

>> Thank you so much, Anvita. Please join me in giving her a round of applause for her time and comments. Next up, we have Inaaya. Inaaya, you can please come on video and share your audio and begin your remarks.

>> Hi everyone, thank you again for having us here today. It's really like amazing to be a part of the conversation for once. So, my name is Inaaya, I am from Chicago and I'm with iCAN. I'm 16-year-old, a rising junior in high school and I'm a two-time cancer survivor. I was diagnosed with osteosarcoma in 2020, when I was 11, and I had nine months of MAP chemotherapy and had a limb salvage surgery at 12 that gave me a titanium femur and a knee replacement. I then relapsed in my freshman year of high school in 2023, with the same type of cancer in the same leg. And because of the recurrence in under four years, I had the option to either save my leg with a 95% chance that the cancer will come back in under two years, or amputate my leg with a hip disarticulate procedure that would essentially remove my femur from my hip leaving me with only my hip and my pelvis.

So, I chose to amputate at 14 years old. And then I had six months of ifosfamide and etoposide chemotherapy and had my amputation at MD Anderson. And, I am now one-year cancer free since April and I'm reliant on a prosthetic. I've been a part of iCAN since last November, so seven months after surgery, which gave me the opportunity to have friends to turn to for support. I also recently started my own podcast, "Sickening (not just medically)" it's @sickening.podcast on Instagram to interview teenagers who

have similar experiences with illness, civilian hospitalization plus professionals in those fields. As a childhood cancer survivor I am very grateful for the treatments that saved my life; treatments that wouldn't have existed without the pediatric legislation like the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act. But I also see the gaps when it comes to kids like me. The existence of legislation like PREA and BPCA have made a tangible difference in treatment availability for kids like me. During treatment I was fortunate to receive therapies that were either developed specifically or tested in pediatric populations, but it's not the case that every child has access to, in the past. As a childhood cancer survivor, I've experienced firsthand the impact that pediatric legislation has had, not only on my own journey, but in the broader cancer survivor community.

The legislations like the BPCA and the PREA have played crucial roles in driving research and clinical trials, specifically for peds patients, and I have seen differences that this makes. In my case, I benefited from the treatment plan that was shaped by more recent clinical studies focused on children, giving me more chances of survival and long-term side effects. I have also seen families who have participated in clinical trials that wouldn't be here today without this push for legislation. However, despite progress, there is still major unmet needs. Childhood cancers are biologically different from adult cancers and too many types lack targeted therapies. For rare or aggressive cancers like brain tumors, relapsed leukemias, and osteosarcoma, which is the cancer that I had, treatment options are limited and very, very outdated. Additionally, survivorship care and research into long-term side effects for childhood cancer treatment are still lagging behind.

From my perspective, continued support and expansion of pediatric-specific drug development is very essential, especially for survivors. We need more investment and treatments designed specifically for children, and not just from the adult versions, and more focused on reducing lifelong burdens that many kids survivors face that lead into their adult life. For example, my amputation. This legislation has saved lives, including mine. But more can be done to ensure that every child has access to effective, safe, and modern treatment. So, as a cancer survivor, I've come to understand how critical requirements under the PREA and incentives offered through the BPCA are to ensure kids like me have access to safer and more effective treatment. Before these Acts, especially, many drugs were used to treat children including chemotherapy and other cancer therapies, were only developed for adults. Though there has been a noticeable shift in recent years. Drug companies are now required or strongly incentivized to conduct studies in children leading to more tailored and informed treatment options.

This translated into a treatment plan for me, personally, that was more based on research that included kids like me, and was very more personalized, and demonstrated the need to continue to keep doing this. I was very, very lucky to benefit from clinical trial data that would not have existed without this legislation. That being said, I very, very much believe in the balance between requirements and incentives that still need to work. More rare and high risk pediatric cancers don’t see the same investment because they affect fewer children and aren’t as nearly profitable for pharmaceutical companies. This is where the incentives under the BPCA become very vital. They encourage companies to study drugs for conditions that may not have as much of the larger market, but the need is still life or death for these kids.

Also, international alignment is incredibly important. Because childhood cancer does not recognize borders. And aligning pediatric drug development across countries can mean faster access to better treatment globally. Right now, some therapies are more approved in Europe and not in the US or vice versa which creates very much unnecessary delays for families that are seeking help for their kids. I see these families that are affected through the iCAN summit where I meet families and kids from around the world that have similar yet very different conditions to me but still face the same kind of struggles like this. Scientific innovations like pediatric exploration, adaptive trial designs, biomarkers, real-world data, have the potential to dramatically accelerate the development for better treatments. In my case, I was very, very fortunate to have treatment during this time where newer protocols based on recent data and evolving trial designs were starting to shape care in pediatrics. That contributed to both my survival and my quality for life today. Pediatric exploration, for example, can help apply data from adult trials to children potentially speeding up the process to access therapy. But as a survivor, I know that children are not just small adults. Our bodies respond differently to treatment and cancer itself can behave incredibly differently from a child and in an adult.

So, while this exploration is very helpful in some cases, it doesn't replace the dedicated pediatric trials, especially for diseases that are unique to children like, for instance, osteosarcoma. Adaptive trial designs and the use of biomarkers are really exciting because they also allow trials to be more flexible and more personalized. This can mean that fewer kids are exposed to treatments that aren’t working and faster identification of therapies that do. These innovations hold a lot of promise, but they also

require infrastructure and expertise that not every pediatric cancer center has access to, especially in underserved and rural areas. Real-world data is an incredibly powerful tool as well. Because, I want my experience and the experience of other kids, especially kids at iCAN, who went through treatment to contribute to better care for the next child going through this. But collecting and using real-world data in pediatrics comes with its own ethical and logistical challenges especially around privacy, consent, and data standardization. But since we have seen the successes, and I'm living proof of the progress that medicine has created, we still face challenges ensuring scientific advances that benefit all children and not just those that live around major research hospitals or with common types of cancers. We need to continue investing in infrastructure, data systems and equitable trial access to truly realize the promises of these advances. In short, science is evolving and it is going to continue evolving as years come. The question is whether we can evolve the systems fast enough to bring science to the bedside. Because as we say at iCAN, “For every child, everywhere.” Thank you so much.

>> Thank you so much, Inaaya. And next we will hear from Meghan, who, again, has shared a video.

>> Hello, my name is Meghan Harrington and I’m 19 and a sophomore at Brown University, with dreams of attending medical school in a few years, and eventually pursuing a career as a pediatric physician for young patients with chronic illnesses like myself. However, if I were in the same disease state as I was at twelve years old battling what my doctors called one of their most complex cases, I perhaps would not be here speaking to you or aiming for such big dreams. At that age, I spent several weeks

in the hospital, missed over 50 days of school and was the weakest I'd ever been. My doctors prescribed me with a heavy dose of steroids, which not only resulted in me gaining 10 pounds in one month, but hardly masked the symptoms of my ulcerative colitis. Upon stopping steroids, my body weakened even more. In response to this, my doctors ran through a cycle of various treatment cocktails to no avail.

The next course of action was to place me on biologic infusions alongside weekly injections of methotrexate. I began with Remicade infusions which only slightly alleviated symptoms but also introduced some challenging side effects- most notably a severe case of plaque psoriasis covering my whole body. My doctor, short of luck, and eager to find a solution, took me off Remicade and placed me on a treatment of Entyvio infusions instead. Shortly after the psoriasis appeared, a plethora of other mysterious symptoms manifested. I was inflamed from head to toe with styes in my eyes, canker sores, swollen lymph nodes and a persistent pain in my back and legs.

After being admitted to my local hospital for a week and undergoing several tests and scans for a handful of different specialists, my rheumatologist diagnosed me with chronic recurrent multifocal osteomyelitis, or CRMO, an inflammatory disease affecting my bones- which explained the sudden emergence of all of the inflammatory symptoms. I started pamidronate infusions alongside my Entyvio infusions in an attempt to treat both the colitis and the osteomyelitis, but the psoriasis still persisted. After much discussion with all of my various specialists, we decided to abandon the infusions all together and switch to Humira injections which could treat the colitis, osteomyelitis and psoriasis all at once. I was overjoyed to not have to trek to the hospital any more for my

dreadful infusions and to be able to self-administer my medications by means of a simple auto-injector pen.

After a few months on Humira, my symptoms and pain subsided, I lost my moon face weight and I felt strong again. I have now been on Humira for five and half years and I can confidently say that I'm the healthiest and happiest I've been thanks to having found the right treatment for me. But this was only possible through a complex process of trial and error with each individual treatment. I'm extremely grateful for being diagnosed and treated in time where funding was available for IBD research but in the past year, over 40% of the NIH budget has been cut. Which, according to a survey by the Chrohns and Colitis Foundation, has led 62% of federally funded IBD researchers to have concerns about continuing their work.

Additionally, with the recent release of the Big Beautiful Bill, coverage for Medicare is being stripped for millions of Americans. And federal student loans are facing restrictions, prohibiting several students from pursuing careers in medical research. I can only hope that future pediatric patients will be as fortunate as I was to receive such incredible care and treatment. But this is ultimately dependent on continued funding for pediatric drug advancement research. We need more ongoing research for young patients who are failing the current drug options on the market. In fact, if not for the extensive research that produced Humira, I don't know where I would be today. I would likely have few treatment options left and be considering surgery or maybe even still suffering through symptoms. I didn’t intend to give this entire speech for sympathy or just to give some corny inspirational recovery story, but rather to stress the ways in which pediatric drug research has saved my life. Thank you.

>> Thank you so much, Megan, for those comments. And let's give all three another round of applause for sharing their perspectives. Each of these young ladies chose to develop these remarks so that they can participate and use their voice in this meeting. Next up to the podium, we have our next speaker, which is Dr. Rachel Greenberg, who is joining us from the Pediatric Trials Network.

Session Two: Interested Parties Comments

Pediatric Trials Network (PTN); Rachel G. Greenberg, MD, MB, MHS

>> Thanks very much for the opportunity to present here today on behalf of the Pediatric Trials Network. My clinical background is as a neonatologist and pediatrician and I'm one of the Network leaders for the Clinical Coordinating Center of PTN at the Duke Clinical Research Institute. I'm really excited to be here today to tell you about the Network's impact thus far within the BPCA program, and our vision for next steps moving forward. So, the PTN, as you've heard from others, is an infrastructure for investigators to conduct pediatric drug and device trials.

The network is sponsored by NICHD under BPCA to perform studies in off patent therapeutics and devices. Since it was established in 2010, we've enrolled over 12,500 individuals across over 300 sites. The Network studies not just one therapeutic area but is focused on many different therapeutic areas from intensive care to psychiatry to maternal and infant health. We've performed over 50 studies, and importantly these studies have been done under the rigor of FDA oversight, and as a result we have been able to submit data from these studies in support of changes to pediatric labels in 26 instances, where we added or changed the guidance within the pediatric label. To give

you a sense of the breadth of what PTN has accomplished, here is a list of the molecules that we've studied. So when you take a look at this and you're either an inpatient or outpatient pediatric clinician or even if you are a parent who has a child receiving a medication, there is a reasonable chance that PTN, in some way, has impacted that molecule that you are prescribing or taking. And the impact, as I mentioned, the reach of PTN, is really not just in one particular geographic area, but is spread across 45 states where we've enrolled participants. And, for areas that have not enrolled participants, we are setting up partnerships and training programs to increase the ability and knowledge to enroll in pediatric clinical trials.

PTN exists because there's a gap in knowledge of pediatric medication dosing, safety and effectiveness. And the reason that this gap exists is because pediatric clinical trials are really difficult to do for a lot of reasons. I'm going to talk about a few of those and the way that PTN has been able to be successful in responding to those. So one challenge is the difficulty of contracting and startup. A problem that is magnified in pediatrics because of the number of sites needed to enroll the number of participants to have a successful trial. In order to minimize these logistical challenges, we've created master protocols platform trials, like Dr. Benjamin described, where we can study multiple drugs under a single protocol, under a single contract with a site and that minimizes the challenge. An example is our maternal infant lactation study that we call, "CUDDLE," and the CUDDLE study, for example, has led to two label changes already for ondansetron and oxycodone. And there is more than 20 drugs in the queue to follow. As we know, another challenge in pediatrics is that children, and in particular, infants, have a very limited blood volume.

So, while it might not be a huge deal for an adult to have a six or eight tubes of blood drawn to measure concentration, that kind of intervention in a 500 g infant would be their entire blood volume or more. So as part of the Network, we worked with regulatory compliant laboratories to develop sensitive assays that require just a few drops of blood to determine blood concentrations and then we work to make those methods available to other researchers who are wanting to study those molecules in children. A huge challenge for pediatric trials, of course, is the limited number of available participants. So, in order to address this, we've negotiated trial design with FDA upfront, often at pre- IND meetings, to make sure we are doing just the right trial with the right design that makes the most sense that will actually lead to a label change in the end. And we've also worked very hard to incorporate real world data and real world evidence to minimize the number of participants that actually need to be enrolled to make a difference.

I'm going to give a real quick example of our real-world evidence in action. We did this study of the pharmacokinetics of ampicillin where we enrolled 64 infants in an open label multicenter study and we also looked at safety in that study. But in only 64 infants, it can be very challenging to pick up a safety signal. So, we leveraged a partnership that we have with a pediatrics medical group and looked within their clinical data warehouse at over 100,000 infants who received ampicillin. So, we used the data from the PK study to calculate the exposure of ampicillin and looked at how that exposure was associated with outcomes in the much larger population using real-world data. And we found that higher exposure was associated with seizures- not something that we could have picked up in the original study with only 64 infants; we just didn't

have the numbers. So, those data in that analysis was submitted to FDA which led to a label change.

Another place that PTN has made an impact is in our interaction with patients and families. We know that in pediatrics there is comparatively low consent rates to participate in studies, and as a result, we've tried always to design our studies with families in mind with simplified trial designs, minimizing participant burden, where the procedures that are performed as part of the studies, are as much as possible, those standard of care procedures that children would already otherwise be receiving. We work hard to engage participants and families in the planning of our studies and for those who participate, we thank them for participating and we share with them the results of our studies. We've partnered with iCAN, who you have heard from earlier, for this results reporting so that when our team creates a results-at-a-glance summary, a one page summary of what happened during the study and what the results were, we work with these wonderful young people from iCAN to create videos so that people can listen and hear about the results of studies in common language and understand them and those are available on our website.

Beyond the actual studies, another focus of PTN is to train the next generation of researchers. We've supported over 300 trainees from really every level across the training spectrum, and we are also embedding trainees into the leadership administration of our network so that they can learn from the process and also have a voice. Trainees and early career investigators design and lead studies within the PTN and they are incorporated often as study authors and often as lead authors as you can see here. In this iteration of the PTN we are also working on expanding our training

program and all of our steering committee members will have a role in training by mentoring or providing projects for training and mentoring.

With all of these activities I've talked about, really, our traditional focus in the studies that we have performed has been in the phase 1 and the phase 2 space with the substantial FDA interactions that I've mentioned. We had a lot of success in those areas but we would love to be able to do more; we would love to be able to do phase 3 studies. Those phase 1 and phase 2 studies are great; they are what we have been able to do to lead to label changes; the 26 label changes that we've had so far, but they are really the low hanging fruit. They are often opportunistic studies; they are studies where we have been able to change labels by extrapolating efficacy from adults.

But if we want to get to the next level and really get to the higher hanging fruit, we are going to need more resources. We would love to be able to do the phase 3 studies and would love to be able to explore new indications for pediatrics for which there is no adult indication. And with sufficient funding, I believe that we could narrow the gap between the low hanging fruit and high hanging fruit and really make a difference that's even greater. Our next steps in PTN, then, are to continue to strengthen the collaborations that we have in terms of both the institutional partnerships we have, the program partnerships that we have, and our hope is to be able to leverage these collaborations so we can continue to do what we have been doing successfully making those label changes, making those differences as part of the BPCA program. But then we hope to extend the reach of PTN's successful methods. Given our experience in pediatric and neonatal and maternal and infant trials, we can work with these other partners and share and leverage our experience to be able to implement

larger studies. We want other groups and collaborators to be able to use PTN as a consultative resource so that we can elevate as many pediatric therapeutic and device trials as possible, that are done both within the BPCA program, and even outside the BPCA program. So, that is our vision. Thank you very much for your attention.

>> Thank you very much Dr. Greenberg, for those remarks. So, next we are moving into Session 3 and we have our next speakers who will be joining us at the podium. We have Dr. David Horton and Dr. Anne Martin Robinson who are joining us from AbbVie.

Session Three: Interested Parties Comments

AbbVie: David Horton, PhD and Anne Martin Robinson, Pharm D

>> Alright. Good morning, everyone. For those that don't know me, my name is David Horton and I'm a Senior Director, Therapeutic Area (TA) Head for our Neuroscience TA within Global Regulatory Strategy. Before we begin, I'd like to thank the FDA and all the interested parties for allowing us to be part of this really important meeting today. For those that aren't familiar with AbbVie, Abbvie is a global pharmaceutical company. We bring novel therapeutics to patients all over the globe across multiple TAs including neuroscience, oncology, immunology and others. Abbvie's mission is to discover and deliver innovative medicines and solutions that address complex health issues and enhance people's lives. All of our 50,000+ employees work tirelessly to support this mission with patients as our north star. As a result of this, Abbvie's had the ability to help more than 60 million people in over 175 countries.

We continue to bring novel therapeutics to the market and we've got a robust pipeline that we are looking to advance to this effect. Many of these products have

included numerous pediatric innovations and we recognize the complexity of pediatric drug development, however, the importance of timely provision of this data so that prescribers can get the information that they need to make the best appropriate choice for their patients. So, our comments today are really built upon this experience with pediatric drug development. Not only the multiple therapies that we are bringing through development but also a lot of the approvals that we have been able to achieve with pediatric indications. The focus of our comments today are really on collaboration with the Agency, particularly focused on three key themes: aligned, transparent and agile pediatric regulatory standards and processes; consideration of the unique aspects of pediatric study planning; and consistent application of extrapolation to rapidly advance approvals. So, with that, I will hand it over to my colleague, Anne.

>> Thank you, David. I'm Anne Robinson, a VP of Regulatory at AbbVie, and our comments are really built upon many of the comments that we have heard from other speakers today. But, maybe focusing on some of the unique aspects of being an industry sponsor and interacting with regulatory agencies. We note that we do have several opportunities to interact with FDA and other global agencies when we are designing and executing pediatric programs. We would support enhancements to these processes to be more agile, transparent and predictable to really achieve the goal of accelerating completion of pediatric development plans and approvals. For instance, provision of post marketing requirement language often comes very late in an application review and will preclude our ability to have a dialogue with the FDA before that language is finalized. That can kind of hamstrings us in terms of the types of study designs we are able to design to achieve the pediatric program. We have a recent

experience where just that happened, and the language would have dictated a study design that we anticipated would have taken decades to complete. So, if we had a very agile and collaborative process where we can have dialogue with the FDA to allow revision of the language both for PMRs and pediatric study plans when needed based upon emerging information, that could accelerate the sometimes months that it takes for us to achieve agreement.

We have often also struggled with addressing different feedback between global agencies as we try to write global development programs for most of our assets. And if we had a more established clear and predictable process to allow parallel agency dialogue, that could help facilitate achievement of a harmonized program. Finally, we note that written requests, we would urge the Agency to consider more focused and static written requests to incentivize non-PREA mandated development. Our recent experience into the current scheme is that FDA requests often to include indications in the written requests that are not necessarily of high interest to the medical community which can ultimately serve to reduce the incentive to develop indications that are of great interest. We've heard themes throughout multiple speakers that pediatric development brings unique executional challenges.

We recognize the FDA's need for substantial evidence to support pediatric approvals and would like to highlight that this can be supported by somewhat broader application of discretion that considers these challenges. We urge the FDA to consider the rarity of diseases in many pediatric indications that should support novel designs and endpoints that might not always match the adult programs. Treatment patterns and prevalence often differ between children and adults and we recommend that the Agency

further consistently consider how these influence trial enrollability because really, ultimately what delays pediatric development often is just study execution and enrollment.

We recommend that FDA provide opportunities for live dialogue rather than written responses through the pediatric study process to allow rapid resolution of issues or adjustments based upon emerging information. I will note that a few of the patients that presented are taking Humira for pediatric IBD. I worked closely on that pediatric UC (ulcerative cholitis) program. There was a nine year delay between the adult and the pediatric approval. And I think we had about nine meetings with the FDA over that time period to ultimately adapt the study design. I think we all learned from that, that, but moving forward, it would be great if could have found ways to do that a little faster on both sides.

Finally, we do support FDA's endorsement of the ICH E11A pediatric extrapolation framework. And, we would encourage FDA to consider expanded implementation of full extrapolation across indications to reduce the need for pediatric studies particularly in rare diseases. We applaud the FDA's recent expansion of full extrapolation in several pediatric arthritis indications which we note has led to several recent approvals in the US. We urge FDA to consider expanded use of alternative data sources such as real-world evidence as you've heard from other speakers, in lieu, or in support of, maybe smaller clinical trials to support extrapolation when necessary. We note that the EMA has started to do this. There's a pediatric IBD indication that is now approved in Europe, that is based on real-world evidence, that is still pending in the US. Finally, we would encourage ongoing dialogue between FDA and sponsors to have

notification of when FDA's thinking is evolving around extrapolation or other pediatric development considerations in support of the goal of ongoing collaboration. If we collaborate, we can all hopefully achieve approvals more rapidly. Turning back to David. Thank you.

To wrap up our comments today, we really want to thank the FDA, again, for the opportunity and reiterate AbbVie's commitment to providing timely evidence to support the pediatric use of novel therapies. As we have said many times already today, pediatric clinical development is very complex and is very difficult, however it provides the real opportunity for partnership and collaboration, and I think, flexibility, as Anne pointed out, given the complexity between sponsors, between FDA, flexibility on both sides really will help achieve this goal. And again, AbbVie looks forward to continuing this partnership and continuing to share our experience with pediatric clinical development and look at ways to again, lift up this collaboration and really bring these much needed therapies to the pediatric patients faster. Thank you very much.

>> Thank you very much, Dr. Horton and Dr. Robinson. So, next I will invite to the podium our next speakers, which are Dr. Michaela Schultz and Ms. Aditi Shah from Otsuka Pharmaceutical Development and Commercialization.

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Otsuka Pharmaceutical Development & Commercialization: Michaela Schultz, PhD and Aditi Shah, MBS

>> Thank you for your time, today. I'm really grateful for the opportunity to be able to speak in this forum and really grateful for Otsuka's dedication to engaging with patients

and the community that really has a stake in the outcome of our medicines. My name is Michaela Schultz, I'm the Director of Global Regulatory Affairs at Otsuka Pharmaceutical Development and Commercialization. I will be speaking about the impact of reducing the scope of BPCA per the recent FDA draft guidance. On the bottom right, you will see a figure that has demonstrated the success of BPCA and PREA over time. We've seen it a few times today, and overall, we see that pediatric labeling is increasing over time. The Agency broke this down more granularly in the recent draft guidance released in 2023 showing that 23% were due to PREA, I'm sorry, 63% were due to PREA, 21% due to BPCA and 16% dual leveraging both guidances.

The small overlap between the two, was the Agency's justification for a significant change in the Agency's long held interpretation of the law. If the guidance is finalized with this current text, the Agency moving forth, does not expect to issue written requests solely for studies required under PREA. With the intent to address the two questions on the bottom of the slide, in the next two slides, I hope to show you that pediatric labeling relative to industry growth is unfortunately not increasing. And that decreasing the scope of BPCA could have further reduction in pediatric labeling. Reducing the scope of BPCA may also have unintentional consequence of prioritizing rare disease over common disease and have delayed or reduced innovation.

To begin with the first matter, is pediatric labeling increasing? In otherwords, are PREA and BPCA effective enough? On the left we analyzed FDA data on new drug pediatric labels and normalized this to FDA reported new drug approvals by year. We used new drug approvals as a proxy for industry growth to really understand if pediatric labeling was keeping up with industry growth. It appears that pediatric labeling is

actually steady to decreasing over time indicating that there is more that we can be doing. On the right, we narrowed in on the FDA analysis of percent pediatric label changes attributed to PREA, BPCA, or both. PREA uptick has been steady over time while BPCA, or BPCA combined with PREA, has been generally low and decreased.

Despite the reduction in label changes attributed to BPCA, new draft guidance is proposing to further reduce its' scope. Further the Agency seems to imply that the 16% of products that leverage BPCA and PREA would be absorbed by PREA. From an industry perspective, this would more likely result in a lack of investment and, in turn, reduce pediatric investigations. Next, I will share why this is and provide some insight into industry decision-making in hopes of optimizing the use of BPCA and PREA. One of the most important decisions that industry makes upon nominating a candidate drug is target indication selection, and this occurs years before we ever enter a healthy volunteer study. We work cross-functionally to consider multiple factors. A candidate drug has the theoretical opportunity to benefit multiple populations as numerous diseases share a same underlying pathophysiology.

An example here, shown as Disease A and Disease B. Industry typically selects between the two by comparing the probability of technical and regulatory success, prioritizing one as the lead indication and the other as secondary and lifecycle management indications. Factors in this assessment include preliminary data on scientific feasibility, strength of understanding of disease pathophysiology to inform technical success, heterogeneity of population, and how to define a population. We also consider how to define and measure clinical benefit in each and how many trials it's necessary to achieve substantial evidence of effectiveness. Reducing the scope of

BPCA influences these factors, and as a result, will have the following consequences. The first is most clear: prioritization of rare diseases over common diseases. This is because exemption from PREA inherently makes the incentive under BPCA higher. The second, is decreased innovation with secondary indications. And this is a little bit more complex, so I will explain it a little further.

So, when we are looking for additional studies to satisfy BPCA, FDA often looks to your other open INDs or early studies for that additional study. That helps us reach beyond the PREA-required studies when issuing a PWR. If the studies in the lead indication are not sufficient, sponsors are encouraged to delay lifecycle management indications and opening of those INDs until a PWR is issued in the lead indication and that optimizes that success. Delay of these additional studies delays potential access and opportunity, potentially forgoing their investigational together. I'll note that BPCA has the ultimate timeline locked into it, because you have to complete your PWR before your exclusivity period ends. So, we've spent a lot of time today talking about the delay of pediatric studies, but I would encourage that rather than pressing the breadth of BPCA to additional indications, a feasible approach and collaboration on this, would more effectively leverage this legislation to achieve pediatric studies in a timely fashion.

In conclusion, we would like to ask the Agency to continue to leverage both the carrot and the stick. Rather than considering the dual leverage as double dipping, we ask the Agency to think of the regulations as a concerted effort to increase the quality of pediatric care. Further, we request that the Agency consider the available data before requesting pediatric studies and exploratory indications to preserve innovation. Thank you for your time and I will now pass it to Aditi to speak about the importance of global

collaboration and rare diseases without a PREA requirement to ensure that global research benefits US patients.

>> Thank you, Michaela. Hello, and thank you for the opportunity to speak here today. My name is Aditi Shah and I am an Associate Director in Global Regulatory Affairs at Otsuka Pharmaceutical Development and Commercialization. I'm here today to share one key concern and gaps identified by the industry within the rare pediatric space in connection with FDA's Best Pharmaceuticals for Children Act. Industry sponsors have faced constant challenges in conducting separate rare disease pediatric studies. Sponsors and FDA have worked recently to design creative trials using natural history data and extrapolation. However, due to differences in health authority requirements across the globe, there is no fit for all studies, meaning sponsors need to conduct more than one study when recruiting subjects from rare pediatric populations, which is already extremely difficult to recruit. The biggest loss here is to these pediatric patients who are already suffering from rare disease with unmet need.

Sponsors in the rare disease space with orphan designation are typically exempt from PREA. However, they may be required to conduct these pediatric studies elsewhere to fulfill other health authority requirements. In conclusion, we request that FDA work with sponsors on ways to leverage these pediatric plans and studies that have already been developed to provide access to patients through labeling and further collaborate to provide scientific justification on how these studies could be leveraged to fulfill BPCA, thereby seeking both indication in the US, which, in turn provides access to pediatric patients in the US and sponsors gaining six months of exclusivity. This would be a win-win situation for both sponsors and patients who are much in need for this

treatment option. Additionally, I do want to stress that the issues not only observed in the rare disease space but also persist in other therapeutic areas and are compounded when it's not in the rare disease. Thank you for your time.

>> Thank you very much Dr. Schultz and Ms. Shah, for your comments. So, we have our next speaker who is proceeding to the podium, Mr. Eeshan Khandekar, who is from the Pharmaceutical Research and Manufacturers of America (PhRMA), who will be sharing remarks. Thank you.

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Pharmaceutical Research and Manufacturers of America (PhRMA): Eeshan Khandekar, MSc

>> Good afternoon everyone. I know I am the last person standing between us and lunch, so I will try and zoom through as fast as I can. Thank you all for having me and thank you all for sharing your perspectives today. My name is Eeshan Khandekar and I am the Director for Science and Regulatory Advocacy for PhRMA. For those of you who don't know, PhRMA represents the country's leading innovative biopharmaceutical research companies which are focused on developing innovative medicines that transform lives and create a healthier world. Together, we are fighting for solutions to ensure that patients can access and afford medicines that prevent, treat and cure disease. PhRMA member companies have invested more than 850 billion dollars in the search for new treatments and cures over the last decade supporting nearly 5 million jobs in the US. PhRMA and its' members are dedicated to advancing drug development to expand the availability of safe and effective medicines for children.

Over more than 20 years, PREA and BPCA have worked together to transform the way medicines have been developed and labeled for pediatric populations. According to FDA's database, as of June 3rd of this year, well over 1,000 pediatric labeling changes have resulted from studies conducted under these pediatric legislations including more than 250 under BPCA alone, and 130 under both BPCA and PREA. PhRMA and its' member companies are committed to working with FDA to build on this progress.

Today, my testimony will focus on five key topics. First, I will identify open questions about requirements for molecularly targeted pediatric oncology study under FDARA that we believe the FDA should address. Second, I will outline our recommendations for advancement of international harmonization of pediatric study requirements. Third, I will address FDA's approach for written requests. Fourth, I will discuss our views on steps that could increase timeliness and flexibility in the development of a comprehensive pediatric study program. Finally, I will provide our feedback on successes and challenges with leveraging scientific advances in pediatric product development. But before I turn to these topics, PhRMA wishes to say their support for the reauthorization of the Rare Pediatric Disease Priority Review Voucher Program, which had offered renewed hope for affected families and patients and is an important tool in pediatric product development.

Under FDARA implementation, PhRMA applauds FDA for releasing guidance on FDARA's requirements for molecularly targeted pediatric cancer investigations. As PhRMA has advocated in prior comments, we encourage FDA to address the following open questions not discussed in the guidance: First, how FDA determines whether

molecular target is substantially relevant to the growth or progression of a pediatric cancer. FDA has said that a specific or minimum evidence standard for determining targeted relevance is not feasible. PhRMA notes that Congress required Agency guidance to discuss the scientific criteria, types of data and regulatory consideration for determining substantial relevance. We are aware that FDA has made some substantial relevance determinations, and we request that the Agency provide greater transparency about how they decided that the evidence met that standard. This transparency is needed because FDA's relevant molecular targets list is advisory only and includes targets that are potentially relevant. By contrast, PhRMA members have found that FDA's non-relevant molecular target list is useful as it clearly denotes investigational products that need not have a pediatric study plan. We encourage FDA to further explain when a molecular target is substantially relevant to the growth and progression of a pediatric cancer.

Second, under FDARA implementation, FDA must determine substantial relevance based on available information. PhRMA believes that certain FDARA guidance is out of alignment with statute and warrants reconsideration for this reason. Specifically, FDA guidance interprets FDARA as requiring the sponsor to generate and submit nonclinical data to inform FDA's determination of whether a molecular target is substantially relevant. This interpretation does not reflect the best interpretation of statute which refers to a molecular target that the Secretary determines to be substantially relevant. The statute does not require sponsors to submit data to inform this determination even though the Act requires sponsors to submit data to inform other FDA determinations. Further, preclinical studies to assess substantial relevance are

often exploratory, speculative, and unlikely to produce actionable information. We urge FDA to revise the guidance to reflect that FDARA is meant to promote pediatric drug development; not mandate foundational research. Namely FDA should clarify that sponsors are not required to generate data to inform substantial relevance determinations and that the FDARA requirements apply only if the FDA has made substantial relevance determination.

My third point under FDARA implementation, FDA may not refer its' determination of substantial relevance. Guidance suggests that FDA can defer a decision about whether FDARA or traditional PREA applies until after drug approval. PhRMA believes that this interpretation does not reflect the best reading of the statute and results in unnecessary uncertainty. The statute authorizes FDA to defer submission of already required assessments or reports under traditional PREA and FDARA. It does not allow FDA to defer deciding which study requirements apply to an application. We continue to urge FDA to adopt a time bound process for determining whether traditional PREA or FDARA applies to an application at the time of, or before, the sponsor must submit an initial PSP.

My fourth and final point under FDARA implementation is that FDA should confirm that a marketing application for an orphan-designated indication is exempt from PREA if the FDARA investigational requirements does not apply. FDA guidance recognizes that drugs developed for rare cancers are generally exempt from traditional PREA due to their orphan designation. We suggest that guidance expressly address the situation where the FDARA requirement does not apply to application. For example, because a molecular target is on the nonrelevant list and the drug is orphan designation

its' indication. Consistent with the statute, the guidance should state that standard PREA applies in this case and the drug is exempt from PREA requirements due to the orphan designation. In our members' experience, questions have arisen about this issue with the Review Divisions. Further, guidance should explain that the orphan exemption applies to submissions for subsequent orphan indications when the FDARA study requirements did not apply to the initial application.

By its' terms, FDARA applies only to the original application for a new active ingredient and thus cannot apply to the subsequent applications. Turning towards my second topic on international issues to advance harmonization and promote governance efficiency, PhRMA recommends that FDA adopt procedures and processes to harmonize scientific expectations for pediatric study designs across Europe and the US, moving towards the eventual goal of a single pediatric testing program for all agencies. Harmonization would reduce the likelihood of diverging advice from regulators on pediatric study plans and reduce duplication of effort. PhRMA members have experienced significant differences between approaches of FDA and EMA to delineating pediatric requirements in PIPs and PSPs. For example, our members have seen differences with the two regulators in the required number of studies and their design including when extrapolation can be applied to support the same indication. We recommend that FDA and EMA also work better to align timelines for reviews of PIPs and PSPs when possible.

These approaches could reduce redundancy and administrative burden for agencies and sponsors and potentially accelerate the availability of new pediatric treatments. PhRMA encourages FDA to foster global alignment for pediatric studies as

appropriate including through the expanding the scope and transparency of the Regulator's Cluster meetings and Common Commentary. Currently, these meetings do not provide a systematic, consistent and transparent opportunity for sponsors to engage with the regulators and achieve scientific convergence on complex development issues.

Shifting to my third topic on Written Requests, PhRMA is concerned that FDA's recent policies and practices concerning Written Requests has undermined the BPCA's incentive framework. In recent years, our members have received an increasing number of Written Requests that exceed exploratory studies. PhRMA believes that this practice presents legal, policy and ethical concerns, it does not align with statute which provides for issuance of Written Request when information about a pediatric use may produce health benefits in that population. This text requires some expectation that the drug will result in health benefits for pediatric patients as to ethical considerations. PhRMA members have also observed a trend towards written requests that span a broad range of indications. Issuing overly broad or exploratory written requests is counterproductive. It discourages sponsors from attempting to complete any of the studies in the written request or pursue a Written Request in the first place due to significant feasibility challenges with completing all of the requested studies in time to earn meaningful pediatric exclusivity. We urge FDA to consider these issues when discussing potential Written Requests with sponsors. The agency should consider the practical implications of its current approach and provide greater transparency regarding its decision-making process to ensure that sponsors remain engaged in evaluating their products for additional pediatric indications and that incentives remain a viable option.

We'll have a bit more about Written Requests in our written comments so I will skip over to our third topic about timeliness of discussions on PIPs, PPSRs and flexibility in PSPs. Our members have encountered challenges with obtaining timely feedback on pediatric development programs including for the purposes of both PREA and BPCA. We recommend that FDA take action to address this issue which may lead to drug development delays. For example, in the context of pediatric study plans or PSPs, the sponsors often face lengthy delays in receiving Agency feedback on study protocols. Certain Review Divisions are also unwilling to discuss proposed studies, especially for BPCA purposes, early in the development phase. These delays not only make it difficult for sponsors to execute and plan pediatric development programs but also complicate development in other jurisdictions like the EU that require pediatric plan submission much earlier in a drug's development. We encourage FDA to prioritize the provision of timely and reliable feedback on PSPs and PPSRs which will increase government efficiency and allow sponsors to initiate studies as soon as possible.

I think I am out of time, so I will say we will have more comments in our written submission on leveraging scientific advice on product development. Thank you all for having us here. We look forward to submitting written comments and working with other stakeholders in this field.

>> Thank you very much Mr. Khandekar. And so, that actually concludes our morning session and we are at the lunch break. I want to thank all of our speakers from this morning. We will take a lunch break now until 1:15 PM Eastern, which will resume with the remaining speakers for the day. Thank you everyone and enjoy the lunch break.

(Lunch)

(Please stand by for captions)

>> Good afternoon, everyone and welcome back. Will open Session 4 with our first speaker Mrs. Betsy Pilon who is with Hope for HIE. She is joining virtually.

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Hope for HIE: Betsy Pilon

>> Thank you so much. I will kick off the neonatal session. And I am a representative today for Hope for HIE, but I started as a parent sitting in the NICU. It is special to be here and to be able to elevate the unmet needs of critically important neonatal populations. The picture on the left is me sitting in the NICU 13 years ago after giving birth to my first child Max, who is a bright and wonderful 13 1/2-year-old. Many of you are wondering what HIE is because typically you don't hear much about it, when it comes to the NICU, it stands for Hypoxic Ischemic and Encephalopathy (HIE). What you may not know is that it is the 2nd leading cause of infant morbidity and mortality globally. It primarily affects full term infants. Significant uncertainty in outcomes even with advanced prognostic tools. Traditionally there has been a lack of investment and follow-up care and research.

Although that is changing, and we are excited to share and collaborate, it is tricky because there are so many different causes of HIE. It is structural although there is a genetic overlap in about 5% of the cohort that current studies have identified. It has a perception that it's difficult to make an impact because it is structural and it has been met with shoulder shrugs in various research meetings and when looking at therapeutic advancement. In particular, neonatology struggles with this more broadly than just HIE.

With neonatal clinical trials and neonatal drug development, it's very tricky and it's for a vulnerable and needy population. There is a lot of high-stakes and difficulty with this. But we need to make sure that these incentives to advance therapeutics that are available through the mechanisms we are talking about today are more applicable and thought of as well for neonatology, which works a bit different than just general pediatrics. Because primarily, these babies are getting enrolled in an acute care setting versus outpatient clinical office. We need to really look at where these things are needed to advance and where we can work more strongly in the ecosystem with industry and regulatory patient advocacy to meet these critical unmet needs.

What does HIE look like in the NICU? This was Max and he was a candidate, (13 and 1/2 years later) and we still have one approved therapeutic intervention. It is a non-pharmacologic, it is called therapeutic hypothermia, and you are cooling down babies. It sounds like science fiction to families but to decrease inflammation and the brain injury that has occurred for whatever reason that has led to HIE. It's time and resource dependent. You must be in a Level III or Level IV NICU, that is tooled up for the intervention. It is sometimes difficult for babies to get there in time. You have to initiate it within six hours. So, if there are transportation delays, if you are in a rural area they can disqualify you for cooling. You can see in this picture of Max. This was not long after Max was transferred from our community hospital to Level III NICU for cooling.

The Level III NICU is part of NRN Therapeutic Hypothermia Multicenter Study, which we were fortunate. Our providers knew about the treatment, and it was available and in use. In 2012, it was on the cusp of going from clinical trials to standard of care.

You will see that Max is on a cold blanket. There is water pumping through the blanket to cool his body down. He is on EEG. He has his eyes covered, he has an umbilical line going, he is on an oscillator. So he had to go on the highest respiratory support to save his life. He was on anti-seizure medications and pain control because obviously it's not a normal experience for a baby to be cooled down. Neonatal seizures, HIE is the top cause of those. So, it is very typical, if you are in the moderate to severe range of HIE for your baby to be on an antiseizure medication. Phenobarbital is the front-line medication currently. Any system can be impacted through this acute care process and forward. They're managing critical levels of cardiovascular care, renal

and vision. And babies are often too unstable to even be held during cooling. So families have to wait until they come out of the cooling. And often families are separated due to the level of care needed, depending on where mom is delivering. And where the access is to this critical resource.

HIE is a catalyst diagnosis causing many different diagnoses. There is a huge range of impact areas. Cooling has improved the state of HIE significantly for babies in the US and high-income countries where it's available more widely. But the endpoints that have been seen as successful markers are reduction of mortality and morbidity. But a lot of the morbidity and neurodevelopmental impairment index is focused on cerebral palsy, which is an early important marker of motor outcomes. But as you can see there are so many other areas of focus that are important to families and impact quality of life for babies and their families, outside of morbidity and mortality. Things like epilepsy, later-onset epilepsy. Max didn't actually develop epilepsy until age 8 and a half. That was a long time to wait to know how he would be affected by that. There is a

giant wait and see. Learning and attention issues can often be learned if the impact is known, those early Bayley scores.

There is a lot of prognostic uncertainty, when looking at endpoints and when we are looking at bridging these barriers that currently exist in neonatology and working more closely with patient advocacy. We are able to energize the lived experience. We connect over 10,000 families worldwide. We have 15 years of anecdotal data-share. A lot of unmet needs are elevated and known because the data is so scant currently. Because funding normally stops at age 2 or three years. Sometimes extended to age 5. But follow-up care needs to go further, to get a better picture of the natural history of this population. We do struggle from real-world data gaps because of the medical coding and the ICU-10 coding issues. Often pulling it, is a diagnosis-by- exclusion versus a fully diagnosed state, which are some of the challenges that our community faces and that we are working across the ecosystem to decrease. Who is on first in neonatal drug development? For HIE, we get caught very often between neonatology, neurology and rare. Is HIE rare? The FDA says so, we meet the criteria, other clinical providers don't think we are rare.

Again, pediatric incentives don't reach neonates. There's agency fragmentation within and across the current agency structures. We feel strongly that this regulatory research and culture change in neonatology is overdue. I get to spend my time, sometimes in neonatal advocacy, sometimes neurology advocacy, and sometimes in rare neurology. The things that I have learned about from my colleagues in advocacy and rare neurology seem to be much further ahead than in neonatology. So how do we get that to be more equitable in neonatal advancement? Babies, children and families

are hanging in the balance every day. Babies are born every day with HIE and they need better therapeutics.

Also, I think one of the interesting parts that we learned, especially as we are partnering across the ecosystem in both academic and industry therapeutic advancement, is looking at how bias can impact things in the neonatal space. We have a significant cultural issue across neonatology of protecting babies from research. That bias exists across all areas, clinical research and regulatory. HIE funding, in particular, is deprioritized in the context of neonatology. Again, structural is hard and people want to focus more on cracking the codes of genetics, which is totally an amazing area of medicine as well, but it leaves a lot of kids like ours out. And we need to continue to listen to the lived experiences and creating and developing endpoints that matter and stop lumping death and disability into one outcome. They are very different in the lived experience. We do still have paternalism in medicine and regulatory challenges in neonates. Where we have had feedback on why families were not enrolled who met inclusion criteria in trials. Families were “going through too much” quote unquote and they were never approached for these studies. As a parent and as a representative of a community, that's unacceptable. We have to change the culture because these families and these babies deserve a chance to have these therapeutics tried in the population.

Again, like I mentioned, neonatal clinical trials are tricky - there’s lots of variables working against researchers and families. Again, time sensitive - it does not matter if it’s HIE or something else. Typically, there is a significant time sensitivity resource variability in existing clinical trial networks or those that don't exist and should. Separation between mother and baby health and separation of facilities depending on

what's going on. There are overwhelming consent processes that are insisted by IRBs that are prohibitive for the average parent. We have so many varying literacy levels in the US and abroad and health literacy in, particular, and first language. These are all barriers that make things very difficult. Currently we are facing an unprecedented mistrust in the medical system and in our country's research institutions. It is very disheartening to hear on all sides of that, and we have to address that in this era of rampant medical misinformation. But there's real trauma that people experience from the fragmented systems that exist currently in this country. And again, looking at the bias, gatekeeping and misperceptions of families and systemic inequity that exists across different cohorts.

I just want to share that there are things we can do when we look at the gap areas. When we look at the silo's bias and impact to enrollment, we can look at things like centering the community and avoiding tokenization for funding, early multi-disciplinary stakeholder involvement. The FDA has done an excellent job when approached by those exploring neonatal indications, such as, HIE to partner with patient advocacy early and often on study design and feasibility. And thinking outside of what best practices exist outside of neonatology that we can bring to neonatology. And looking at when we get into the studies, what the communication training is for those consenting and decrease the bias of protecting families. We talked about measures and then just looking at after babies are enrolled, in the midst of trauma because acute care with the NICU is often very traumatic for families. And your brain is just not processing information the way it would in a calm situation. We have to look at how

families are supported and engaged longitudinally, so we can have families stay in these trials.

One of the things that worries me most with a lot of the advancement is that attrition for a very small trial can be a breaking point for something that could actually work if we don't have the ability to partner early on and make sure families are supported holistically longitudinally and are able to feasibly participate in the trials to get the best most comprehensive data that we can. That's it. Sorry, there's lots of exciting work going on with researchers and families, so I want to leave you on a positive note. We are really excited that there is 30+ years of research with HIE and there is lots of things going on and lots of people that are dedicated to this. My heralding cry is as I pass the torch to my other colleagues, in this section, is really to see how we can open the channels of communication and focus on neonatology for these mechanisms to translate more productively into neonatal advancement.

>> Thank you so much, Ms. Pilon. Our next speaker is Dr. Kanwaljit Singh from the International Neonatal Consortium (INC) joining us today.

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International Neonatal Consortium (INC): Kanwaljit Singh, MD, MPH, MBA

>> Good afternoon. I want to start by saying that neonates [premature babies] are perhaps one of the hardest populations to study, even harder to develop drugs for them. There's been studies that show in neonatal intensive care units setting up to or even more than 90% of the drugs in NICU are actually used off label, with no specific studies being done for their safety or efficacy in an age-appropriate manner. Because of that,

neonates are actually called therapeutic orphans in literature. My name is Kanwaljit Singh. I am the executive director of the International Neonatal Consortium at Critical Path Institute. I am going to talk about what INC or International Neonatal Consortium is doing to change that.

Therapeutic orphans, very few drugs developed specifically for infants. There is a very specific reason for that - premature infants have a very rapidly developing physiology. Their physiology changes daily, and in some cases hourly, weekly. There are injuries happening at the same time. Those injuries are healing at the same time. There are no pharmacodynamic or pharmacokinetic models that explain how drugs will interact in that situation. As it is it's pretty much impossible to study drugs in this. This leads to an off label cycle, where most of the drugs end up tend to be used in an off label fashion, because there is nothing else that is happening And in practice it's kind of considered to be sufficient and leads to a cycle where industry doesn't want to develop drugs for them, which leads to more off label use and it keeps going on and on.

As you heard today, BPCA/PREA has done some wonderful work to advocate and develop more drugs for children. Their impact hasn't really extended to neonates. Children are not tiny adults and neonates are not really tiny children. There's a huge amount of difference in that and there is a huge amount of disease mismatch. Most neonatal conditions are caused because the babies are born prematurely. This is like BPD or HIE, they have no adult analogues. There are no validated biomarkers or specific standardized clinical trial endpoints, which will enable sponsors to actually do clinical trials in an easier, most efficient fashion. Right, so the path forward to advocate for better and more neonatal drug development is by innovative clinical trials design

methods, validated biomarkers and regulatory data platforms to reduce uncertainty that people can actually use to create qualitative tools and solutions for their studies.

The point is this type of effort cannot be done by anyone alone, not by a single sponsor not by a single company, not by a single organization. It requires everybody to come together and it basically requires a village, quite honestly, where everyone is coming together and working together. Collaborating, even with those people who are their competitors, collaborating with each other on the science and competing on the basis of product is basically the mantra we follow at the Critical Path Institute. This is exactly what we are doing at the International Neonatal Consortium. It acts as a home where neutral pre-competitive large scale database solutions can be created. That's basically the mission of C-Path and that is exactly what we have been doing for the past ten years of our existence.

We will talk a little bit about the past work that INC has done. We started at the basics. There was a white paper published way back in 2017/2018, that acted as a consensus paper on how exactly to conduct neonatal drug development. It brought together stakeholders from FDA, EMA, all the regulators, a lot of people from industry, and academia, and patient groups. And it basically provided the first global framework on how to design and conduct neonatal clinical trials. It addressed fundamentals; basically ethics, dosing, pharmacodynamics modeling, safety, endpoint, how long to follow the babies. All of those things were covered in that paper. It mattered because it actually showed that pre-competitive collaboration can actually work. Where people who might actually be each other's competitors can come together toward a shared

common vision to make it easier for everybody to do clinical trials in the neonatal population.

Another thing that the INC did was the Neonatal Adverse Event Severity Scale (NAESS). This was done in response to the fact that in the NICU there was no standardized adverse events severity rating for this population and people tended to use adult or older pediatric scales, which do not capture neonatal physiology and the things that matter in any NICU setting adequately. First, there is the neonatal specific adverse event severity scale that was created and focused on thirty-five (35) AEs across five standard categories. It's been used or everyone uses NAESS in their clinical trials to conduct safety assessments. Other things we discovered over the past several years after NAESS was published, was that the 35 definitions that we had were not enough. So we are actually in our next phase of NAESS expanding the scope to more than 35 AE's and we are digitizing it to create a digital app that people can use to enter data and select adverse events and print reports to be included in the trial files and basically just make NAESS more useful than it already is.

I just wanted to say that the way C-Path does pretty much everything is to create quantitative drug development solutions, like biomarkers and endpoints. Typically, we use clinical trial standardized data to do that, but in neonatology everything is off label and there are no regulated drugs, or not that many that we would really need. We wanted to focus on the data that is actually available. Every premature baby that is admitted in the NICU setting is admitted from their birth until discharge. The entirety of the health information is available in the EHR. We basically gathered approximately 380,000 NICU patient data longitudinally, across 30 hospitals, and we're using it for

multiple different purposes to create clinical trial endpoints, BPD trajectories, external control arms and predictive models, and a whole host of other things that are going to be useful for conducting neonatal drug development easier, faster, and more efficiently.

One example I wanted to specifically highlight is our Neonatal Lab Values Initiative. You may be surprised to know that in the neonatal population there are no standardized generalizable reference ranges for most commonly used labs. And we basically took the data that exists in our real-world data analytics platform and harmonized 14 of the most commonly used lab values and created generalizable reference ranges across multiple different hospitals. In the first version, this focused on the 14 key labs like hematology, chemistry, liver function, and metabolic labs. And we just didn't stop at that. We created a digital tool that people can use and visualize the labs across different standard deviations and different percentiles and will be available publicly in the next month or so. The work is ongoing.

The next one is neonatal brain injury collaborative, which we are working with Hope for HIE. The purpose of this initiative is one of the critical issues in HIE and white matter injury, neonatal brain injury, drug development - there are no biomarkers that are validated to be used in regulated clinical trials. We are partnering with Hope for HIE and industry and academic groups and regulators to integrate clinical trial data that's already been completed with HIE and white matter brain injury, with the hope to validate biomarkers like MRI injury patterns, EEG background activity, and other biomarkers, as prognostic enrichment markers and so on and so forth. That's one of the things we believe will be critical in setting the drug development in this population forward.

The final work on one of our proposed works that we will be starting very soon is our work on digital twins and external controls. The reason we want to do this is because it's very difficult to conduct clinical trials in the neonatal population. It is ethically very difficult to do double-blinded placebo controlled clinical trials in neonatal populations. You are not going to be injecting a placebo into a newborn baby, right. One of the things we will be doing is using our real-world data platform to create high quality comparator data in cases where randomization is not possible. We are also going to be using the same data to develop predictive virtual competitors, also known as digital twins, that mirror neonatal trajectories using a whole host of clinical biomarker and imaging data. I think this is going to reduce the cost of drug development by reducing trial failure and making the conduct of clinical trials easier and more efficient and more feasible. We will focus on BPD, HIE, neonatal sepsis and other rare disorders. But I think the sky is the limit in terms of how far we can go with this one.

I will close by saying that neonates remain therapeutic orphans. There are a whole host of reasons for why this is the case. INC and Critical Path Institute exist to fill this gap and we provide a neutral table where everyone can work together to accelerate drug development in this population. This is a message to everybody, if you care about neonatal drug development, please collaborate with us. My information is all there and I would love to hear from you and collaborate.

>> Thank you so much. Next is Dr. Augusto Schmidt from the Neonatal Research Network who will join us virtually. Please feel free to turn on your video and start your audio.

Session Four: Interested Parties Comments

Neonatal Research Network (NRN): Augusto Schmidt, MD, PhD

>> Good afternoon and thank you on behalf of the Neonatal Research Network. The NICHD and I set up the Neonatal Research Network in 1986, as a network of 15 clinical centers and data coordinating centers to perform randomized controlled trials for pre-term and term newborns to address the paucity of evidence-based therapies in this population. The network has since contributed, with landmark studies, that have guided the management of the newborns in the delivery room, use of inhaled nitric oxide for persistent pulmonary hypertension and use of therapeutic hypothermia for newborns with hypoxic ischemic encephalopathy among other interventions. While we recognize that these initiatives that we are discussing have major gains in the pediatric world, newborns are still the least studied group. Most label changes under BPCA and PREA did not include newborns and the incentives provided by those initiatives often fail to generate trials in newborns.

Why are newborns different? Newborns are a distinct population. We often deal with unique diseases that aren't shared between pre-term and term infants and older children and/or adults. Pre-term infants are further complicated by their physiological immaturity of multiple systems including respiratory, digestive immune and metabolic, which affects their response to drugs and metabolism. The results that we cannot reliably extrapolate information from older children for drug development in newborns. Many therapists have bypassed newborns under BPCA and PREA. There are several diseases with unmet needs in preterm newborns. I will list a few examples. For instance, broncho-pulmonary dysplasia (BPD), which is the most common complication

of prematurity and can result in lifelong respiratory impairment and it still has no approved therapies. Necrotizing enterocolitis is less common, but it is potentially devastating and there are currently no proven prevention or treatment strategies. Barriers to studying probiotics in newborns is in progress is an area that is a promising prevention strategy. Intravascular hemorrhage and brain injury in preterm newborns still remain without treatment or prevention and retinopathy of prematurity, which is an important cause of blindness and vision impairment in preterm newborns. The current standard of care, which is an anti-VEGF antibody, is still used off label with limited neonatal pharmacokinetics and safety data.

In turn in newborns, hypoxic ischemic encephalopathy, which Betsy eloquently talked about, I want to elaborate a little further. Therapeutic hypothermia remains the only proven therapy but has several limitations. We know that it is effective in preventing long-term impairment and reducing long term impairment for newborns with moderate to severe HIE, but data shows that newborns with severe HIE benefit the least from therapeutic hypothermia. The benefit, if mild hypoxic ischemic encephalopathy, is still unclear. In preterm newborns one of our recent trials done in the network shows lack of effectiveness of therapeutic hypothermia and possibility of harm in infants less than 36 weeks gestation. While there's a lot of movement for adjunct treatments, they have been so far unsuccessful in clinical trials.

For neonatal opioid withdrawal syndrome, which is a consequence of in utero exposure to opioids, care is variable. Most treatments used are off label with limited data on pharmacokinetics or safety for newborns. Trial consent in this circumstance is further complicated by the maternal and social context. For example, buprenorphine,

which is a promising treatment, in its current formulations include ethanol. While an alcohol-free formulation has been developed, the requirement for individual consent is prohibitive with one recent trial attempt for buprenorphine in the treatment of neonatal opioid syndrome, stopping after enrolling only 7 infants. The consequences of these gaps are that the routine use of drugs remain off label in the NICU.

There is a lot of heterogeneity of care which complicates further the design of clinical trials. Our sickest and most vulnerable children, that are newborns, lack evidence-based therapies. The long-term consequence of the public health burden and chronic diseases include neurodevelopmental diseases, chronic lung disease, increased cardiovascular risk in adulthood and metabolic syndrome/diabetes, all of which are increased in our pre-term newborns. Among the barriers that affect the pre-term and term newborns, as I mentioned, extrapolation is an impossible for pre-term and term newborn-only diseases because those diseases do not have analogs in older children or adult populations. We are dealing with very small populations, which leads to slow enrollment in clinical trials and often acute and unpredictable events such as timing of birth, onset of disease such as NEC or HIE which are harder to capture clinical trials. Long-term outcomes, which is currently the standard of care for neurodevelopment outcomes in preterm newborns, is done between 18 and 24 months (corrected age) and is very resource intensive. While this follow-up at two years of age is resource intensive, we know it's very limited in predicting further future development including childhood outcomes at 5 to 6 years of age. There's a lot of barriers and practice and consenting for clinical trials. These infants are often in an acute illness setting and mothers of pre-term newborns are often also dealing with their own illnesses, and it is a

high-stress environment with a lot of trauma and difficulty in consenting families. For interventions that are required in the delivery room, antenatal consent is needed and this is a very resource intensive process with which the Neonatal Network has experienced, but requires much more experience and resources for implementation.

There are several formulation issues for drugs that lack neonatal friendly preparations. For the most important and common diseases, we still lack validated neonatal endpoints for diseases such as BPD, necrotizing enterocolitis, and brain injury. The NRN has had success and demonstrated that a lot of these challenges can be overcome. The NRN was designed as a multi-site infrastructure for rapid startup and efficient recruitment of newborns with use of a central IRB and standardized outcome measures. We have a standardized follow-up protocol that follows all infants that are less than 26 weeks through 18 to 24 months (corrected age) with a very rigorous neurodevelopmental assessment using Bayley Scales and neurological assessments. The result is that we have increased the available population for recruitment and increased the likelihood of successful trial completion within the network. We have experience in time-sensitive consent models, such as antenatal consent, as well as consent required in a few hours after birth. such as the case was for therapeutic hypothermia for hypoxic ischemic encephalopathy. We have a new system in the Neonatal Network that allows external investigators to propose studies, and we also have experience with innovative trial designs including Bayesian trials and target trial emulations.

To conclude, there are scientific advances that give us powerful tools to improve clinical trials and development for newborns, but this really should be an effort among

several agencies, including our Neonatal Research Network trials, across the world. We have the use of external controls and real-world evidence from NICU registries that can replace or supplement placebo groups in some of our conditions. We need model informed drug development and population PK models that allow dose selection tailored to the neonatal physiology. Adaptive Bayesian designs can conserve newborn enrollment. And the NRN remains a potential resource for sampling bio-banking and the development of biomarkers and imaging across multiple pre-term diseases that can facilitate the delineation of early neonatal endpoints and completion of clinical trials. Thank you for the opportunity to present on behalf of NRN.

Next speaker is Deborah Discenza from Preemie World.

Session Four: Interested Parties Comments

Preemie World: Deborah Discenza, MA

>> Good afternoon, my name is Deborah Discenza, and I am the mother to Rebecca, who was a 30-week premature in 2003. I am the co-founder and Executive Director to the Preemie World Foundation. For years, parents like Betsy who you have heard earlier and me, we have come to FDA meetings and said babies need help. It's true, but today I want to go further, and I want to tell you how you can help them in very concrete ways. Families are ready to work with regulators, industry and to make neonatal drug development possible. There is an unmet need. BPD, no new approved drugs in over 30 years. NEC and HIE, no approved drugs at all. Families live the consequences: repeated hospitalizations, feeding tubes, oxygen at home, lifelong disability. This is not rare, as it happens in every NICU, every year. I know this, I

support families around the world. Parents see progress in adult diseases like Alzheimer's and Parkinson's driven by advocacy and regulatory innovation. Our babies deserve the same urgency, especially as they are paying the highest price in the hospital and in post-discharge provider settings. I see this as an endpoint problem. For personal reference, my child, Rebecca, came home on oxygen at 36 weeks and was on it for around two months. No one wants a child at home with medical equipment, but we saw the benefits as Rebecca grew strong and healthy and thrived, it was worth it. Right now, most children use oxygen at 36 weeks as the endpoint. That's too crude. Parents don't care about a number on a chart at 36 weeks. We care whether our child can breathe comfortably at home, avoid those re-hospitalizations and grow and learn. What's worse, some trials require three days of repeated oxygen assessments at 36 weeks. Again, it does not help families. It destabilizes the fragile babies; it burdens the nurses and still doesn't reflect what really matters.

We need smarter endpoints in between, like respiratory morbidity, through 6 to 12 months. A composite of re-hospitalizations. Medication use and caregiver-reported outcomes that is both feasible for sponsors and feasible and meaningful for families. Overall, I am using BPD as a case example. But these endpoint challenges are the same across NIC, HIE and other neonatal conditions. Everywhere we look we see the same problem. Crude, short-term surrogates that don't reflect what truly matters. The case for external controls, most neonatal trials today are open label. The so-called placebo is just standard of care and the data for both arms comes straight from the EHR into the trial CRF. The families ask if you are already using the EHR data, why not use external controls instead of placebo arm? It is the same data but without putting fragile

babies through randomization that families hesitate to accept. I hear this all the time from families. The benefits families see, faster, smaller and more feasible trials, higher willingness of parents to enroll, no duplication of data collection. Families are ready to contribute their data to help others.

I'm working on this with a data portal that's basically a registry with a twist called “Preemie Crystal Ball’. What we need is for FDA and sponsors to validate and embrace external controls as fit-for-purpose. Again, while I highlighted BPD here, families in the NEC and HIE and other conditions tell the same stories. Trials are too small, too slow and too burdensome. External controls aren't just a BPD solution, they are a neonatal solution. Parents deserve to know that a trial is set up to succeed. Think outside of the box and know that the infant will receive the best care while enrolled. We need innovation and to put our hands together in partnership now. I can count on both of my hands the number of families I supported whose babies died of BPD. The same with NEC. I'm sure Betsy can say the same.

In fact, I've one family struggling to transfer to another NICU because their child has BPD and severe swelling and their NICU team cannot get it down properly. It should not be up to a parent to have to sort through the fact that the NICU that their infant is in is not up to par to the top ones in the country. Their job is to be a parent. This isn't just an FDA problem or an industry problem or parent problem. We can no longer maintain such silos. If we don't move together, nothing changes. If we are allied, we can break a 30-year stalemate in neonatal drug development. Today Rebecca is 22 years old. We are so proud of her. While being a brilliant scholar and artist is incredible, the autism, the ADHD, the feeding issues, the sensory issues and the

cerebral palsy that happened at 13.5 years old. All of these were earth shattering, especially that last one. I kept asking about the walking gait for the better part of a decade and to Bec that CP is anything but mild, as we head into a world of wheelchairs and a disability placard on the rear-view mirror. We are not the only family to have these surprise diagnoses over time.

As Dr. Schmidt noted, there are issues in adulthood and into the geriatric years. Our children are not damaged goods. To us, they are the best part of ourselves and hope for a better future for all. Preemies have been known to be the prime minister of England, Sir Winston Churchill. They have become famous writers, as Mr. Mark Twain is known. They reached into the NFL, Olympics and more. And sometimes they testified before the FDA. Yes, I was a 36-weeker in 1967 when they had nothing. I too have scares from my premature birth. I don't stand here asking for sympathy I am looking for progress. Don't let another decade pass without approved therapies for our most vulnerable patients. If external controls and better endpoints cannot unlock progress, please do it. Families are ready, regulators are ready, industry is ready. Let's not lose this moment.

While BPD is the example I used today, please remember that this is a systemwide problem across neonatology The solutions we are proposing can have progress for every neonatal disease. So, remember, no new drugs for BPD in 30 years. Three-day oxygen checks, burden babies and don't help families. Families are ready to share their data. External controls can make trials feasible. BPD is the example of the challenges, which are the same across all of neonatal diseases. Neonates in the NICU

are capable of meaningful and productive lives-- in their honor, and in Bec's honor, let's work together to do better. Thank you.

Session Five: Interested Parties Comments

Children's Oncology Group (COG): Elizabeth Fox, MD

> Good afternoon I am Beth Fox, a Pediatric Oncologist based at St. Jude Research Hospital in Memphis, Tennessee, and I am the chair of the Developmental Therapeutics Committee for the Children's Oncology Group (COG), as well as the Chair of the Pediatric Early Phase Clinical Trials Network of the PEPCTN. Thank you for the invitation to share the Children's Oncology Group's and the PEPCTN's perspectives on PREA and BPCA.

The Children's Oncology Group is celebrating its 25th Anniversary this week. It is part of the NCI-funded National Clinical Trials Network or NCTN. It is focused on practice-changing trials for children and adolescents with cancer. The other NCTN focus is on adults with cancer. The COG has more than 12,000 experts to conduct more than 100 active trials at more than 220 leading hospitals, universities, and cancer centers. The Pediatric Early Phase Clinical Trial Network was established by a competitive process in 2018 to align early phase drug development in children with the NCI-supported Early Phase Clinical Trial Network in adults.

The PEPCTN's predecessor was the Children's Oncology Group Phase 1 Consortium established in 2001. The PEPCTN is dedicated to early phase dose determination activity trials for infants, children and adolescents with cancer. The PEPCTN has 21 sites to conduct phase 1 dose determination trials and can expand to

additional sites for biomarker-selected cohorts and activity studies in specific cancers. PEPCTN is uniquely positioned to design and conduct histology-agnostic trials that align with the RACE For Children ACT.

Since the BPCA was last renewed in 2022, representatives of the COG and other academic groups have periodically met with the FDA. The FDA has provided vital education regarding the goals and processes of Written Requests. COG and pediatric oncologists from academic intuitions have discussed priorities for clinical trials to meet the unmet need for children with cancer. Interest for certain pediatric studies, including combination therapies, optimal dosing, targeted therapeutics and biologics have been discussed. These meetings were not product specific and provided a productive forum for education and dialogue.

On this slide the impact of the voluntary BPCA on pediatric oncology drug development is seen. As you can see, it is not as pronounced as perhaps in the other diseases in common medical conditions in children. However, the impact to ensure safer drugs through clinical trials in children is impressive. The table lists the 46 anticancer drugs, or oncology supportive care drugs excluding antibiotics and pain medications, that have received exclusivity as of March 2025. Of the 335 total exclusivity determinations and 316 total approved drugs granted exclusivity, these 46 oncology drugs account for approximately 15%. Examples include trials for the BCL-abled inhibitors such as, imatinib, nilotinib, and bosutinib. These are relevant for children with Philadelphia chromosome –positive acute lymphoblastic leukemia and chronic myelogenous leukemia and allow for safe dosing and trials to demonstrate the benefit to children with drugs that treat specific resistant mutations in their leukemia,

similar to adults but not exactly the same. The antibody drug conjugate brentuximab vendotin in lymphoma biospecific antibody blinatumomab in leukemia have revolutionized therapy for children and the ability to test these drugs in children was critically important in demonstrating that. Targeted agents include mec and BRAF inhibitors, such as cobimetinib, trametinib, as well as dabrafenib, are critical components in the treatment of children with low-grade gliomas and radiopharmaceutical lutetium dotatate for children with neuroendocrine tumors is an important addition to that armamentarium for young people.

Given the economic challenge of the climate of oncology drug development overall, and for children in particular, we anticipate additional agents important for children with cancer will be granted extensions for exclusivity through BPCA in the coming years to help incentivize our pharmaceutical partners. On the next slide, The RACE For Children Act became statutory requirement in 2020 for new targeted drugs and biologics for cancers in adults to be evaluated in children, if the molecular target is relevant to pediatric cancer. The goal of this law is to focus drug development on the mechanism of action, rather than individual cancer types, and accelerate development of trials in children. The RACE for Children Act has certainly increased the number of planned trials for children with cancer. However, it perpetuates the dependence of innovative therapy development on adult cancers and doesn't ensure that planned trials for children are activated or completed.

Overall, these legislative initiatives have had a positive impact on the number of drugs with safety data and the number of planned studies. However, the potential to decrease time for first-in-human to first-in-child trials has not aligned with the timelines

for negotiating pediatric study plans or pediatric investigational plans. In addition, there is an increase in the number of planned trials, but not activated or completed trials, for children. This is not just because trials take a long time. They are planned but either never get activated or the drugs are pulled from the trial before the trial is completed because they are dependent on adult development. Incentives, condition for deferrals and new economic models for drug development are needed to fill the gap in clinical drug development plans for practice-changing trials in children.

In conclusion, BPCA and PREA and this body for legislation has created an environment for pediatric oncology drug development that can foster research; it enhances safety and expands treatment options for children with cancer. However, ongoing efforts are needed to address the challenges related to appropriate dosing in children and to ensure the development of innovative therapies, not just a plan for individual trials, but a complete development plan for all types of childhood cancer. I want to thank you for hosting this important forum and for inviting me to participate today. Forums such as these are critical opportunities to interact with the FDA and the community to advocate on behalf of children. Thank you.

>> Thank you Dr. Fox. We have the next speaker at the podium, Dr. Malcolm Smith from National Cancer Institute

Session Five: Interested Parties Comments

National Cancer Institute (NCI): Malcolm Smith, MD, PhD

>> I am Malcolm Smith from the National Cancer Institute. I'm in the Cancer Therapy Evaluation Program. The views that I will be presenting are my own and not the official

positions of the NCI. As Dr. Fox outlined, NCI supports clinical trials for children with cancer. We support the Children's Oncology Group (COG) that she described for conducting and developing definitive practice-changing clinical trials. We support the consortia for early phase trials that she described in the PEPCTN. Our goal in supporting these groups, and others, is to reduce the barriers for testing new agents and treatments to do what we can to expedite the highest priority agents moving into clinical trials to improve outcomes for children with cancer.

Measuring success is one of the things we will talk about today, and how do we measure success? There are the short-term measures that are similar for NCI in our clinical trials program, and for FDA and BPCA and PREA. How many clinical trials did you start? How many written requests for you? How many PSPs's were approved? But of course, these short-term measures can be misleading. We can start dozens of trials, but if all are negative it's a Pyrrhic victory. Similarly, lots of Written Requests that really are not that productive also, Pyrrhic victory. We do have a very hard measure for showing whether we are making success or not. That's the number of children that survived their cancer diagnosis. Therefore, they survive and childhood cancer mortality is reduced and finally, a metric for success.

If of course if we do have the curative therapy, then how can we reduce the long-term late effects of our curative therapies? How are we doing in terms of improving treatments? What are our successes in these ventures? For some cancers we are doing well. For non-Hodgkin's lymphoma, since 2000-2023, nearly 60% decline in mortality for children and adolescents with non-Hodgkin's lymphoma. On the other hand, for soft tissue sarcomas, rhabdomyosarcoma, really no progress at all. For

Hodgkin lymphoma, a really dramatic improvement since 2000. About 80% decline in mortality from Hodgkin's lymphoma for children and adolescents. Whereas, for brain tumors, barely a 10% decline, a significant decline but barely 10%. And finally, for acute lymphoblastic leukemia, a 40% decline in mortality with 11 off in recent years. But for bone cancers, this is cancers like osteosarcoma, and Ewing's sarcoma, the mortality is actually higher today than it was in 2000.

How can we make sense of these differences, and some successes and others where there is so little progress. And one thing that explains these in the simplest way, what are the cancers for which we have active new agents and what are the cancers where there's not been active new agents. When you look at ALL, when you look at NHL or you look at Hodgkin's lymphoma, multiple very active new agents have become available that we can do clinical trials for and improve survival for children. Quickly, an example. Hodgkin lymphoma, as I have described rituximab, very active for children and adults with Hodgkin lymphoma. If you take an active drug like rituximab and add it to the very active standard of care agents, you get something that is even more active and survival goes up. Nivolumab, an anti-PD-1 agent, again very active for Hodgkin's lymphoma, and you add it to standard of care agents and survival goes up even more. Whereas, for all the soft tissue cancers and bone cancers and CNS tumors, really a paucity of active new agents.

This isn't unique to pediatric cancer. Active new agents for CML, you can tell when imatinib was first introduced in the clinic. Active new agents, checkpoint inhibitors pembrolizumab, ipilimumab, nivolumab were introduced into clinical testing. What to do? – what do childhood cancer researchers need? We need active new agents. It's

not that the sarcoma docs or the brain cancer docs are not as smart as the leukemia or lymphoma docs, or don't work as hard, or don't have statisticians who can use the right clinical designs. They just don't have the active new agents. So, what can we do to make progress in this area? It's challenging. One factor that's always been true, that in some ways is increasingly more true in this precision oncology era, in the era of precision, immune-oncology agents that are more effectively targeting adult cancer characteristics often become less and less relevant to pediatric cancers. Many, many agents developed for adult cancers entering the clinic today have little or no relevance for pediatric cancers. How can we effectively spend little to no time with those agents? There are some agents, a minority, but there are some that can really make a difference for pediatric sarcoma, and pediatric brain cancers.

The other challenges are ones that I think apply to many pediatric populations. Small populations that limit the number of agents that we can study. If there are multiple agents and classes, as there are often in oncology, we can have multiple trials with no trial completed. Of course, we want to enter testing early. But sometimes, if we do, then that means the agent gets dropped from development and we have to go to something else. And finally, the Pharma timeline for pediatric development is driven by adult cancer milestones. The thing that could be really important to us, and could really be important for one of the sarcomas, may be on the timeline that’s really not at the pace that we would hope it would be for the pediatric cancers that we are interested in.

Looking at the curve for the bone cancers, we want to act with a sense of urgency to bring active new agents into clinical testing. Without these active new agents, maybe we can improve outcomes, but it's hard if you don't have the active new

agents. How can we bring the sense of urgency? What are the metrics for this? Steve DuBois published, was a senior author in a paper published in 2019, looking at how quickly to agents progress from first-in adult trials to first-in-children trials. It was at that time, it was the pre-RACE For Children ACT era, six-point five years. Over 25 years ago we published a white paper on early phase clinical trials for children. Our metric 'When could you begin' if those things were right for pediatric cancer trial? 'When could you begin', well you need to know the right dose in adults and the safety profile in adults. You really want to know it's active in adults, so the agent is probably going to continue in development. There is some rationale that it is going to be active in children. But that's basically what you need. This might take 2 to 3 years versus, the six-point five years before. I would love in a few years to see a really rigorous analysis of how quickly agents are now progressing from testing first in adults for cancer indications to children the first time. My sense is that it is not going to be better than six years. I think of agents to be really promising, and I think many pediatric oncologists say these are promising agents entering the clinic in 2019 and 20 that won't have their first pediatric trials initiated until 2026, so that's six years or more.

How can we act with that sense of urgency to increase the chance we will make progress in the next 10 years, and we are not going to look at a trial mortality rate figure like this and see it hasn't really made a difference. It's extremely challenging and it involves picking from among the universe of cancer drugs, a small group important to osteosarcoma, a small group that may be important to rhabdomyosarcoma, saying these are what we will focus on and have everyone buy into it. Have the FDA buy into it and have companies buy into it - the academic researchers that are experts leading the

way. These are the important things to study. We don't have the regulatory set up to do that now or the clinical infrastructure to do that now. But that would be the goal. How to get these agents into testing more quickly. We don't have it now, but we have really knowledgeable, dedicated folks at FDA and folks in Pharma and folks in academia that can work to bring this to fruition in the future.

I want to end now hoping that is going to be the case. But also, just to say these are uncertain times. Disruption of normal activities for sure. I want to acknowledge and say how grateful we are to the dedicated public servants at FDA who are doing such critical work to ensure the safety and effectiveness of the drugs that we use. To my colleagues at NCI, who are doing the work to keep the clinical trial infrastructure growing, the COG, PEPCTN uses, and all the folks that are making these trials. To Pharma and biotech research teams, and to the patient advocates who are educating themselves on topics they never would have thought they would be learning about - so they can be more effective in advocating for policies that will help children. And of course, for the families that allow their children to participate in the clinical trials that will define the more effective treatment for future generations of children. Thank you.

>> Thank you very much Dr. Smith. Our next speaker is Ms. Nancy Goodman with Kids V. Cancer.

Session Five: Interested Parties Comments

Kids v. Cancer: Nancy Goodman, JD

>> Thank you very much for inviting me to speak today. My name is Nancy Goodman, and I am here both as a mother and as a lawyer. My child, Jacob, died of medullar

blastoma in 2009. I became an advocate because the drugs used to treat Jacob were all over 40 years old and there was no theory of efficacy. I'm a lawyer, so I chose to address this challenge through new laws. In Jacob's honor, I put together a team and we developed and championed the Priority Review Voucher program and the RACE for Children ACT, and we are now working on the Give Kids a Chance Act.

My message to you is this. In the past three, four years, all incentives and requirements for pediatric drug development have been devastated. Completely diminished. We have a legal construct where we have three laws that address pediatric cancer. The Pediatric Priority Review Voucher (PRV) Program and BPCA, and PREA. All three have taken major hits and I really hope we can do something about this. What's the purpose of this meeting? The purpose of this meeting is really to prepare the FDA and assist the FDA in its analysis and Report to Congress, in preparation for the next PDUFA negotiations that will conclude in 2027. I would like to direct my remarks in that direction.

First of all, the PRV program, as you all probably know, it expired in December 2024. All of a sudden, there's a program that evaporated. Congress must pass the Give Kids a Chance Act, I certainly hope before 2027, but that would be a priority. The second priority is that Congress must have, or I hope considers, a "carve out" in the Inflation Reduction Act for the BPCA. In 2022, Congress passed the Inflation Reduction Act (IRA). In that law, is a provision that permits Medicare and Medicaid to negotiate pricing of drugs 7 and 11 years after their approval. The problem this sought to address is that drug pricing made these approved drugs inaccessible for many Americans. But

here is the problem with this law, and here's why this law has entirely rendered BPCA a very very small incentive now.

As written, BPCA had a significant limitation which Congress accepted and that is that. Companies would only voluntarily undertake a Written Request if drugs were profitable. If drugs aren't too profitable, companies have the right not to pursue a Written Request, but now after the IRA is passed, we face this situation where a company won't do a Written Request if a drug isn't too profitable. But a company also won't do a written request if a drug is too profitable and the company believes there is significant risk that Medicare and Medicaid would identify that as one of the companies that they would choose to negotiate pricing in year 7 and 11. For this reason, I hope Congress carves out of the IRA, BPCA.

I will also say one more thing. I've seen arguments, that the counterargument is, well in fact many companies don't have exclusivity or patents all the way to 7 years or 11 years, and so there's still this opportunity or Medicare and Medicaid may not come in at year 7 and 11. Perhaps, for some companies they will come in later. This is true, but the issue is that from the company's perspective there would be a risk that a profitable drug could be subject to these Medicare and Medicaid negotiations. It is the company's perception of the risk that will render BPCA a relatively irrelevant law.

My third point if that's not enough. If BPCA has a little bit of incentive for drugs that are a little bit profitable, but not too profitable, both BPCA and PREA have been significantly diminished in 2025 by the hits FDA has taken on its budget and personnel. In particular, personnel for BPCA and PREA to fully work, it's just critical that FDA have its entire workforce fully staffed and well-funded and supported. In particular, their

pediatric program. But to the extent that their pediatric program uses experts in all parts of the FDA, whether toxicology, pharmacology, biostatistics. It is so critical that we fund the FDA.

As you know, the impact of 2025 has been to diminish FDA's ability, and as a result its ability -- excuse me. I'm getting tongue-tied. As a result of DOGE and other decisions this year, there have been thousands of FDA staff who have chosen to leave or who have been RIF'd and this can't but cause the FDA to have a much more difficult time enforcing and applying PREA and BPCA. No matter how hard FDA officials dedicate and no matter how much effort they dedicate. Of course, I trust that they will. The fact is, if they are not adequately resourced, they can't do as good of a job with BPCA and PREA. It's just not possible. Why is this so critically important? Why are BPCA and PREA so important?

There's no drug development for any kind of indication whether it be pediatric or adult, without a legal framework to create incentives and requirements. This is even recognized in the US Constitution, which article 8 provides intellectual property rights to inventors. But Congress decided in the 1980s that these incentives, which became patents, were not adequate for drug development. That's what Congress passed the orphan drug act to create three-year market exclusivity for rare disease drugs. But then Congress decided that new molecular entities didn't have adequate incentives. So Congress passed five-year market inclusivity and then seven-year market exclusivity. Congress subsequently passed 12-year data exclusivity and came back again for antibiotics. This is all great and this is how we create a regulatory structure, so that companies develop the amount of drug society wants.

Congress also passed BPCA and PREA as part of this effort to get the right amount of drugs that society wants for children. But BPCA and PREA are different from all the other laws that were passed, insofar as they require intensive, intensive FDA oversight for them to be executed. We need significant FDA resources to write Pediatric Investigation Plans, Pediatric Study Plans and Written Requests. Enforcement is very labor-intensive and very resource intensive by the FDA. And we know that for the FDA it is not possible for them to do as thorough of a job going forward as they have in the past because they are not adequately resourced. Those are my points.

In summary, I hope the Give Kids a Chance Act is already passed by the time FDA writes their report. But if not, I hope Congress passes the Give the Kids a Chance Act as soon as possible. There must be a carve out in the Inflation Reduction Act for BPCA. So that once again it really has impact for drugs that are very very profitable. And finally, it's just critical that we support the FDA. It's not just about the good government, it's about what is fair. Adults, patients that need rare disease drugs, antibiotics for whom data is relevant, they all get market exclusivity. But children get BPCA and PREA and we must have a fully resourced FDA. We must have that to get the incentives and requirements that Congress developed for pediatric drug development. I really urge Congress to fully resource the FDA and the FDA to ask to be fully resourced. Thank you. That's it.

>> Thank you Ms. Goodman for your remarks. We are concluding Session 5 and we are running a bit ahead of schedule. We will take a brief break now and ask everyone to come back by 3 PM Eastern and start our Open Public Comment period. We have more remarks this afternoon, so we ask you to come back at 3 PM. Thank you.

(Break until 3 PM ET)

(Please stand by for captions)

>> Good afternoon, everyone. It is 3 PM and we will get started. We are running a little ahead of schedule and we will keep the meeting moving and maybe we can depart a little early. Next up, we are in the Open Public Commenting period of the meeting. As mentioned at the beginning of the meeting, we have had several speakers who have requested to provide remarks during this period, and each commenter will have five minutes to share their remarks. The first three speakers will be here with us at the podium. I will introduce all three now and ask each speaker come up one after the other in turn. First Dr. Albert Allen, then Dr. Ron Bartek, and then Dr. Diana Zuckerman, in that order. Thank you.

Open Public Comment: Speaker #1

>> Hello, I am Dr. A.J. Allen, and I am a child psychiatrist and pharmacologist and former clinical researcher, and spent time in both academia, industry and advocacy more recently. I will give comments that stretch those experiences. First, some observations over my 25 years or more in pediatric drug development. One, I think we need to celebrate all that's been accomplished. It was talked about in the beginning, and a number of people have talked about it, but when I first came to industry from academia there was one or two drugs in my specialty that were out there and available. Now, there is a whole formulary for pediatric and child psychology. It is largely due to the benefits of BPCA and PREA. We would not be here if it wasn’t for all the

successes. We haven't done as well in some areas, but you always have to have areas to learn and do better. Hats off to everyone here and online.

Second, resources are scarce in pediatrics and even scarcer these days as we have heard there's been a number of cuts in different areas of research through NIH and academia has felt those effects. In industry, we have also seen cutbacks in terms of groups dedicated to pediatric research, and as a consequence it's even more important today to have collaboration between the different groups. We had it for a long-time, it's been an important feature. One thing I will say, candidly, because no one pays my bills except me now, is that there are issues with trust between all of the groups, and I think we need to acknowledge those; but, we also need to work on overcoming those issues. Because people wouldn't be in this room if they didn't recognize that pediatric drug development wasn't important. While we may have differences on points and there may be different conflicts and things like that, everybody is here at the table. We need to take advantage of that and listen to everybody.

So, just that observation over time. As I said, in industry, resources are tight also. And what we are seeing is this creates not just headaches for individual companies, but headaches for patients and families and FDA and everyone else. I belong to a coalition, Pediatric Inclusion Alliance, that is looking at earlier inclusion of kids in studies and in drug development programs and there in one of the groups, there is Duchenne's Muscular Dystrophy and Limb Girdle Muscular Dystrophy. And the people in the Limb Girdle space, they are really suffering because of deaths that occurred with some patients and Sarepta's treatment for Duchenne's and additional requirements that they are having to deal with. That has patients and families concerned about their situation.

And I think we need to recognize that in particularly in the rare disease space, small biotech space, some of these companies live and die by a thread. And that has implications for the patients and families, just as much as in the research programs as it does anyone else.

Collaboration is also important because we need to try and overcome many of the inefficiencies and challenges that are present in pediatric drug development. We can do that, but we have to do that and start with pediatric development earlier and it really needs city integrated into drug development. Not the way it is now, which is pediatric drug development is regulated to the end of the drug life cycle unless you are talking about rare diseases or it would obviously be earlier. But for many drugs, they get approved in adults, second indication and third indication in adults. Somewhere down the road is the pediatric trial that has to be completed by a deadline. Often dictated by PREA and it maybe also dictated by BPCA. That's a long time for pediatric patients who live in the wild West.

I will run out of time here, so I will just say that I think what's important is we think about this as a drug development ecosystem. Companies need certain things, incentives and requirements. The incentives have to be in the eye of the companies. It does not help to say, "we're gonna give you this", if it's not valued. We heard from Nancy Goodman a good definition of those challenges. I really encourage people to think about this more and also we need to think about the economics of the whole system. Because a very fragile system like we have where everything is built on collaboration that when you knock out 60% of something at NICHD, it has ripple effects

in that it hits patients, families and companies. So, we need to have a more comprehensive look at those things. Thank you.

Open Public Comment: Speaker #2

>> Thank you, A.J. and thank you very much for including me in today's meeting and for allowing me the opportunity very briefly to explain why, for myself and our rare disease community, BPCA and PREA and related statutes are so very important. I am Ron Bartek and in 1997 our then 11-year-old son Keith was diagnosed with Friedrich's ataxia (FA), which is a rare genetic neurodegenerative disorder, in which the debilitating mulit-system damage begins in the womb and progresses relentlessly until death in early adulthood.

My wife Rachel and I co-founded the Friedrich's Ataxia Research Alliance or FARA the following year. Which quickly became the world's largest non-governmental funder of FA research. We began immediately to collaborate fully with all other interested organizations and with the wonderful people at the NIH and here at the FDA. We support academic research around the world and have attracted a growing number of pharmaceutical partners to this joint effort. All that hard work and collaboration have resulted in a great deal of progress, including on Rare Disease day of 2023, the announcement of the FDA's first approval of a therapy for Friedrich's Ataxia. That was a very exciting day for us, but there was a major problem.

Despite FARA's best efforts with the developer, the clinical trial and subsequent label were limited to patients of ages 16 years and older. Despite the fact, that about one-third of our population is under 16, and as I said, the damage for these patients

begins in the womb. We had strongly encouraged the developer to include younger children in the clinical trial, but they said they were convinced that the FDA was insisting that they begin with adults, and they also admitted that they had not done the pre-clinical data collection on adolescent and pediatric animals. We told him about the rare pediatric disease Priority Review Voucher program and that talked them down to an age from 18 to 16. Now our younger patients, about one-third of our population, will have to wait for any number of years to gain access to a treatment already approved for adults, and for which we have convincing evidence that it would have been even more effective for them.

In that trial, we decided immediately that should never happen to us again and that it should not happen to anybody else. We decided to change that reality, not just for FA kids, but for kids of all different disorders as well. With some like-minded colleagues, we began to explore the policies and attitudes among the key players: regulators, industry partners, patient advocates, bioethicists and regulatory advisors. And we were thrilled to learn here at the FDA, the thinking about pediatric inclusion was evolving. With the help of some FDA colleagues, we organized a full-day pediatric inclusion roundtable last July. Bringing together 350 stakeholders and began with two fireside chat panel discussions. The first by the three FDA medical product Center Directors and the second by the NIH's Directors of Neurological Institute and the National Center for Advancing Translational Sciences.

Those discussions were followed by panel discussions focused on CDER CBER, and CDRH. The message was very clear and very powerful. The FDA has already pivoted from trying to protect children from clinical trials, to try to protect them with

clinical trials, appropriately designed, so as to provide safe, effective therapies for children at the best time for them. So we can finally begin to prevent some of the symptoms, rather than trying to treat them later, sometimes, much too late. That roundtable was so successful, we decided to establish what we call the Pediatric Inclusion Alliance consisting of industry partners, patient groups, clinicians, the IRB Association, bioethicists and regulatory advisors devoted to clarifying and socializing that powerful message. And we are planning a second, such roundtable discussion, half a day for this December 3rd to assess progress to date.

There's been substantial progress and also focus to assess remaining challenges. We appreciate the contributions that BPCA and PREA have made to early pediatric inclusion, and we would welcome any adjustments that might enhance that inclusion. We would support, for example, removing the well-intentioned exemption of rare disease development from PREA requirements. We also believe it is important to review the definition of a prospect of direct benefit (PDB) for children, so as to avoid impeding the early inclusion of children with initial dose findings and PK studies. It's clear that getting children engaged in clinical research much earlier will require much more than adjustments to statutes. It will require a change in culture involving the regulators, the industry, medical researchers, IRBs, bioethicists and patient advocates. We are deeply grateful to the FDA for its irreplaceable leadership in partnership in advancing that cause and making that culture shift. We look very much forward to continuing close collaboration on getting safe, effective treatment to children as early as possible, at the point of maximum benefit to them. Thank you very much.

Open Public Comment: Speaker #3

>> I have worked with Ron for years, but I never knew your whole story. Thank you. I am Dr. Diana Zuckerman, President of the National Center for Health Research. We are a non-profit think tank that helps to bridge the gap between scientific evidence and public policy. We scrutinize evidence on the safety and effectiveness of medical products for children and adults. We don't accept funding from entities with a financial interest in our work. So, I have no conflicts of interest. But with Ron, I am on the Alliance for a stronger FDA. I'm a founding board member and I think you are too. The Alliance is an informal coalition of industry and nonprofits. We disagree on a lot of things, but we agree that the FDA is so important that it needs more appropriations, so that's what we lobby for.

I appreciate the chance to share the National Center for Health Research's perspective on BPCA and PREA today. We all know that these laws have made a really important difference in the lives of children and their families. The statistics speak for themselves. I agree with many of the suggestions that we have all heard today on how to improve the impact of these laws. I will focus on just a few of them. PREA is a great success, but as you have heard, the exemption for orphan drugs has slowed the progress, because so many rare diseases are devastating for children. RACE [for Children Act] has helped expand the impact of PREA, but is it enough? And can't we do more? I agree with the suggestion that the exemption should be focused on treatments for rare diseases where clinical trials are not practical. But, the definition of orphan diseases, is generally those affecting less than 200,000 people in the United States only, and if many of those potentially 199,000+ patients are children, it should be

possible to conduct appropriate clinical trials. And of course, there are children in other countries as well that could be included in these clinical trials. If necessary, some of those children -- sorry, it would be an improvement if the definition of the orphan disease exemption would specify a lower number of children with the disease. A more subjective or fluid exemption standard is likely to cause more problems than it solves.

So that's why I think it would be very helpful to come up with a range of numbers. The lack of FDA enforcement, when companies delay studies of children under PREA, has also been raised by the American Academy of Pediatrics today. We also agree with that concern. We agree that civil monetary penalties would be helpful, and it would also be helpful if the FDA made public information about who is complying and who isn't and who is delaying and who isn't. Shaming, we know, can be very helpful and calling out the companies that haven't complied can be at least as much of an incentive as financial penalties, which we know are sometimes just seen as the cost of doing business.

We also share the Academy's concerns about the difficulty of tracking when PREA requirements have or have not been met. The number of those that have complied is not very useful information if we don't have the denominator. And the same of course is true if the information about non-compliance is easy to find in a public database, but the information about compliance is not. You need all that information. The FDA is trying to improve transparency in a variety of ways this year. This would be an important addition to those efforts. As we all know, BPCA does not have requirements, it has an incentive of additional six months of exclusivity. This law would save more children’s lives, if the law required earlier deadlines for clinical trials.

Currently, a rather small percentage of these studies are completed within six years. Unfortunately, the current law creates competing incentives, saving children's lives by making approved drugs available as soon as possible, which competes with the companies making more money before generic drugs are available to compete with those drugs. In conclusion, I just want to say that I'm so thankful to be here and hear what everybody else is doing. But I do also want to add that the issue has been raised about double dipping with both of these laws, and I think the law is really quite clear the way it was written. But, also, it's consistent with HHS policies generally which do not allow double dipping. Thank you very much.

>> Thank you very much. Those are our three in-person Open Public Comment speakers, and we have three more who will be joining us virtually. Dr. Angela James, Dr. Ian Liu, and Mr. Steve Wosahla, who will all speak virtually this afternoon. I ask you to go ahead and please come on camera and we will first start with Dr. James and please follow each in order. Thank you.

Open Public Comment: Speaker #4

>> Good afternoon. My name is Dr. Angela James. I am the Founder and CEO of Diversity Health Networks. I have been a drug developer for nearly 25 years. I have worked in the clinical development space for the majority of my career and I have worked on a number of pediatric oncology programs. I am a first-hand witness to the positive impact of the BPCA on the biopharma industry. I also recall the uphill battle to change the approach and mindset in treating children as small adults without appropriate data to assess dose, dose regimen, safety and efficacy.

Yes, BPCA has created the ability to have pediatric specific labeling, but there are limitations. We need innovative study designs and use of our quantitative skill sets to bring children into the drug development paradigm earlier and not wait until late phases. Children are one of the most underrepresented populations in clinical research. For there to be inclusive clinical trials, they must include children. Especially those with life-threatening conditions, who would benefit from the same scientific rigor and access to innovation, as adults. We are still running this race and must do so with collaboration and cohesion. Thank you for this opportunity to lend my voice to this conversation.

Open Public Comment: Speaker #5

>> Good afternoon, I am Ian Liu. I think I have some slides up too, perfect. I am a pediatrics resident, and I am a lawyer and health policy researcher. I want to thank Dr. Aaron Kesselheim, my collaborator and research mentor, for assistance with these slides. A lot of this represents work that I conducted as a post-doctoral fellow at the Program on Regulation, Therapeutics and Law at Brigham and Women's Hospital at Harvard Medical School.

As we know, the goal of PREA was to make sure children are no longer a therapeutic afterthought by ensuring all drugs are studied for pediatric use at the time a drug comes to market. PREA applies to all new active ingredients, indications, dosage form, dosing regimens and routes of administration. The law was written with multiple exceptions. So, the most prominent has been brought up multiple times today, that is the Orphan Drug Act designation. There are also waivers that were built into the law. There are 3 statutory reasons why PREA studies may be waived if studies are

impossible or highly impracticable and if there is evidence the product could be unsafe or if the drug will not offer a meaningful therapeutic benefit for children. These waivers can be complete or partial. They can exempt the entire pediatric age range or a smaller sub-set of that.

Over time, as various people have noted today, rare disease exemptions have become more common. So, the first four years prior to the passage of PREA, about 15% of new drugs were Orphan Drug Act designated. That increased to about 23% from 2003 to 2012. Then research that we published in *JAMA* last year, 47% of new drugs approved from 2015 through 2021 were exempt under the Orphan Drug Act designation. Congress has taken some actions to limit the Orphan Drug exemption loophole.

So, in 2017, the RACE Act was passed that eliminated the exemption for certain pediatric cancer drugs. The study we published in *Pediatrics* last year, we found that the RACE Act was associated with earlier initiation of pediatric trials by a time of about 2.8 years. Although the main impetus for changing this exemption would be Congressional action, I believe that Dr. Deshmukh noted earlier that there is room here for the Agency to promulgate regulations that might be able to limit the Orphan Drug Act loophole, as well. In addition to the exemptions from the Orphan Drug Act, there are also waivers. So, 22% of new drugs approved from 2015 through 2021 were granted complete PREA testing waivers and we are not testing pediatrics at all. And in unpublished research, we found that 50% of drugs granted these complete waivers have observable pediatric usage within three years of approval, some of which is quite high. As others noted as well, almost 6 years after approval, only 28% of required

PREA studies were actually completed. We also note that federal spending on drugs with these delayed or deferred pediatric trials is significant. In a paper, we published a couple weeks ago in *JAMA Pediatrics,* we estimated federal government spending on these drugs to be over $27 billion over the seven years in our study.

We suggest that the FDA should consider a firmer stance towards these pediatric trial delays and especially for those delays that are plausibly within a manufacturer's control. Although enforcement options are somewhat limited at this time, non-compliance letters can be used to incentivize timely trial completion. We'd also suggest that the FDA ensure that PREA waivers, especially those granted for impossible or highly impracticable trials, which constitute about 80% of complete PREA waivers, are supported by high quality evidence. BPCA, as we have talked about, adds six months of market exclusivity for manufacturers to complete voluntary trials. This appears successful at generating valuable pediatric labeling information. This is a reference to a study from the *Journal of Pediatrics.* However, we would note that in our study that looked at drugs from 2013 through 2023, these label changes that occurred on average almost 9 years after the drug's initial approval.

In the Written Request documents, the Agency has the authority to request earlier trial deadlines, and we believe the Agency should do so, in order to make this valuable clinical data available earlier for children. I would also note, in the 2023 guidance, that the Agency does not expect to issue Written Requests for studies that are solely going to be acquired under PREA. And I would agree that with continuing regulatory action, companies shouldn't be rewarded for conducting trials that are

already required under PREA. I agree with Dr. Zuckerman that double dipping isn't in the spirit of the law. Thank you for your time.

Open Public Comment: Speaker #6

>> My name is Steve Wosahla. I am a CEO for Children's Cancer Cause. It's great to be here and to follow Dr. Liu during the public comments. The Children's Cancer Cause is a national non-profit advocacy group that was established in 1999. We were founded to ensure that the needs and perspectives of children with cancer, survivors, and their families were integrated into federal discussions about healthcare research and cancer policy. During the past 25 years, we have worked to accelerate anticancer drug development, so that children and adolescents can have access to less toxic, more effective therapies.

We have talked at great length today about BPCA and PREA and it's been a terrific meeting. BPCA and PREA, and amended in 2017 by the RACE for Children Act or Research to Accelerate Cures and Equity, were really enacted to incentivize and require sponsors to increase the development of therapies for pediatric malignancies. Without such mechanisms, childhood cancer is rare and complex diseases that offer sponsors little market incentive as has been noted to develop new agents. Our remarks today and what I wanted to talk about is changing the PREA and RACE Act provisions to correct what we see as some limitations and to make it more effective to accelerate pediatric oncology drug development. The proposed recommendations are in two areas.

First, we propose changing the timing and scope of the PREA and RACE Act requirements for pediatric studies. How do we envision this? It would be in two parts. The first part would be requiring sponsors to submit initial pediatric study plans earlier than the end of an adult phase 2 trial or at an initial pre-IND meeting as appropriate. Currently, sponsors typically begin to fulfill RACE Act requirements after approval of an adult cancer drug has been noted. But there is no obligation to conduct follow-up studies. Sponsors can arrive at an iPSP agreement with the FDA, in no later than 210 days, allowing for review periods and time for re-submission. iPSPs require timelines for the conduct of studies that FDA could enforce before the approval of the adult agent and such a requirement would increase sponsor's focus on the details and implementation of pediatric development of the drug.

The second part of the recommendation is to amend PREA and RACE to require full development of effective agents. As everybody knows, RACE contains no requirements for companies to develop fully pediatric anticancer agents when shown to be effective in studies that are specified in the iPSP. We know that FDA lacks this enforcement authority regardless of when a study is conducted either before or after an adult approval of a drug. Legislation to amend PREA and RACE should become a priority for advocates and clinicians, we believe, to allow FDA to have this authority.

And lastly, the second recommendation is recommending that FDA of course be fully resourced but also be required to report meaningful analysis of the RACE Act impacts every 2 to 3 years. We've heard some great data today and preliminary evaluations have shown that sponsors are complying with the requirements of RACE and data reported in the *Journal of Pediatrics* in 2024, show that from 2017 through

2020, 21 adult cancer drugs were approved and were associated with 15 pediatric post-approval testing requirements. We also know from the FDA that they reported 12 approvals of novel agents have been implemented since the RACE act went into effect.

We feel that the questions remain about how the RACE Act in it's current form is being implemented. Some examples include sponsor's time it takes to start pediatric studies if they occur after an adult agent is approved. Noncompliance letters for unnecessary delays and conducting required pediatric studies. Whether or not sponsors have requested common commentary mechanisms to address regulatory challenges. And lastly, an assessment of sponsors' plans for additional studies beyond fulfilling their RACE requirements. We think that reports of such evaluations would enable clinical investigators, family and policymakers to know whether the RACE Act is being efficiently managed to maximize its impact.

In conclusion, thank you for allowing me to speak today and in summary, Children's Cancer Cause believes that patients and families are eager to facilitate innovative ways to improve survival rates for patients and reduce late treatment effect for survivors. Accordingly, we are really pleased to see new FDA proposals that hold potential for advances in drug development, especially for rare diseases. We look forward to working with FDA on how to integrate the complexities of pediatric oncology drug development and the Commissioner's National Priority Voucher Program and Rare Disease Evidence Principles. We hope that our recommendations for reforming PREA and RACE, along with the new FDA programs, will help turn emerging scientific discoveries rapidly into medicines that result in lifetimes of health and productivity in children and adolescents with cancer. Thank you so much.

Closing Remarks: Dionna Green, MD, U.S. Food and Drug Administration (FDA)

>> Thank you so much Mr. Wosahla, and I want to thank all of our open public commenting speakers, and actually, on behalf of myself and my FDA colleagues, we want to thank all of the Interested Parties that provided remarks throughout the day. We also want to thank everyone who attended here in person and online. I hope everyone has walked away with some food for thought. I know we certainly have here at FDA, and we will take back this information that we heard today and digest it and summarize this information and think about the ways that we can continue to improve the way we develop safe and effective medicines for children. With all of your input, I think we are all in agreement that we heard some great suggestions today and we definitely heard some great themes today; but, we also heard that we have lots of work to continue to do to make sure that we all do right by children.

With that, I do want to remind everyone that we do have an open docket for this meeting that will stay open until September 30th, 2025. We invite you here, and those online, to please send any comments or additional thoughts on some of the prompts that we included in the Federal Register Notice for this meeting. That is open until September 30th. So, we are ending a bit ahead of time. But again, we want to thank everyone for joining us today. At this point, we will go ahead and close the meeting. Have a great week ahead.

The End.