FOOD AND DRUG ADMINISTRATION (FDA)
STAKEHOLDER INPUT ON PEDIATRIC LEGISLATION

OPEN PUBLIC MEETING

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CALL TO ORDER

DR. MCCUNE: All right. I think as people are kind of taking their coats off and getting settled, we're going to get started. I want to welcome everyone this morning. I'm Susan McCune. I'm the director in the Office of Pediatric Therapeutics, and I want to welcome everyone to the stakeholder input on the pediatric legislation public meeting. If that's not what you want to hear about, there are other rooms. And for those of you that are here early, I think there are still some donuts left, not paid for with government funds, out of my pocket, to thank you all for coming to this discussion today.

So I'm going to make a couple of announcements before we get started and then I'm your MC for the day, so please be a little patient with me.

We had our first stakeholder meeting, and I'll go through this in my background a little bit, in March 2015. And at that point, the FDA did the majority of the presentations. Over the last five

years, we've really made great progress in the pediatric arena and so today we're actually going to turn over the presentations to you, our stakeholders, so that we can hear more about your experience.

Today we have 13 invited speakers who represent multiple stakeholder groups impacted by the BPCA and PREA legislations. We have broken today down into three sessions to facilitate breaks and lunch. There is no difference between the sessions. Each one has a group of stakeholders that represent multiple points of view so every session is really just organized so that we can, kind of, get people in based on their travel schedules and then based on the breaks that we need.

And I will say that for each session, I'm not going to -- because we're a little tight on time today, we're not going to take clarifying questions at the end of each person's presentation. But for each session, if we have a little bit of extra time, we can see if we can open the floor for clarifying questions at that point. We do have time after 2:00 today to

open the floor for any additional discussion from stakeholders, especially who are not giving presentations today.

So we have some folks who have requested to speak prior to coming in today and they will have the opportunity to speak first during that comment/discussion session at 2:00 and then after that we'll open it up to additional discussion.

If you are not scheduled to speak and you would like to speak, there is a signup table outside the room, and we will accommodate as many people as time permits after all of the scheduled speakers. And I will say that we are scheduled to finish a little early today at 3:00 so if we need to run over, Terrie will probably not be happy with me, but we could certainly accommodate that.

Okay. Webcast viewers, if you have questions for us, please type your questions or comments into the discussion pod and we will address as many of those as time permits as well as after the scheduled speakers today. All comments will become part of the

record and will be taken into account as we draft the report to Congress that's due in July of 2021. We would appreciate it if you would submit your comments to the docket. The docket is formally open now and you can access that through the FR notice, and you can provide your comments either electronically or paper-based, and the docket is open for comments until December 19th, 2019.

A transcript will be available on the meeting webpage in a few weeks for this meeting and as some folks have probably already noticed, the kiosk in the lobby will be open during breaks and lunch for refreshments.

So now that I have taken care of the logistics for today, I want to introduce our first speaker, and I'm not going to do big bios for folks so if you want everyone in the room to know your extensive bio, feel free to do it when you talk. But Nina Hunter, we're very fortunate to have her as our director. She's the director of the Office of Clinical Policy and Programs in the Office of the Commissioner at the FDA and she's

going to kick us off today. Nina.

WELCOME AND OPENING REMARKS

DR. HUNTER: Hi, good morning. Thank you all for being here today and welcome to those joining us on the webcast. My name is Nina Hunter and I am the director of the Office of Clinical Policy and Programs which is the umbrella office for the Office of Pediatric Therapeutics and the Office of the Commissioner.

I would like to welcome you to our meeting today where FDA is seeking public input from all stakeholders including patient and their parents, advocacy and consumer groups, health care providers, regulated industry, academia, and other interested parties for a report to Congress that we will be submitting in 2021.

This report is mandated as part of the Food and Drug Administration's Safety and Innovation Act, FDASIA, which was signed into law on July 9, 2012.

Under FDASIA, the first report was published in July 2016 with subsequent reporting required every five years thereafter.

There is an additional requirement that FDA consult with stakeholders to obtain recommendations on modifications to improve pediatric therapeutic development. We specifically would like to hear from all our stakeholders about the public health impact that the pediatric legislation has had on our communities, organizations, or businesses. We would like to understand the effects that the requirement of pediatric studies under PREA or incentives under BPCA have had on the healthcare ecosystem including on drug biologic development plans, and we'd like to understand if there are any barriers preventing the undertaking or completion of studies under PREA and BPCA.

Among the FDA's foundational responsibilities is regulatory policy. At the highest level of engagement, FDA staff and leadership worked diligently and collaboratively with our stakeholders to protect

and promote public heath, advance scientific rigor, and support the development and access to innovative products. This is especially important for our most vulnerable populations, such as children. We remain committed to ensuring that children have access to safe and effective medical products, and we look forward to hearing your input in this process. Thank you.

And with that, I'll turn over to Dr. McCune to get us started on the overview of FDA legislation. Thank you.

FDA OVERVIEW ON PEDIATRIC LEGISLATION

DR. MCCUNE: Okay. All right, so I already introduced myself. This is my disclaimer as always. The views presented here are personal and don't reflect, necessarily, the views of the Agency. And I just would remind everyone that for specific drug development questions these should be discussed with the relevant review division.

So I know this looks like a really long agenda, but actually, I have about one slide for each of these. So I'm going to go through the history of the pediatric legislation; a little bit about the requirements under the FDASIA report; our BPCA/PREA experience, update you on that; touch briefly on the NICHD/BPCA experience because Perdita will follow right after; the RACE for Children Act; pediatric labeling of orphan products; rare pediatric disease priority review voucher program; the Pediatric Advisory Committee; some information on international pediatric therapeutic development; patient-focused drug development; a word about extrapolation; and then a summary.

So this is one of my favorite slides. As you look at the top half -- I think I have a pointer, do I? Oh, I do have a pointer. So if you look at the top up here, this is pre-1900 and this is post-1900. And pre-1900 on the top left, Cantharides or Spanish flies were chiefly used as blistering agents. They were adulterated with lots of other insects and beads

and things and this resulted in the Drug Importation Act of 1848.

Early safety is really interesting. In 1890, there was actually an effective antitoxin for diphtheria that was development from the serum of animals injection with diphtheria toxin. Unfortunately, in 1910, a five-year-old girl died of tetanus after receiving diphtheria antitoxin and this resulted in the Biologics Control Act of 1902.

Around the turn of the century, we had quite a few patent medicines. These are two of my favorites. The one of the top is Peters' Specific Blood Purifier. It claimed much and divulged very little in terms of its contents, but this was quite legal before 1906. And then my absolute favorite at the bottom is Mrs. Winslow's Soothing Syrup for teething and colicky babies. Lovely picture. It was unlabeled and laced with morphine and it killed many infants and resulted in the 1906 Pure Food and Drug Act.

In the middle, sulfanilamide. The Elixir of Sulfanilamide was introduced in September of 1937. At

the time, they were looking for compounding products for use in pediatrics that tasted good. We're still trying to do that. And this one tasted really good. It was a raspberry compound. Unfortunately, in order to get it into solution, it was compounded with an untested solvent known as diethylene glycol which is chemically related to antifreeze and this resulted in 107 deaths including many children, and subsequently resulted in the Food, Drug, and Cosmetic Act of 1938.

And then in 1962, the Kefauver-Harris Amendment was based on information about thalidomide. The manufacturers at that point had to then prove efficacy as well as safety. Thalidomide was not approved in this country but was used in Europe and resulted in phocomelia in many babies.

So as you can see for many years, pediatric patients have been the canary in the mine and so we have really wanted to improve therapies for pediatrics. And so you would think that we would have a lot of pediatric development based on this. The problem is because pediatric patients were really

viewed as vulnerable, no one wanted to do studies in pediatric patients, and they became what Shirkey defined as the therapeutic orphan.

And so if you look at the history here, historical milestones in legislation just to get everyone up to speed, I kind of covered the early history in the previous slide. And in 1974, the AAP Committee on Drugs issued guidelines for evaluating drugs for pediatric use in an effort to try to encourage the development of pediatric therapeutics.

In 1979, the FDA required sponsors to conduct pediatric trials before including pediatric information in the labeling. We then had the proposed pediatric labeling rule in 1992 and the final rule in 1994, but it allowed a disclaimer that labeling of drugs was not evaluated in children and that was the default.

So subsequently in 1994, the Pediatric Plan encouraged the voluntary development of pediatric data and this in 1997 was FDAMA that created the pediatric exclusivity provision, the voluntary provision for six

months of exclusivity incentive that ultimately wound up being the 2002 FDAMA/BPCA legislation.

In 1998, the pediatric rule was mandatory in terms of products that were required to include pediatric assessments. Unfortunately, the pediatric rule was stuck down, but subsequently in 2002 that pediatric rule was struck down. But in 2003, PREA reestablished many of the components of that 1998 pediatric rule, and at the time, orphan products were exempted from PREA requirements and we'll talk a little bit about that in subsequent slides.

In 2007, the FDA reauthorized BPCA and PREA for five years, established the Pediatric Review Committee, and in 2012, FDASIA was the legislation that made permanent both the BPCA and PREA and PAC, the Pediatric Advisory Committee, was permanently reauthorized under Section 507.

All right. So why are we here today? We're here because in 2012, FDASIA, as Dr. Hunter mentioned, required in Section 508 that the secretary of HHS report by July 9, 2016 and then every five years

thereafter on various activities resulting from the implementation of Sections 505A and 505B of the Federal Food, Drug, and Cosmetic Act.

The 2016 report was submitted in accordance with that provision and is online and contains a brief discussion of various pediatric drug development laws, regulations, and guidances, as well as an assessment of the pediatric programs and suggestions for improving pediatric research. We are required that at least 180 days prior to the submission of each report under subsection A that we consult, or the secretary will consult with representatives of patient groups including pediatric patient groups, consumer groups, regulated industry, academia, and other interested parties to obtain any recommendations or information relevant to the report including suggestions for modifications that would improve pediatric drug research and pediatric labeling of drugs and biologic products.

I am not the world's best at reading legislation, so I apologize. And my slides are a

1 little wordier than my usual. But for those of you in
2 looking at the requirements say, well, what's 505A and
3 what's 505B? BPCA is actually 505A and PREA is 505B.
4 And as I said, FDASIA permanently authorized 505A and
5 505B, but only authorized funding for Section 409I,
6 which Perdita will talk more about later today, of the
7 Public Health Service Act for five years. At this is
8 the part of BPCA which authorizes testing of pediatric
9 therapeutic products by NIH, which included the
10 development and funding of the Pediatric Trial
11 Network, PTN by NICHD and we'll be hearing from folks
12 from the PTN later today as well.
13 I mentioned that 505B in the original
14 legislation did not apply to any drug for an
15 indication for which orphan designation had been
16 granted. This was amended by the RACE Act for
17 Children in 2017 and I'll talk briefly about that.
18 All right. So we talked, preaching a little
19 bit to the choir here today, but PREA versus BPCA, we
20 talk about PREA as the stick and BPCA as the carrot.
21 And I had to find this really happy picture of the

stick because we have to all be happy about doing pediatric studies, even if they're required and not voluntary. So my little doggie with the stick, PREA, they both apply -- both BPCA and PREA apply to both drugs and biologics. As you can see on the left, PREA is required, BPCA is voluntary. And under PREA, one of the differences is that studies may only be required for approved indications whereas under BPCA, studies relate to the entire moiety and the indications for studies may be expanded. And then products with orphan designation are exempt, other than the molecular targets relevant to pediatric cancers under the RACE Act for PREA. BPCA studies may be requested for products with orphan designation and for both PREA and BPCA, the pediatric studies must be labeled.

All right. So where are we since kind of the last time we talked and since the beginning of time in terms of the pediatric legislation? So if you look here, over here, we're 1998 and over here we're 2019 and these numbers are up through September of this

year. As you can tell, we started out with a very low number of label changes on a per year basis with two in 1998. Since then, we have continued to increase and we're pretty steadily keeping this level. We're at 46 right now. We expect this to be above 50 for the 2019 year. So for the last five years or so, we've been really pretty close to 50, a little over 50 labeling -- pediatric labeling changes per year.

And how does that break down? Well, if you look at -- there have been a total of 818 labeling changes, 738 of them from CDER, 80 of them from CBER, and as you might expect -- I didn't actually expect this, but every audience I've asked, they've all expected this so clearly I was more positive about the bunny and the carrot than the doggie and the stick. But clearly, the doggie and the stick is responsible for more of our labeling changes.

Okay. A couple of words about the NICHD piece of BPCA. In 2002, the BPCA legislation provided provisions for off-patent drugs. It authorized a research program through the Department of Health and

Human Services with implantation through NICHD. They are responsible for developing a priority list of needs in pediatric therapeutics in consultation with FDA and pediatric experts. They are sponsoring relevant pediatric clinical trials and submitting the resulting data to FDA for labeling changes. The priority list for pediatric therapeutics for 2018/2019 is published and the link is here. NICHD and BPCA, you'll hear more about this today, has funded more than 30 clinical trials, has produced 11 labeling changes, two of which are devices, and the Pediatric Trials Network which was established in 2010 is part of the NCHID/BPCA program and coordinated by the Duke Clinical Research Institute.

All right. Two seconds on the RACE for Children Act. This was incorporated as Title V of the FDA Reauthorization Act or FDARA. It was enacted in August 18 of 2017, and for those of you -- because people say to me, well, what does RACE stand for and I can never remember it, so I had to write it down -- a Research to Accelerate Cures and Equity, RACE for

Children Act. And this requires the evaluation of new molecularly targeted drugs and biologics that are intended for the treatment of adult cancers and directed at a molecular target that is substantially relevant to the growth or progression of a pediatric cancer.

Molecularly targeted pediatric cancer investigations mean a clinically meaningful study data that use appropriate formulations that understand dosing safety and preliminary efficacy that will inform potential pediatric labeling. And it eliminates the orphan exemption for pediatric studies for cancer drugs directed at relevant molecular targets.

In terms of -- we had a request to report to Congress recently on the pediatric labeling of orphan drugs and it's probably a little hard for you to see. But we went in and we looked at the total number of approved orphan indications. There were 548 of these and then we asked, does the indication warrant pediatric labeling? And the answer for 200 of them

was no, and the answer for 348 was yes. So if you just look at this side over here in terms of the yes side, we looked at how many of these products were fully labeled and how many were incompletely labeled for pediatric use.

And of these fully labeled, 221 which is 64 percent were fully labeled for pediatric use, 36 percent were incompletely labeled. And then when we dove a little bit further into this 127 that were incompletely labeled, 81 or 64 percent had no pediatric information and 36 percent had some but were missing key pediatric information. And as you might expect, it's generally in the younger age groups.

All right. One of the other incentive programs is the rare pediatric disease priority review voucher program. This is where FDA may award a priority review voucher to a sponsor of a rare pediatric disease. Upon approval of their product, this entitles the holder to a priority review for a subsequent application. This, in effect, started in October 2012. It sunsets in 2020 and at that time,

FDA may only award a voucher if the drug has rare pediatric disease designation that has been granted by September 30, 2020.

Our office collaborates with the office of Orphan Product Development on the reviews and that started in May 2017. As of November 2019, there have been a total -- so since the beginning of the program in 2012 -- a total of 199 designations. I will say since we started collaborating, we've done 120 -- we've worked with OOPD on 128 of these and the number is continuing to increase. I think we're going to see substantial increases. We bump up against the deadline of designation, the September 2020 deadline for designation.

So there is a difference between designation. You are designated as a rare pediatric disease, but that does not mean you're going to get a voucher. You have to fulfill the requirements of getting a voucher when you submit your application under your NDA or BLA, but it does mean that we've taken the first step in evaluating whether or not the disease is a rare

pediatric disease.

So the first priority review voucher was issued on February 14, 2014 for Vimizim, for treatment of Mucopolysaccharidosis type IVA or Morquio A Syndrome. To date, there have been a total of 19 pediatric rare disease vouchers that have been awarded, and I'll show you a graph in a minute. And just so everyone is aware, there was a new definition of what a rare pediatric disease is, and this was from the Advancing Hope Act of 2016. And it defines a rare pediatric disease as a disease -- is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals from birth to 18 years including age groups often called neonates, infants, children, and adolescents.

Okay. So this is not our data. This is from a public source called Priority Review Vouchers so I can't totally confirm the numbers other than the numbers of vouchers that are on here. So if you look at this graph, this goes from 2009 up to 2019. The

gray bars are the number of vouchers that have been awarded and this includes all of the Priority Review Voucher Programs. So this includes neglected tropical diseases, rare pediatric diseases, and medical countermeasures. And so there are 32, if you're doing the quick math. There are 32 here of which 19 I already told you are pediatric.

But what I wanted you to be able to see, so you're looking at these numbers here. These are in millions and this is for those vouchers that have been sold. So a company is awarded a voucher. They can then sell that to another company for a priority review. So in 2014, the first voucher that was sold was sold for 68 million dollars. In the 2015-2016 timeframe, the sale value seemed to peak at 350 million, and since about 2017, it looks like the price for selling a voucher has come down to closer to the 100-million-dollar range.

All right. Let me take two seconds to talk about the Pediatric Advisory Committee. Beginning on September 27th, 2007, it was established that during

the 18-month period beginning on the date of a labeling change that's made pursuant to subsection G, that all adverse event reports that have been received for the drug would be referred to our office, the Office of Pediatric Therapeutics. And then we would provide for review of the reports and then we would present them to the Pediatric Advisory Committee and obtain any recommendations from that committee with response to taking any kind of action on the reports.

So as you might imagine, we've been doing safety to the Pediatric Advisory Committee since before that mandate. The first pediatric safety presentation to the PAC was on June 12th, 2003 and to date, there have been 506 products that have been presented to the PAC for safety review.

So you saw how we're having an increase in the number of pediatric labels, or labeling over the last, especially over the last five years. And if you think about every 18 months we're going to have to look at the safety of each one of those products, during a presentation which is limited -- we have a limited

ability to do presentations to the PAC, we're going to get behind. And so we were starting to get a little bit behind, and we were also evaluating whether or not we were seeing significant safety signals that needed to be discussed by the Pediatric Advisory Committee.

And so what we established in 2016 was that if we had reviews where there were no new safety signals, we would post those reviews, web post those reviews for review, but we would not take the time to formally present them to the Pediatric Advisory Committee. So to date, there have been 135 product reviews that have been posted to the web of which 105 are CDER products, 14 CBER products and 16 CDRH products. So we expect that we will continue to have an increased number of products being reviewed for the PAC.

In terms of international pediatric therapeutic development, the Pediatric Cluster was established in 2007. They meet at least monthly. Matter of fact, they were meeting this morning, to have informal discussions between regulators that currently include FDA, EMA, Health Canada, Japan's

PMDA, and Australia's TGA.

Between 2007 and 2019, there have been 149 teleconferences with a discussion of 537 products, 177 general topics, for example, safety concerns pertaining to a product class. And since October 2012, we've completed 38 common commentaries. Frequently discussed issues include the scope of pediatric development, safety, trial design, and study populations.

We have converged on approaches. It doesn't mean we are identical about how we approach things, but we have convergence on approaches that have been achieved for about 72 percent of the issues discussed over the past three years.

I just put this up here to remind folks that this is a very collaborative international pediatric therapeutic development area. On the left side is the other side of the pond and PRIMA and conect4children or c4c. On this side, you'll hear today from both Pediatric Trial Network and I-ACT, the Institute for Advanced Clinical Trials for Children. And then one

of the areas that I've been involved in since its inception is the International Neonatal Consortium.

And then it's really critically important that we really think about how we do a better job of incorporating patient input into medical product development. There are a couple of efforts that are ongoing in the agency. One is the Patient-Focused Drug Development Program Staff in CDER. They're the liaison for all the externally-led Patient-Focused Drug Development meetings in that program and this is using what initially starting as an FDA-led Patient-Focused Drug Development public meetings initiative. And I will say that a great number of these of are pediatric and we, as FDA members, attend quite a few of them.

Patient Affairs staff and the Office of the Commissioner coordinate the patient listening sessions and then for those you that weren't aware last week, we actually had the Advancing Development of Pediatric Therapeutics or ADEPT 6 meeting on pediatric clinical trial endpoints for rare diseases with a focus on

pediatric patient perspectives and it was lovely. We had nine pediatric patients that came and did multiple panels for us. And they certainly were not shy about getting up and telling us what was important to them.

So and I don't know if any of you listened to the testimony of Dr. Hahn yesterday, but there was a focus on making sure that we have patient input at all levels of therapeutic development.

We're going to talk about innovative trial designs, I think, probably a little bit today and so I just want to remind folks about pediatric extrapolation that was first mentioned in the final regulation in 1994. Pediatric use statement may be based on adequate and well-controlled studies in adults provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients.

Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dose, and

additional pediatric safety information must also be submitted.

So what we're saying is that efficacy may be extrapolated from adequate and well-controlled studies in adults to pediatric patients if the course of the disease is sufficiently similar and the response to therapy is sufficiently similar. And we were talking earlier today, all of the ICH activities in Singapore are all discussing the document around pediatric extrapolation. I think they're all on their way home today. But just a reminder that dosing cannot be fully extrapolated, but we can use modeling and simulation and information that we have from other programs to try to establish a more appropriate pediatric dose and safety cannot be fully extrapolated, but that doesn't mean that we don't want to leverage all the information we have from all the sources.

All right. So in summary as Diane Murphy and a number of others have said in the past, children are protected through research, not from it. We've had

some successes to date. They are noteworthy, but we must continue to move forward and improve. Our role at the FDA is to ensure the protection of human subjects during all phases of therapeutics development, to review the adequacy of data to support the approval of therapeutics, and to promote collaboration to increase the availability of approved therapists for children.

Scientific and regulatory advances have broadened the types, collection methods, and analyses of data that can be used to support approval of products for use of children and all of the stakeholders play an important role in the development of safe and effective therapies for children. But the problem is, the bridge is still out and what we need to do is we need to be able to provide the science so that we can build the bridge.

So with that, I'm going to say, and I'm going to introduce the first of our speakers in the sessions -- what we are here today -- you know, we're here to hear from all our stakeholders and we're here

to hear the public health impact of the pediatric legislation and what that impact may have had on you personally, on your community. We want to understand the effects of the requirement of pediatric studies under PREA or the incentives under BPCA in drug and biologic development and how that affects your drug and biologic development plans. And we want to understand if there are any resource issues or any barriers to understanding or undertaking studies under PREA or BPCA.

So with that, I'm going to close and I'm going to turn the meeting over to our first group of stakeholders. And I thought I saw Perdita -- yeah, there we are. I thought I saw you come in and then I did see you sit down. So Perdita Taylor-Zapata is the program director in NICHD who's going to talk to us today about the NICHD/BPCA experience.

And be careful not to trip over that.

DR. TAYLOR-ZAPATA: Don't trip over that. Okay. Good. Excellent.

NICHD PRESENTATION

DR. TAYLOR-ZAPATA: Good morning, everyone. Thank you to Susie, Terrie, and the staff here at FDA for the invitation to come and talk about the BPCA program and the NIH. Just as my usual caveat, I am a government worker, so I have no conflicts. I have not proprietary information I'm going to share, and I have no particular position on any legislation. We'll just make that clear so there we go.

So just to give you some information. I'm going to focus primarily today on the NIH aspect of the BPCA legislation. As you know, BPCA and PREA are there to improve the safety and efficacy data for children and improve labeling. And within the BPCA legislation, there's a Section 409I which gives NIH the authority to actually conduct pediatric clinical trials and develop and Drug Development Program. That responsibility has been on the National Institute of Child Health and Human Development, which is where I work, and has been delegated to the Obstetric and

Pediatric Pharmacology and Therapeutics Branch.

So I'm going to tell you a little bit our program, what we're doing. You'll hear a little bit more details about our program from our Pediatric Trials Network Leadership, that sort of sponsors and conducts all of our trials. But my focus here today is to tell you sort of about where we are, what we've learned globally within the program and then the things that we think still need to be done.

So again, our NIH program is primarily in the off-patent world. Of course, FDA has the largest responsibility for BPCA in the sense of forming collaborations with pharma to make sure that on-patent studies are done, giving companies six months of exclusivity to conduct the studies. Our program, again, is primarily focused on off-patent drugs, drugs that no longer have a patent, and still needs data to be done in children. Again, our focus primarily are on older indications and no patent status. If there is a patent, of course, that's done via PREA, or if it's new indication via PREA, if there's a patent,

it's done through BPCA. So just give you a framework of sort of where we fit within in the program, that sort of old indications and no patent status.

But what's interesting is that even though you have this clear delegation here about the legislation, the challenges in implementing pediatric drug development goes across patent status and it's common, I think, to all of us. And that's some of the things I think I'm going to focus on today.

This is sort of our mandate within NIH which are these components here: to prioritize what studies need to be done and looking across therapeutic areas about where the needs are in different therapeutic areas, to actually sponsor those clinical trials, and in that sponsorship, we actually since 2010, had a pediatric trials network that’s run by Dr. Danny Benjamin and Dr. Kanecia Zimmerman. And they'll speak more to that again later, but that's sort of our infrastructure and our framework for how we sponsor those clinical trials. And I'll talk a little bit more about infrastructure later.

After we conduct those trials, we actually submit them to the FDA for review and this is where the uniqueness, I think, of our program is. We don't just work with one actual FDA division. So if I was in Infectious Diseases, you're probably working with one or two divisions. If you're in the Diabetes and Digestive Diseases Institute, you're probably working one or two divisions.

Within our branch, because of the mandate to look across therapeutic areas, we work with at least 10 different FDA review divisions and so I think that brings a uniqueness to our program and a strength to our program is that we are able to be cross cutting across multiple divisions. And so once we submit that data to FDA, we also submit that data to the public domain. Initially in the program, we would submit that data to the Federal Register Notice. Not many people look at the Federal Register Notice, probably those of us in the room may, but general public may not. So in the last five years or so, we at NICHD have a data and specimen hub called DASH where we

actually submit all of our study data that's done under the BPCA program. Data stats and all data are there for anyone to use and to see. So that data is important because that's data that otherwise may not be available if not done by our particular program.

And then once we submit that data to the FDA, FDA reviews it, just like they would any other data for data quality and to make sure we've hit all our milestones and then that drug is considered for label change. And none of us actually ever anticipate how complex this process is. It looks very nice on the slide, but the actual complexities of getting this done from A to Z is very, very intense. But we've actually been through this process several times and have had a good amount of success.

So again, our overarching role is to really produce -- prioritize what studies need to be done and we do that and place that on a priority list that's on our website, the BPCA website. And again, that just highlights what we think the needs are in the therapeutic areas. We actually conduct the clinical

trials and we also fund pharmacology-focused research through a U54 grant mechanism to look at cross-cutting things like outcome measures, biomarkers, pharmacodynamics, and things of that nature as well. We also have a T32 training program as well as a mentorship program within the Pediatric Trials Network. And the ultimate goal of our process really is to improve data, to improve care and disseminate that data to those who actually really need it.

Again, for us priorities -- thus far, we have prioritized 150 drugs and those are on our BPCA priority list and that's across 50 therapeutic areas with 17 overarching themes. And that's the link to the website if you'd like to get more information on the priorities and the studies that we're doing.

This is just a snapshot of the prioritization process. No need to actually look at that. It's actually on our website, but it's a nice process, I think, we've developing over the years of soliciting nominations from outside stakeholders, such as yourself, determining where the needs are, reviewing

those needs for different things like how it impacts the population, what's the evidence for that need, and what's the population that that need will address. And based on that review and based on the feasibility of whether we can conduct that study within our infrastructure, we'll then prioritize it, coordinate very closely with our colleagues within FDA, particularly within the Pediatric Division, to determine what the actual needs are and then publish those needs annually.

Again, once that list is done, we then forward that list to -- share that list with our Trials Network and based on feasibility, we conduct those trials based on the priorities that have been done. But also, in addition, if we don't have the infrastructure to be able to conduct that trial for various reasons, if it's a large Phase III trial that, you know, requires lots of numbers as far as patients and lots of funds, that may not be within our constraints to conduct that particular trial, but there may be a network that already exists that could

potentially conduct that trial with us. And so we collaborate very closely with other networks if we ourselves are not able to do that trial.

Again, this is the website for the Pediatric Trials Network which, again, is the infrastructure for how we conduct our trials. And I'll just say as a brief history, initially when we started BPCA back in 2003 or so, we actually initially did individual contracts with academic centers to try and get these trials done and we did that for about five or six years and then had an enlightenment that it'd probably be better to have an infrastructure to actually be able to do these trials and have a way to manage the sites across multiple therapeutic areas, have the regulatory experience and assistance with the sites to be able to do the trials effectively. And this has been done since 2010 and it has worked magnific- -- whatever that word is. Magnificent -- whatever, that one. It's worked very well to be able to really push trials through and be able to get the number of trials done.

So in the beginning, we were only able to perform one or two trials every year or every two or three years even, because of the intensity of and the amount of resources it requires to do one large trial. And with actually having the infrastructure in place, we were able to do 20, 30 trials within this mechanism. So again, you'll hear more about that from Dr. Benjamin and Dr. Zimmerman, but this importance of infrastructure, I think, is one lesson that we've learned that we've taken over the years from how to really do pediatric drug development trials well, and really having experts at the table to be able to do this well.

So again, this is our -- what we think the program brings to the table. We have pharmacology expertise, and able to assay development, modeling, simulation. We have it all right in hand. We have the experts right there within the network to be able to assist any investigator in any type of trial design that they're interested in doing in the area of drug development.

We have also worked very closely with the Trials Network to -- and they have really promoted innovative trial designs. Some of that because of feasibility, but also just because of the way to do pediatric trials. Some of that could be in the way of opportunistically collecting data on patients through this mechanism to be able to collect samples over time and to that feasibly and do that very well. Again, you'll probably hear more about that. Things like master protocols as well that we've been able to do. Obesity-based dosing is another thing that we've been able to do and even devices we've been able to do in this infrastructure.

We definitely have, I think, trail-blazing efforts, as I said before, in working across multiple FDA divisions and that really has given us, I think, regulatory expertise in our program and even, I think, at the NIH.

The cost efficiency, I think, has been a real key model for us as well as promoting investigating training. So these are things, I think, our program

brings to the table and that we've learned over the years as well.

So far we have studied at least 120 drugs in some way or form, either via opportunistic study, dosing studies, efficacy studies, safety studies; 40 clinical studies done to date, and 26 of those studies submitted to the FDA for label change, which I think is a great feat at this point. These are the therapeutic areas that we have been involved with. And as you see, it goes from a wide range, from outpatient pediatric trial in bipolar disorder to a NICU, neonatal trial in apnea prematurity and heart failure. So multiple types of therapeutic areas including a new study that I think we'll talk about later which is drug exposure in lactation which is a new area for us where we actually study maternal and infant pairs to look dosing in breast milk. So we have the infrastructure to really be able to do innovative trial designs within our network.

These are our label changes; we've had 11 label changes to date. A different law from the 700,

almost 800 plus from BPCA overall, but again, given the complexity of what it takes to actually change a label, I think this has been an amazing feat. And again, the areas go from in the ICU, sodium nitroprusside, things like meropenem and acyclovir which actually have changed both the way studies are done and trial design and actually acyclovir in particular, giving data that needed to be done for years regarding underdosing kids with a really serious disease such as HSV and having the right dose actually in the label. So really important studies, I think we've done for public health.

Again, I think what we've learned over the years is that you need a funded infrastructure to be able to conduct these trials. Again, initially we were only able to do limited numbers given the static funds that we have and now with this infrastructure, we actually are able to do multiple studies at one time.

You definitely need your experts at the table from the beginning, collaborations with experts in

biostatistics and even now, I think we're learning that we need other experts, even outside of what we initially think like bioinformatics or informatics or people who do types of -- data science experts are important if we want to do registry studies and things of that nature. So really that collaborative field that Susie was talking about earlier is really important and one of the lessons I think we've learned as well. You need a good support team. Your study coordinators rule the world and so it's important that you have the infrastructure in place to be able to assist them and to be able to do the trials effectively and for the sustainability of your infrastructure as well.

And then, of course, you need, as I said, a good question. We need -- I think the one thing that we've learned now is that now we have the infrastructure to do studies, we're coming up with issues where even though the studies need to be done, there are things -- that science bridge that Susie talked about is still an issue that impacts us. Is

there a validated outcome measure? You know, is there an actual endpoint for this actual -- a validated endpoint for this disease.

And so that sort of science of drug development and those tools still need to be done. I think we are in a position to be able to provide resources for those types of funds, but we need to do that in collaboration with our industry sponsors, with our academic sponsors, and with our patient population as well.

So I think, yeah, as I was saying earlier, these are the challenges that we face in drug development and that we all face in pediatric drug development. But I think a lot of things that I talked about earlier as far as the way we've structured our infrastructure really helps to improve these areas. We have microassays. We have things in place as far as how to identify and how to provide incentives to sites to be able to get them to do research as well. So we have a lot of, I think, innovative things within the program to be able to

assist us in moving pediatric drug disease forward.

Even though our goal is sort of label change, there's still a lot of things that need to be done and these are the gaps that we all, I think, in this room need to address concurrently, sort of the basic needs of pharmacometrics, biomarkers, drug transporters, as I said, outcome measures, endpoints, and actually innovative trial design and innovative technology. These are the drug development tools that we would like to see done within our program because we think those can be utilized by anyone here in the room as well, and that's our goal, I think, for the next few years.

And I think ultimately our goal is to really move drug developments from the sort of linear process to really a feedback loop so that what we learn in our Human Phase III and Phase IV trials we actually can use to actually identify new targets in pediatrics or in obstetrics as well. So it's important that we do that.

I think that's the last thing. Yeah. These

are our, again, deliverables. We do push -- make sure labels are updated. We also get the information to our scientific community and we actually disseminate the data as widely as we can, as I said, through DASH and other mechanisms, and we really want to build collaborations to really be able to push drug development forward as it should be.

If you have any information that you'd like to get from me, any additional information, any type of information about DASH, about our programs from priorities to studies, this is my contact information. Feel free to contact me any time and I think that's it. Yeah, definitely my job today is really to let you know that we're here, we're doing this, but we don't want to do this alone. We can do this together as a collaboration to really move the field forward.

So thank you for your time. Thank you to the organizers for allowing me to talk.

DR. MCCUNE: All right. Thank you very much, Dr. Taylor-Zapata. We really appreciate that update.

Next, we're going to hear from Michelle Adams

who's the Director of Federal Policy with the National Organization for Rare Diseases. Michelle.

NORD PRESENTATION

MS. ADAMS: Thank you, Dr. McCune.

Hello and good morning. On behalf of the 25 to 30 million Americans with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders, NORD, thanks the U.S. FDA for the opportunity to speak here today at the Pediatric Stakeholder meeting.

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare, also known as, orphan diseases, and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

The Best Pharmaceuticals for Children Act, or BPCA, and the Pediatric Research Equity Act of 2003,

or PREA, are landmark pieces of legislation designed to improve information about how to safely and effectively use therapeutics in children. Both laws were enacted at a time in which many drugs were not directly approved for pediatric populations were being used on children without adequate information on safety and efficacy nor proper dosage.

The two laws operate differently. As Dr. McCune mentioned, they are often referred to as a carrot and stick approach. BPCA, or the carrot, offers and incentive in the form of an additional six months of exclusivity for the conduct of pediatric studies that would be beneficial for children. Under PREA, or the stick, FDA can require a sponsor to conduct certain pediatric studies and to submit such studies with a marketing application.

As a result of these two important laws, there have been 765 labeling changes to include pediatric information. NORD recognizes the importance of these successes and supports efforts to ensure the continued efficacy of these laws.

Although not the central focus of this meeting today, I want to discuss another law for which NORD has a long history of support, the Orphan Drug Act. In 1983, there was a serious lack of treatments for those living with rare diseases. Only 34 existed. Out of sense of desperation, a small group of patient advocates, many of whom were parents, led by Abbey Meyers mobilized. Abbey founded NORD and she and NORD played a pivotal role in the enactment of the Orphan Drug Act that same year.

The goal of the Act is to encourage the development of drugs for rare diseases and it has been a huge success going from less than 35 in 1983 to over 800 FDA-approved indications for rare disease treatments today. But other numbers suggest there is more work to be done.

There are still over 7,000 rare diseases that afflict almost 30 million people in the United States alone. More than 90 percent of these disease still have no FDA-approved therapy. Patients with rare diseases live this reality on a daily basis. With the

serious unmet need in mind, NORD has continued its fight for policies that foster orphan drug development from 1983 to today.

Of course, rare diseases impact adults and children alike. Estimates suggest that anywhere between half to two-thirds of the 7,000 rare diseases begin in childhood. Many continue to be fatal in these young children. Yet, scientific advancements leading to early diagnosis and improved treatments have resulted in more children with rare diseases surviving into adulthood. And we hope that someday treatments will allow all children with rare diseases to live to adulthood.

When PREA was enacted in 2003, Congress decided to exempt orphan products from its requirements. In other words, when a sponsor pursues an orphan designation and approval, that sponsor is not required to conduct the pediatric studies that would otherwise apply to sponsors of non-orphan products. Under the law, FDA has the authority to revoke or change this exception through regulation.

In the 2017 passage of the FDA Reauthorization Act, Congress required FDA to report on the lack of pediatric information in the labeling of drugs for indications that have received an orphan designation. In August 2019, FDA issued its report entitled "Pediatric Labeling of Orphan Drugs" responding to this mandate. FDA found that of the 548 total approved orphan indications from 1999 through August 2018, 200 did not warrant pediatric labeling while 348 did warrant pediatric labeling. Of the 348 approved orphan indications that warranted pediatric labeling, FDA found that 221, or roughly two-thirds, were fully labeled. The other 127 were incompletely labeled with 81 having no pediatric information and 46 missing some pediatric information. NORD applauds FDA for completing this comprehensive and thorough report.

NORD is extremely concerned about FDA's findings in this important report. It is unacceptable that roughly one-third of all orphan products that warranted it had inadequate labeling and one-quarter failed to contain any pediatric labeling at all. NORD

recognizes that children are not just small adults. Ensuring that pediatric patients, their families, and their providers have the information they need to make not only dosing decisions, but treatment decisions is of utmost concern to NORD.

Without adequate labeling for children, healthcare providers and caregivers are put in the difficult position of guessing whether and how much of a drug to provide. This could have dangerous consequences for children.

This is a situation that cannot be sustained. NORD supports efforts to ensure that adequate and complete information on pediatric uses for all appropriate age groups can be obtained for orphan drugs.

Orphan therapies represent an increasing number of products approved by FDA and that is good news for patients with rare diseases, especially given the 90 percent of rare diseases with no approved drugs. But under current law and regulations, this means that more products coming into the market will

be exempt from PREA, potentially exacerbating the concern highlighted in FDA's report.

As we explore ways to remedy the lack of pediatric information on orphan drug labeling, NORD believes it is critical to keep in mind some key considerations. Again, we must remember that 90 percent of 7,000 rare diseases still do not have a treatment that has been developed and is FDA approved. We need to ensure that any requirements to increase pediatric labeling about therapies do not impede innovation in the rare disease space. Any such requirements must also be applied only when necessary. Studies in children shouldn't just be interesting, they must be necessary.

There must also be transparency and predictability around requirements with respect to pediatric studies. Companies in this space must know the requirements in advance and understand when and how such studies might be required.

Some therapies do not necessarily lend themselves to pediatric studies and incorporating

children may not be practicable. All of these factors must be considered carefully, incorporated into the process, and communicated and applied clearly and consistently across the centers and review divisions. Such protections are in the interest of both children and adults with rare diseases.

NORD stands ready to work with FDA, Congress, and other stakeholders to achieve the dual goals of ensuring that innovation in the orphan drug space continues and that more robust pediatric labeling makes it ways onto orphan products. The status quo as detailed in FDA's report is unacceptable and we need to find a way to address it. Thank you.

DR. MCCUNE: I know I'm going to trip over this one time today. Thank you, Ms. Adams, very much for your comments.

Next, we're going to hear from Dr. -- sorry -- Estevan Santana, sorry. We had a little switch in the program today -- who is the Director of Science and Regulatory Advocacy at PhRMA. Good to see you again. I know we had a shift in the program today, so thank

you very much for coming and talking to us.

PhRMA PRESENTATION

DR. SANTANA: Thank you, Susie. Yes, if you're looking at your agenda, you'll notice that I am not Lucy. She had a conflict today, so she sent me in her stead, but I think you guys are good hands with me.

So thank you to the FDA, to Susie, and to Terrie for inviting us to provide comment today. My name is Estevan Santana, Director of Science and Regulatory Advocacy for the Pharmaceutical Research and Manufacturers of America, or PhRMA. PhRMA represents the country's leading innovative biopharmaceutical research companies which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives.

Since 2000, PhRMA member companies have invested more than 900 billion dollars in the search

for new treatments and cures including an estimated 79.6 billion in 2018 alone. PhRMA and its member companies are dedicated to advancing drug development to expand the availability of safe and effective therapeutic options for children.

We are thankful that FDA is convening this meeting and appreciate the opportunity to provide comments to help inform FDA's report to Congress pursuant to Section 508 of the FDA Safety and Innovation Act, or FDASIA. PhRMA will also provide written comments to the docket.

PhRMA strongly supports FDA's continued implementation of the Pediatric Research Equity Act, or PREA, and the Best Pharmaceuticals for Children Act, or BPCA.

PREA and BPCA have worked together to fundamentally transform the way drugs and biological products are developed and labeled for the pediatric populations. According to FDA's database, as of August 31st, 2019, 190 pediatric labeling changes resulted from BPCA legislation, 448 from PREA

legislation, and 127 from both BPCA and PREA.

PhRMA and its member companies are committed to working with FDA to build on this progress. We believe that the continued success of these programs will require adequate resources for FDA to promote pediatric drug development including with respect to new technologies such as cell and gene therapies.

We are committed to working with FDA to advance the use of innovative trial designs, build upon pediatric clinical trial networks, to provide efficient pediatric studies, and facilitate the use of digital technologies and tools to advance pediatric studies.

Today, my statement will focus on maintaining the balance between BPCA and PREA as well as on the timely and transparent implementation of Section 504 of the FDA Reauthorization Act of 2017, or FDARA. PhRMA believes that FDA's approach on these issues will prove essential to the continued advancement of public health objectives regarding pediatric testing and labeling.

To these ends, we offer comments for the Agency's consideration on four topics. First, I will discuss the importance of timely agency guidance on pediatric issues. Second, I will address our views on enhancing the BPCA and PREA processes including through timely communication with sponsors. Third, I will provide comments on FDA's approach to written requests. And fourth, we recommend increasing transparency about international collaborations and steps to advance international harmonization on pediatric testing obligations.

First, PhRMA strongly recommends that FDA promptly release guidance on pediatric testing issues. Guidance is important for stakeholders because it will provide clarity and transparency about FDA's current thinking including on the many new issues raised by FDARA. In particular, there is a substantial need for FDA to release congressionally mandated guidance on implementing the new requirement for molecularly targeted pediatric cancer investigation. The final version of this guidance was due for release in August

of this year, just one year ahead of the August 2020 implementation date for FDARA Section 504.

Congress prescribed seven categories of information that the guidance must include. This content is critical to the successful implementation of the statute and the new target base pediatric testing requirements. For example, Congress required the guidance to address the scientific criteria, the types of data, and regulatory considerations for determining that a molecular target is substantially relevant to the growth and progression of a pediatric cancer. As another example, the guidance must address considerations for waivers where several sponsors are studying medicines directed at the same molecular target.

Given the complexity and novelty of the FDARA pediatric testing requirements, PhRMA is concerned that even draft guidance remains unreleased less than a year before the new investigation requirement goes into effect. We urge FDA to issue this guidance without delay.

We also recommend that through this guidance or otherwise, FDA clarify when it will determine whether a particular application is subject to the new clinical investigation requirement or traditional PREA. PhRMA recommends that FDA communicate its thinking on this critical issue to sponsors by the time the initial pediatric study plan for a drug is due. This approach would provide certainty to sponsors and streamline pediatric drug development.

Beyond the need for guidance on FDARA, we recommend that FDA issue guidance on pediatric testing issues more generally. Existing guidance on PREA is fragmented with two guidances both still in draft form and neither updated to reflect FDARA. FDA also withdrew guidance on BPCA and has not replaced it. As a result, industry lacks clear recommendations on both BPCA and PREA. We urge FDA to publish modernized guidance on these statutes that continue to maintain the importance balance between PREA and BPCA and the importance of the BPCA incentive.

Second, PhRMA recommends early alignment

between FDA and sponsors on a comprehensive pediatric development plan to cover both PREA and BPCA requirements. Sponsors are dedicated to pediatric drug development but recruiting and conducting pediatric studies continue to present significant challenges. These challenges are exacerbated by a lack of clear regulatory expectations and difficulties in obtaining consistent and timely feedback on study designs. For example, sponsors have been encouraged to initiate pediatric studies as soon as possible, yet often face lengthy delays, sometimes approximating one year, in receiving feedback from the Agency on study protocols.

As another example, after a sponsor reaches agreement with FDA on the pediatric study plan or PSP, it might later receive feedback suggesting substantive changes in the agreed study design. Members have experienced this upon submission of the protocol itself after the submission of data in adults, or after approval in the case of a deferred pediatric study requirement. And sponsors have encountered

issues with obtaining timely meetings with FDA to obtain pediatric study advice.

To address these challenges, PhRMA recommends that FDA work with sponsors to reach early alignment on a comprehensive pediatric development plan that covers studies to satisfy both PREA and BPCA. A key element of this recommendation is timely and reliable feedback from the agency which will allow sponsors to initiate studies as soon as possible.

Pediatric exclusivity under BPCA is a critical incentive for sponsors to undertake pediatric studies. PhRMA believes that the important public health interest served by BPCA could be further advanced by improving FDA's current approach to issuing written requests. We have observed three challenges in particular that we urge the Agency to address.

The first challenge is the issuance of written requests that are overly broad or include exploratory studies. The BPCA authorizes FDA to issue a written request for pediatric studies when the agency determines that information related to a use may

produce health benefits in that population. The statue thus imposes a meaningful limit on the range of studies that a written request could include; however, our members have seen written requests in recent years that we believe ask for exploratory studies. Sponsors have had to invest considerable time and resources justifying to FDA why such studies may not be feasible or informative with regard to the disease at issue. These efforts, when combined with the burdens of conducting the other requested pediatric studies, can discourage sponsors from attempting to satisfy written requests.

Second, sponsors have received inconsistent FDA feedback over time with respect to the number of indications that must be evaluated to satisfy a written request creating a moving target for earning pediatric exclusivity. Inconsistent input can undermine a sponsor's ability to develop and pursue a feasible development plan. This in turn discourages pediatric drug development despite that Congress intended for BPCA to encourage it.

Third, sponsors have received written requests for clinical trials that cannot be completed in sufficient time to receiving meaningful pediatric exclusivity. For example, written requests for studies that extend far beyond the expiration of patents weaken the pediatric testing incentive. PhRMA cautions FDA against a view that written requests should be developed without attention to patent or exclusivity expiration. As FDA has acknowledge, the pediatric exclusivity incentive is integral to the success of the current laws as a meaningful driver of development for a population that is widely acknowledged to be difficult to study.

The statutory structure is meant to provide a meaningful incentive for conduct of pediatric studies in an approach that makes this incentive unachievable is intention with the intent of BPCA.

The same concern underlies these three challenges. If the statutory incentive envisioned by Congress becomes effectively unavailable, we fear that the substantial progress resulting from BPCA will also

diminish. PhRMA recommends that when FDA issues a written request to an applicant, it carefully considers the scope of requested testing, the feasibility of the requested timeline for completion, and whether health benefits in the pediatric population can truly be expected of the requested studies.

FDARA gives FDA the opportunity to make significant advances towards addressing these challenges concerning written requests. For example, FDARA requires FDA to define in guidance approaches to streamline and improve the amendment process including when studies contained in a request under Section 505A are not feasible due to the ethical, practical, or other barriers in conducting clinical trials in pediatric cancer populations.

FDARA also requires FDA to describe in guidance a process of engaging with stakeholders to develop and investigation that can be reasonably conducted. These provisions represent and acknowledgement by Congress that FDA should be

realistic about the studies identified in a written request, both in terms of the length and feasibility of the requested studies.

FDARA also required FDA to issue a plan to achieve earlier submission of pediatric studies under Section 505A by August 17th, 2018. This plan is to include recommendations to achieve shorter timelines, when appropriate, for the completion of BPCA studies. As far as we are aware, the Agency has not yet released this required plan. This plan offers FDA another opportunity to address the issues described and ensure the continued success of the pediatric exclusivity as an incentive.

Last, PhRMA urges FDA to continue advancing international harmonization of pediatric testing and increased transparency on international collaborations. Developing global pediatric testing requirements would help to avoid redundancies in investigations and enable sponsors to bring pediatric drugs to market more quickly. Currently, however there is a lack of alignment across regulatory

agency's requirements for pediatric investigations and the lack of transparency into the coordination between regulatory bodies for a particular pediatric matter.

For example, our member companies sometimes receive requests from one regulatory agency to change a clinical study design that had already been approved by another regulatory authority. This lack of coordination serves as a significant barrier to efficient pediatric drug development. We urge FDA to work with its international counterparts to better align pediatric testing advice across jurisdictions. In particular, we suggest that FDA work with the European Medicine's Agency, or EMA, and other stakeholders to provide greater transparency regarding international collaboration on pediatric issues.

With regard to FDA and EMA's pediatric cluster, sponsors would benefit from greater understanding of the substance of discussions between the agencies and the implications for development advice for particular drugs and classes of drugs. Sponsors would also benefit from a formal channel for

communication with this cross-jurisdictional body. In particular, a forum for timely and aligned pediatric testing advice from FDA and EMA would significantly facilitate pediatric drug development. To advance these objectives, PhRMA strongly recommends adoption of procedures and processes to harmonize scientific expectations for pediatric study designs across EMA and FDA.

In conclusion, PhRMA would like to thank FDA for convening today's public meeting and considering our statement. PhRMA looks forward to hearing from other participants today and we look forward to submitting written comments to the docket for today's meeting. We also hope to work with FDA and other stakeholders in an effort to promote meaningful and efficient pediatric drug development. Thank you.

DR. MCCUNE: Thank you, Dr. Santana.

Next, we're going to hear from Dr. Danielle Friend who is the Director of Science and Regulatory Affairs of the Biotechnology Innovation Organization or BIO. Dr. Friend.

BIO PRESENTATION

DR. FRIEND: Good morning. I'm just going to make sure I can advance here. It looks like it's good. Apologies for the technical difficulties.

I'm Danielle Friend. I'm the Director of Science and Regulatory Affairs with the Biotechnology Innovation Organization. BIO is the world's largest trade organization that represents biotechnology companies, state biotechnology centers, and other academic institutions and related organizations both within the United States and across the globe.

First of all, I want to thank the FDA for holding the stakeholder meeting today. I think it's really important for us to have dialogue such as this in order to identify challenges and barriers preventing us from bring safe and effective therapies to pediatric patients in a timely manner.

It's BIO's belief that there's a strong balance -- there needs to be a strong balance between

requirements and incentives in order to support pediatric drug development and we truly believe that the existing requirements and incentives have really driven the increase in pediatric research, pediatric indications, and approved labeling for pediatric populations. These requirements and incentives include not only PREA and BPCA, but also the Rare Pediatric Disease Priority Review Voucher program.

While we have legislation that includes requirements and incentives, there are still strong barriers for initiating pediatric studies. Some of these challenges include the fact that there are limited patient populations, often times with parents not willing to consent due to placebo arms within a trial. There's incomplete scientific understanding of many of the pediatric diseases and conditions. There are other numerous feasibility constraints including formulation development, and certainly different requirements by different health authorities. Additionally, the above challenges are compounded in the context of rare pediatric diseases.

It's through guidance, scientific dialogue, and reflection and evaluation upon the impacts of PREA requirements and BPCA that allow us to better support pediatric drug development as a community moving forward.

For the remaining of my remarks today, I will kind of focus on these three areas that I just mentioned. First, updates to guidance and new guidance document development. That would be helpful in the pediatric space. Evaluation of the impacts of PREA requirements and BPCA, and areas for further stakeholder discussion.

For the first key area, focused on updates to guidance document development or new guidance document development, I just want to highlight that we are very appreciative of the work that the FDA has done over the recent years to issue guidance documents within the pediatric space. We feel strongly that these guidance documents have really supported sponsors as they are thinking about pediatric programs. Some of these guidance documents include issues pertaining to

the rare pediatric party review voucher program, inclusion of adolescence and adult trials, post-market safety reviews, extrapolation from adults to pediatric patients, clinical pharmacology for neonates, as well as clinical trial eligibility.

However, in reflecting upon what would be helpful as we move forward to further support pediatric drug development, I think there are a couple key areas. First, the FDA in 1977 issued a guidance on general considerations for clinical evaluation of drugs in infants and children. BIO requests that the FDA consider updates to that guidance, specifically in terminology that's used, as well as the addition of reference to other pediatric guidance that has been released since 1977.

The next guidance I just want to highlight, I know it was mentioned in the last comments that were made as well, but the FDA had issued draft guidance on BPCA and complying with BPCA; however, the FDA did not finalize that guidance and, instead, developed an FAQ on the FDA website. It's our strong belief that it

would be helpful for the FDA to finalize guidance on BPCA to further assist sponsors in complying with BPCA.

And finally, as was mentioned in the last presentation as well, it's important that the FDA issue guidance on PREA as its been modified by pediatric oncology requirements which I'll be referring to as FDARA if I go forward. I don't want them to be confused with a reference to RACE Act. I'm meaning one and the same for the rest of my presentation.

This final guidance was due out in August of 2019 and we have yet to see it. We, again, understand that guidance document development involves a lot of hard work, but at this time, sponsors are already thinking about the data that they will need to be providing to the FDA to comply with these requirements and guidance on this issue in particular is needed.

The next section of my talk, as I mentioned, I'll focus on evaluation and impacts of PREA and BPCA. I won't touch on this too much because Dr. McCune did

this very nicely, but essentially the FDA is required to provide a report to Congress as outlined in FDASIA reporting on PREA and BPCA. Specifically in that report there may be elements where the FDA is reporting on FDARA Section 504 and how that has impacted pediatric drug development. Importantly, the FDA has made statements indicating that they see FDARA 504 requirements as aimed at accelerating the timeline for initial evaluation of agents that appear to be promising for pediatric populations. And because of that, BIO requests that the FDA consider mechanisms for confirming that pediatric oncology studies are being considered earlier in drug development.

Below, you'll see a couple of bullet points that we've kind of thought of as starting points for making that evaluation, such as the timing of submission of pediatric study plans, number and timing of discussion among sponsors and FDA pediatric oncology drug developments and use of FDARA Section 503 meetings to discuss pediatric oncology development programs.

The last section of my remarks will focus on areas of further discussion. As was pointed out in the last presentation that was made as well, there's a strong need for aligned pediatric scientific advice. I think everyone in this room would agree that our shared goal is really to bring safe and effective therapies to pediatric patients as quickly as possible. And in order to do that, we need both consistency within the Agency as well as across health authorities.

Within the Agency, BIO requests the FDA to consider how we can better support consistency in the use innovative approaches such as use of innovative clinical trial designs, real world evidence, extrapolation, and external controls.

To support consistency across health authorities, we understand that the FDA and other health authorities are already engaged in cluster meetings and issue common commentary and we certainly recognize the importance of those cluster meetings for the health authorities; however, there are still

challenges that sponsors face that are not necessarily addressed through those cluster meetings or through the common commentary process. And to this point, BIO requests that the FDA consider engaging specifically with industry sponsors to hear from them regarding their challenges that they still face regarding alignment of advice across health authorities.

Another area that requires further discussion pertains to the BPCA and written request which we've also heard about briefly this morning. The FDA has made statements that in order to fulfill a written request as outlined for BPCA, sponsors must conduct studies in all applicable age groups and all possible indications for a given therapy; however, as was mentioned before, written requests that are drafted too broadly can make it difficult for a company to make the business case to actually conduct those studies. BIO's concern is that should those written requests be written too broadly, then companies will not be able to fulfill those written requests and we'll actually see a decrease in the number of studies

that are conducted to fulfill those written requests.

So we ask the Agency to, you know, really think carefully and intentionally about the requirements that are included within a written request, specifically, the scientific rationale in order to address unmet need as well as the feasibility of those studies.

And lastly, as far as further discussion, one last point I'd like to make, first off, BIO appreciates the guidance that the FDA has drafted on general clinical pharmacology considerations for neonate studies, for drugs and biological product guidance; however, there remains a need for additional guidance and clarity as it pertains to endpoints, biomarkers, natural history, specifically for neonates.

Given the great difficulty in conducting these studies in neonates, BIO requests that the FDA consider alternative means of gathering data for such studies and we also encourage the FDA to make sure that internal neonatologists and subject matter

experts engage in division communications with sponsors and the Agency consult with additional external experts in order to make sure that they're reaching scientifically sound decisions regarding neonate assessments and studies.

So with that, that concludes the BIO comments for today. We will be submitting comments to the docket, but I would just like to end and say thank you again to the FDA for holding this important stakeholder meeting. We're looking forward to hearing from others and working together as a community to support pediatric drug development.

DR. MCCUNE: Thank you, Dr. Friend. And as a neonatologist, neonatal comments, neonatology comments are always near and dear to my heart.

And I want to thank everyone else. I got us way off track this morning time-wise, and I want to thank everyone for being succinct and getting us back on time. So I think we're a couple of minutes over the 10:30 spot, so at 10:45 we will see back here after the break.

[BREAK]

DR. MCCUNE: All right. I'm going to ask everyone to please sit down.

All right. I want to thank everyone from Session 1 for giving us feedback this morning and I want to go into Session Number 2 now. We're going to have five speakers between now and lunch, just so everyone can kind of plan your thoughts.

So the first speakers in Session 2, kind of a tag team, is Dr. Danny Benjamin and Dr. Kanecia Zimmerman. Danny, Dr. Benjamin, is the professor of pediatrics at the Duke Clinical Research Institute and the chair of the Pediatric Trial Network. And Dr. Zimmerman is the associate professor of pediatrics at the Duke Clinical Research Institute.

So Drs. Benjamin and Zimmerman.

DCRI PRESENTATION

DR. ZIMMERMAN: Thanks very much, Susie.

So Drs. McCune and Taylor-Zapata have given me a good head start. You already know a lot about the Pediatric Trials Network. I'll just highlight a couple of things. One, that we do focus on off-patent therapeutics which will become very important for the rest of this conversation. And then two, our success is really defined by labeling. How are we doing as far as increasing the information regarding dosing and safety for off-patent therapeutics to improve child health?

So with that, fortunately, we have been fairly successful and again, Dr. Taylor-Zapata was talking about some of the successes that we've had. We've studied in 18 therapeutic areas; we have enrolled more than 8,000 children in our studies; we've submitted 26 products to the FDA, and we have 11 label changes to date.

We've highlighted some of these label changes already, some that are -- you know, especially near and dear to our heart is, of course, the acyclovir

label because of the devastation of HSV encephalitis, but we have a number here that had been highlighted previously.

What I really wanted to talk a little bit about is how we've done this and what have been the contributors to our success. And I would really just start by saying that much of this is because we have a very business-like approach and careful consideration of the endgame when we are thinking about what things we need to study and how we need to study them. So that means really careful identification of the regulatory pathway. It means we're in frequent communication with the FDA. We definitely have a collaborative approach within NICHD and with the DCC at EMMES and we have a network of sites who really believe in this mission. And that is very, very important because they help carry things through.

We also keep feasibility at the forefront. So that means cost, size, et cetera. And there are a number of network efficiencies that we have developed to really reduce the cost so that we can do multiple

studies at one time instead of a very large study, one that happens every couple of years. Some of this means that was subsidize, in effect, the coordinating center cost and the studies themselves. So we have junior faculty members who are writing R01s. It's good for their careers, obviously, but it's also very good to have a little bit of extra funding that goes into the pool here. We also have faculty members that write for donations from industry to get drug donated so that we can do a trial of a drug that might be a little bit more expensive, even though it's still on the off-patent range.

The sites effectively also somewhat subsidize the network as well, and that really is because they understand that we're not able to pay them industry dollars. So they are often, kind of taking a bit of a hit understanding that this is for a good cause and they have been very obliging in doing so, so far.

We've also partnered with other networks, like the Trial Innovation Network. It's sponsored by NCATS. Their job is really to be very innovative in

their science and clinical trials and the design of clinical trials in the way that they are done and so we're able to incorporate some of those innovations within the PTN trials at a reduced cost because we're cost-sharing between the two.

Trainees, cheap labor. It's good for people's careers so we use trainees to do some of the trials, to develop some of the trials, but they're learning how to do that, but they don't cost the same as a full professor, for example, in order to do all of those things, but they have lots of guidance from the full professor in moving forward. So it's good for both parties. And then we do have the operational expertise that really includes some of the efficiencies.

I'll let Danny kind of talk about the positioning of the PTN.

DR. BENJAMIN Thanks Kanecia, and thanks Susie. K.Z.'s a little modest about being a trainee. She, 10 years ago, was a chief resident and is now the Steering Committee chair for the Trial Innovation

Network, so a rapid rise.

One of the things folks ask me is, how long are we going to need to keep doing the off-patent studies? Won't we run out, right? And point of fact, drugs go off-patent all the time and they don't always get studied fully in children. So two classic and recent examples, one recently completed, one ongoing. Sildenafil was originally indicated for adults and it's quite different from -- it's indication for adults is quite different for its potential indication for pediatric use. It turns out, it has the potential to reduce pulmonary hypertension and to prevent or treat bronchopulmonary dysplasia in neonates. We in the PTN are obviously studying the pediatric use in an actively and rolling trial.

Sometimes a pharmaceutical company can really fully evaluate a molecule and fluconazole has a bunch of different indications including candidiasis in adults. Candidiasis in neonates has a different disease pattern. The central nervous system is impacted much greater than it is in older patient

populations and the PTN recently completed and submitted data to the Food and Drug Administration that's under review right now for potential labeling change for neonatal candidiasis dosing of the molecule for infants on ECMO and for loading dosing. Those strategies were not studied by the pharmaceutical company and did not have regulatory great data prior to PTN. So we see the need to be long-lasting because drugs are going to continue to go off-patent.

We're also able to improve regulatory science and new regulatory pathways. So when the Agency first submitted or provided the written request for meropenem, which is an anti-infective, the Agency asked for 600 infants with surgical necrotizing enterocolitis to be randomized to get meropenem or imipenem. The neonatologists who are in the room will tell you that's not a feasible study. We actually modeled that out based on what sites had as far as eligible patients and we concluded that it would take 50 sites 10 years to enroll 600 infants which is not really feasible.

We actually modified and worked with the Agency to dramatically change the design of the trial, ultimately getting that enrollment done in 18 months, and now pharmaceutical companies have taken essentially that same design, and by essentially I mean the sentence structure and punctuation looks extraordinarily similar to what I personally wrote about 10 years ago, which I don't mind. It's publicly available. It's funded by tax-payer dollars. We want industry to actually benefit from the trial designs that we put forward and what we were able to do is deleverage the risk, put in the different trial designs, submit those data for labeling, and then industry could follow in a more economical and a more feasible way to improve public health through now new products, now use the pathway that we developed with FDA.

We've also had experience and published on the use of master protocols, setting multiple drugs at the same time, anywhere from 3 to 30 drugs at the same time. Platform protocols, we're now expanding that

into neonatology to do multiple indications across multiple drugs. Our first of these is going to be in the neonatal intensive care unit where we look at BPD, CMB, HSV, and several other indications at the same time.

We do opportunistic studies which is now being referred to in the peer reviewed literature by people other than us as the POPS design, which is satisfactory to us. We are doing understudy populations. So just like when you're making a guess to do dosing in children, you're wrong about 40 percent of the time. You're even wrong more frequently in neonates, children with obesity, and critically ill children. And we template and do master contracts when appropriate.

So POPS is a study that has enrolled in over 82 molecules over 3,500 children, approximately 40 enrolled per month. And we are able to do special populations where the risk of dosing mistakes are especially high. Neonates, most folks in the room will know, that they have drug metabolizing pathways

that we've never even thought of and they shunt molecules all over the place in ways that are totally unpredictable through drug metabolizing enzymes that may or may not exist in adults from anywhere from the liver to the gut, to EMCO where we had the then radical idea that if you took all the blood out of a human being, spun it round and round in a machine and jammed it back into a human being, that dosing might be different. And we've been able to show that through POPS.

The POPS is really a prime example of real-world data that's in context and we get opportunistic PK data and we're now getting PK/PD and safety data for some of the molecules in the POPS design which FDA started asking us for a couple of years ago and we've now incorporating that into the revised POPS protocol.

We've also used it to inform subsequent trials. We initially studied several therapeutics in various dosing strategies and the low-cost POPS domain and then pushed that into a regulatory compliant study of half a dozen different molecules to ultimately go

for labeling in complicated infections in neonates.

We're now moving into lactating women and breast-fed infants, the so-called CUDDLE study. This is capitalizing on or partnering with FDA's guidance documents as it relates to breast-feeding women. This is a prospective study at about 20 different sites. We've already -- we're closing in on 100 women enrolled, and we have 10 initial drugs of interest and we're getting ready to actually analyze the first molecule to come out of this cycle here.

We partnered, the Peds Trial faculty from the Peds Trials Network and Bob Ward and my colleague, John Davis who's here today, partnered together to really put together the white paper that was used in drafting the guidance for clinical pharmacology for neonates. Most of the methods that are outlined in that draft guidance document were either developed or pioneered or solidified within the Peds Trials Network.

So what's not so good right now? One of the problems that we have is that given the amount of

support, we're at the point where we're no longer able to conduct pivotal Phase III trials. The funding has been the same for the last 15 years or so, costs have gone up, and doing Phase III trials, which are important if you want to do an indication in children where the indication is either different or doesn't exist in adults, we're not able to do that with this mechanism.

We're also very limited in our ability to do follow-up. And by meaningful follow-up, I mean if you look at the label for antipsychotics, they, the longest studies that have been done for antipsychotics are 48 weeks. But for those of us who have a child who's receiving an antipsychotic, we know that when our children get placed on these antipsychotics, often at 8, 10, or 12 years of age, they're not just on them for 48 weeks. They're on them for 5, 10, 15 years. And the fact that there's no data for children, there's no meaningful high-quality data for children is morally abhorrent. We're not able to do that under this mechanism with the type of funding that we have

right now. And the sites are subsidizing the work, but they're getting to the point where that's going to become a challenge.

So we want to, you know, continue to improve pediatric information for off-patent therapeutics. We want to continue changing and improving and preventing ill-informed off label drug use. So really, there are aspects of this that, you know, if I had to improve the program, this is ultimately what we're going to need. Some of this is going to be around increased funding. Some of this is going to be around making at least some of this permanent so that it's not -- the entire program isn't put at risk every five years and to potentially expand the scope.

And then I'll just say -- I'm only -- I have 90 seconds. So I just wanted to say a special shout out to the folks in the peds therapeutic office, to CDER Peds, to my colleagues who are pediatricians and who are dedicated to pediatric health, and the FDA. You guys are really making an important difference for children. When I think about, you know, 20 years ago

when I was in training, what drug development was like for children compared to today is that we've come an awful long way.

And the second shout out, who has not been mentioned, is, you know, our colleagues at the American Academy of Pediatrics. The AAP has done a phenomenal job in advocating for children and advocating drug development for children in ways that other professional societies have not. And I got to tell you that if you're a pediatrician, the AAP is working for children in a way that is extraordinarily uncommon for any kind of professional society which are, in my opinion, most of them are largely a waste of time.

So thanks for inviting me to speak.

DR. MCCUNE: Wow, he is tall. Okay. Thank you, Drs. Benjamin and Zimmerman.

Our next speaker is Dr. Albert Allen. AJ is the senior medical fellow on Pediatric Capabilities at Eli Lilly and Company.

AJ, thank you.

PhRMA/ELI LILLY PRESENTATION

DR. ALLEN:: Good morning. My name's AJ Allen, as was mentioned, and I'm a child psychiatrist and pharmacologist at Eli Lilly and Company in Indianapolis.

I want to take a moment to thank FDA for holding this pediatric stakeholders meeting and PhRMA and Lilly for giving me the opportunity to speak at it. And I also want to thank the other panelists that are presenting today. I think I'm learning new things as I usually do at these meetings so thank you very much.

My comments are based on my almost 20 years of experiencing in pediatric subspecialty work at Lilly. The first 10 years leading and consulting on pediatric psychiatric programs in psychopharmacology and the last 10 years working on pediatric programs across Lilly's therapeutic areas, oncology, diabetes, endocrinology, immunology, and pain and occasionally

other fields.

Lilly is a 143-year-old global innovator biopharmaceutical company based in Indianapolis, Indiana, and during its history, Lilly has been involved in many breakthrough discoveries with relevance to pediatrics including the mass production and commercial distribution of insulin to treat juvenile-onset diabetes beginning in 1923.

Prior to 2010, pediatric work at Lilly was carried out largely team by team, study by study with pediatric experts scattered across the company and limited in their collaboration between teams. In other words, pediatrics was carried out in disconnected silos, often somewhat of an afterthought in latent development. Despite this, substantial progress was made in some areas. When I came to Lilly in 2000, there were zero psychopharmacology products that had been labeled for treatment of psychiatric disorders in children. Nothing in the label.

Today as a result of both pediatric incentives and requirements, seven Lilly psychopharmacology

products are labeled for the treatment of psychiatric disorders in children. These medicines are not appropriate for many children and adolescence with psychiatric conditions, but they are appropriate for some and they are part of a growing toolbox of medications that provide options for child psychiatrists, the patients they treat, and families. And this is an important public health benefit, I think, of the legislation that we've seen over the years. And as a child psychiatrist, I'm very proud to have helped Lilly make this possible.

Currently, I co-chair Lilly's Pediatric Steering Committee which is composed of pediatric subject matter experts located in functions across the company. And I might add, increasingly we've got a number of pediatric specialists in the company. And I'm medical lead for our three-person Pediatric Capabilities Function which is dedicated full time to pediatric drug development.

Neither the Pediatric Steering Committee nor Pediatric Capabilities Function existed before 2010.

Both were created to help improve and systematically integrate pediatric drug development into overall drug development efforts across Lilly in response to increasing pediatric work that resulted from global pediatric initiatives since 2007, PREA largely in the U.S., but also BPCA and then in Europe, we had the European Regulation.

The challenge was not just to do better pediatric trials in isolation from each other, but to incorporate pediatric planning from the start with adult planning as part of overall drug development, to weave the two together, not because of this regulatory requirement or that incentive, but because ultimately children need and use the drugs that Lilly develops, produces, and markets. And as a result, integrated pediatric drug development is the right thing for us to aspire for.

Lilly's purpose officially, the company purpose, is to unite caring with discovery to create medicines that make life better for people around the world. And as I love to point out, there is no lower

age limit in that statement and children are people too, so this applies as much to the pediatric population as to any other group that we deal with.

What that has meant within our company is that we've had to work on changing the culture of how people think about and deal with pediatric research. We have made progress in this, though I think there's still work to be done, and a fair amount of work to be frank, but I take great pride in the fact that just recently we had our ninth Lilly pediatric symposium and Tim Garnett, our chief medical officer and sponsor of our pediatric efforts at Lilly said, I think we have made real progress in the pediatric space, finally moving from feeling that this is something we have to do to something we should do, and also increasingly understanding the challenges and opportunities in that space. And Lilly's president and CEO, Dave Ricks, said, I'm really pleased we continue to create this focus on pediatric research.

The culture of pediatrics is changing at Lilly and in the industry as a whole. I just want to pause

here and recognize that that culture change is made possible, not just by the sponsorship of Lilly leaders like Tim and Dave, but also by my colleagues in the trenches on the Pediatric Steering Committee and in Pediatric Capabilities, the sort of folks that are often not mentioned much and you don't hear much about in these meetings, but they're people like my colleague of many years, Mary Short, who has been a tireless champion on behalf of neonates and children. Those are the sorts of people moving this forward day by day, and that's a change from the way it used to be.

So today we're thinking very differently in our company about how to do pediatric development as part of our planning, but that has not been enough. In my opinion, pediatric drug development makes adult drug development look easy. To mention some, but not all of the challenges in pediatrics versus adult research, there are legal ethical requirements that are different. You have to deal with parents and guardians as critical partners in the studies. You

don't have that with adults. The adult people are quite happy with that. There are generally smaller numbers of patients that you're dealing with. The methodology and endpoints may not be the same. School has to be considered in the pediatric population in many studies. And the research infrastructure is often less well developed, and we've heard some of the challenge with that and how to try and improve that today.

At times, we've come -- we've also come with time to appreciate that while children are not just little adults, they also are not space aliens. As science of pediatric drug development has evolved and we've appreciated how complex it is, we've come to routinely propose approaches in pediatric plans that make use of pediatric extrapolation of efficacy from the adult population in many instances. In other words, we're seeing that there are some similarities we can work with.

Pharmacometrics based on adult PK/PD and real-world data, Bayesian methods, advanced analytics,

adapted designs, inclusion of pediatric patients in adult Phase III trials, preclinical testing using xenografts and oncology and so forth, those are all advances that 10 years ago we wouldn't have really been talking about a lot in the pediatric space and industry. And I want to recognize that those approaches have often been encouraged by folks at FDA in the pediatric groups here and, you know, that we've listened, we've heard that, we've taken up and sometimes the FDA review divisions are embracing those innovative approaches as well and sometimes they're not. So one of the challenges that we face is that it's not always clear from one division to another where we stand on pediatrics and that continues to be a challenge even though it's gotten better with time.

I might add that that is an issue that was noted earlier in terms of how soon to come in and discuss pediatrics with the Agency. We've had teams that have been told to well, let's wait and we'll discuss this later only to, at some point in the future, have a call come that's, you know, we really

feel like you need to move on this now and do something and so it pulls it ahead and that just creates, you know, causes all sorts of challenges for us to deal with in an industry where predictability and, you know, a plan is part of what we try and work from. So all of this is tremendously frustrating when we get these mixed signals, both for my team as well as for the individual study teams that are working with different products.

Now, guidance documents would be very helpful in many of these situations, but we're still waiting for final guidance on the pediatric study plans, PSPs that were introduced with the 2012 FDASIA legislation. We're also waiting on new guidance on the Best Pharmaceuticals for Children Act. Proposed pediatric study requests is also something we need guidance on. A draft guidance on Section 504 of 21st Century Cures, or I'm sorry, of the FDARA legislation/RACE Act, and then final guidance on pediatric clinical pharmacology. And we could also, by the way, really use an FDA guidance on pediatric extrapolation of

efficacy, not just have to keep referring to the European one.

While some guidance documents for specific diseases include pediatric recommendations, others do not, and that can be a challenge, especially in new areas. And sometimes we're told that pediatric recommendations -- that the recommendations in a specific guidance can be applied more broadly, but sometimes we're told we shouldn't do that. So again, it's difficult when you're trying to read all of these guidances that aren't really referenced in any one place and collect that information all together.

And I might add that it also doesn't help changing the law every five years so that FDA never gets the chance to finish a guidance because it keeps having something new to add in. So we could use some stability.

My full-time job is to try and follow all of this and advise teams on it, and I have to say that it's really challenging, but then I have to try and explain it to teams and to members of teams who may do

one pediatric trial in their entire career and industry and therefore aren't really, you know, able to fully appreciate the challenges here.

Another learning for myself and others working in pediatrics at Lilly and in other companies is the importance of pre-competitive collaborative in public-private partnerships and advancing pediatric drug development. While there is recognition of the importance of pediatric drug development at Lilly, resources are limited. We have a fixed budget, and this is true for every company. Acting alone, we cannot, you know, do everything that needs to be done to try and improve this system, but by pooling resources, we and other groups working with us, whether academics, regulators, patient-parent advocacy groups and others, we're able to make significant progress. And I would note that public-private partnerships are creating pediatric research organizations and trial networks such as the Institute for Advancing Clinical Trials for Children, I-ACT for Children in the U.S, the IMI conect4children, c4c

effort in Europe, the IMI ITCC-P4 effort on preclinical oncology models in Europe, the Pediatric Clinical Trial Network, PCTN in Japan, and the International Neonatal Consortium which is more of a research organization, not specific on network.

Exploratory efforts are also underway with the foundation of NIH to create another public-private partnership related to preclinical testing and pediatric oncology in the U.S. And while it's not a formal public-private partnership, the International Children's Advisory Network or ICAN, has support from industry and FDA and academics as a means of giving pediatric patients and children a voice in the research that affects them. And as mentioned, they were just involved here this past week with FDA.

All of these efforts are new since 2012, I believe, and they're helping to reshape the whole discussion around pediatric drug development in aiding our research teams. And I think Lilly, but also all of the other companies, FDA, AAP, and others that have been involved in these public-private efforts, should

be proud of what they've achieved.

We are also learning how collaboration can help advance pediatric research in other ways. In the last few years, Lilly has conducted pediatric trials in both sickle cell disease and Duchenne's Muscular Dystrophy. Unfortunately, neither of these trials was successful in showing that the Lilly drugs being studied were effective treatments for these conditions, but this does not mean the trials were not without value to patients and families affected by these diseases. Because we make our trial data available to other researchers after a trial is completed, the data from these studies has been used to advance the science and to improve clinical trials involving these conditions with other sponsors.

Industry science or industry efforts in pediatrics have also advanced the science of pediatrics in many other areas from helping to develop instruments and clarify appropriate endpoints for pediatric trials to bringing advanced analytic methods to bear on pediatric challenges. These types of

industry activities represent a largely unrecognized and unappreciated benefit of industry's involvement in pediatric drug development, one that goes hand-in-hand with the 814 pediatric labels as of August 31st, 2019 that have been modified as a result of industry and FDA working together to better understand the efforts of drugs and biologics in children.

The successes we've experienced in pediatrics are also creating new challenges. In the beginning, we only had the U.S. and the FDA to deal with. Today, Europe and in many places, other countries are starting to pay attention to pediatrics, and this is causing us to have to make not just pediatric plans for the United States, but really global plans to try and address these concerns. And this is a real challenge, trying to get, you know -- as mentioned, it takes maybe a year to get a plan in the U.S. Trying to integrate in then how you're going to deal with Europe and with Japan and with other countries often means that we're taking two years or longer to finalize our plans and meanwhile, you know, patients

are waiting and those trials don't actually get started often until we get the final plan because we're trying to minimize the number of studies that we're doing in kids because you don't want to necessarily put kids in pediatric trials. So that's been a real challenge and any help that can come there would be very useful.

I might also note that one of the other things that happens is as we're successful, as we, in some of these small pediatric populations identify new treatments and are able to advance the clinical care of these children, there's less and less unmet medical need. And so you have even smaller populations you're now trying to look at and this can create real challenges in terms of doing additional trials with newer agents.

I think that, you know, one of the places where that potentially is going to be a real problem is in pediatric oncology where you're already dealing with small populations. People are talking about wanting to prioritize molecules to only look at

certain molecules with a given tumor type, say, from a class, maybe just the first and the second one in line. But keep in mind, we're talking about these molecules during Phase I and from Phase I to approval of a drug is a long pathway. There's a lot of attrition, a lot of delays that occur, so you don't know that the first two molecules at Phase I are going to be the first two molecules that are approved. And if you limit studies to that group, you may very well be in a situation where you have prioritized molecules that, you know, never make it market and then you're left with no studies being done in that particular therapeutic class. So I don't think anyone has a good answer on how to do this. It's a real challenge.

The mention of pediatric oncology reminds me that we also are commenting on Section 504 of FDASIA legislation, otherwise known as the RACE Act. Like the rest of industry where we at Lilly are anxiously awaiting to see the draft guidance on this legislation and the Act at this point hasn't fully gone into effect so I think, you know, it's hard for me to

really say much more than there's a lot of interest, anxiety, et cetera, but it's too soon for us really to comment much on it.

Lastly, the reality is that while there's a public health need for pediatric drug development and the advances that have been made are incredibly exciting, the work is expensive and challenging and innovation cannot be forced. I'm a child psychiatrist and I can tell you that negative reinforcements are much less effective than positive reinforcements, whether used with children or with pharmaceutical company executives. A balance of requirements and incentives is needed and while the current mix has its limitations, I have personally witnessed how PREA requirements, BPCA incentives, and the pediatric priority review vouchers have all encouraged pediatric drug development efforts at Lilly at one time or another. They provide tools for both the FDA and my team, frankly, to encourage drug development teams to address pediatrics.

I hope this statement is helpful to you as you

prepare your report for Congress. I have tried to provide a different industry perspective than perhaps you've heard in the past, that of a pediatric subspecialist who has been working on pediatrics in the industry for many years. My job is part pediatric research specialist and teacher, part advocate for pediatric patients, part representative of industry in different pediatric forums such as this one. I've seen tremendous changes in advances in pediatrics during my career at Lilly, mostly positive on behalf of children mixed with the progress many challenges remain and I think there is room for FDA industry and other stakeholders to do better, but working together, we can continue to benefit children through pediatric drug development efforts. Thank you.

DR. MCCUNE: Thank you, Dr. Allen.

Next, we're going to hear from Ms. Nancy Goodman who's the founder and executive director of Kids v Cancer.

KIDS V CANCER PRESENTATION

MS. GOODMAN: I want to thank the FDA and all those here for inviting me to speak on pediatric legislation. I know many of you in the audience, but some I haven't had the opportunity to meet yet.

So I'd like to start by giving you a little bit of an introduction of who I am and how I came here, and then use that to talk about the specific pieces of pediatric legislation that I in the pediatric grassroots community, have been focusing on for the past 10 years in particular.

So I am a lawyer. I was trained as an international trade lawyer and I also worked on legal technical assistance for developing countries. And so how does that bring me here? My son, Jacob, was diagnosed with widely metastatic medulloblastoma when he was eight and died when he was ten. And the drugs used to treat Jacob were 40 years old. So that caused me to be reborn as an advocate. You'll find -- I'm sure you've all met many pediatric cancer parents. We

are all advocates from the same cloth.

After Jacob died, I founded Kids v Cancer and the question that I wanted to focus on is how to bring the talents and resources of the private biotech and pharmaceutical industry to pediatric drug development. So the first question we focused on is how do we create incentives for pediatric drugs that are de novo for pediatric indications and may not have adult applications? And so with this problem in mind, we drafted the Creating Hope Act which creates the Rare Pediatric Disease Drug Voucher Program and it was a grassroots effort to advocate for it. We were grateful for the support of the FDA, from many of you here in the room from industry and other advocacy groups, and in 2012, Congress first passed the Creating Hope Act.

The Creating Hope Act creates a voucher that incentivizes rare pediatric drug development. I'm assuming many of you here, all of you here, know about how this program works. It's been phenomenally successful. It is an industry funded incentive. It

does not increase taxes for the average American taxpayer. It does not increase drug prices for the patient. And since the Creating Hope Act's passage in 2012, we've had almost 2 billion dollars' worth of incentives, over 30 vouchers have been issued, two new drugs in cancer and many new pediatric drugs in other indications.

The Creating Hope Act has been reauthorized three times and its current sunset date is September 2020. We have introduced a bill in the House to reauthorize it, H.R. 4439, and we'll be introducing a companion bill in the Senate soon. And I really ask all of you here to support this effort. I ask in particular the FDA because we're here at the FDA discussing this, but also because if any party pays for the voucher program it's the FDA. The FDA medical officers, of course, have to undertake priority reviews of drugs that would otherwise merit standard reviews, and I realize this is extra effort for the FDA. I'm very grateful for the FDA's support of this program, and I hope the FDA will continue to support

this program as we as for permanent reauthorization.

After the passage of the Creating Hope Act, I, and many other members of the pediatric rare disease community, focused on a second question which was this: Most drugs are developed for adults. The adult cancer pipeline is over a thousand drugs, as well all know, and yet until recently, only a very small handful of them had been studied in pediatric populations. Now the Pediatric Research Equity Act, which was passed, I think, in 2003, has been a fantastic piece of legislation, but because of two loopholes, it never applied to pediatric drugs. And in fact, to the best of my knowledge, there have been not PREA studies for oncology drugs.

The two loopholes are this: Number one, all drugs that have orphan exceptions are exempted from PREA requirements. And number two, PREA requirements only apply when the disease has a pediatric population. In cancer the way this is defined is that the organ of tumor origin for the adult cancer must be the same organ as the pediatric cancer, and in fact,

what we have learned, what scientists have told us in the last 10 years is that, in many cases, pediatric cancers, while they originate in different organs than adult cancers, may share the same molecular target, the same driver mutation.

So with that in mind, we worked closely with the FDA, with industry, and with other advocacy groups to draft and advocate for the RACE for Children Act, which we are thankful Congress passed in 2017.

Again, here, I want to thank the FDA. You know, the FDA has really been a leader and a champion of children's drug development throughout both pieces of legislation, FDA's technical assistance, FDA's expression of willingness to try this new program. We're really materially important and in large measure, we're part of the success in getting the RACE passed.

So I want to now step back and talk about -- so those are the two pieces of legislation that I, and the grassroots pediatric cancer community, really focused on in the last 10 years. And at the risk of

taking seriously your request to understand our perception of what needs to be done next, I'd like to give you six points in three different areas for the FDA.

First, guidances. We really look forward to FDA publishing the guidance on the RACE Act. As many speakers have said, it's late and we understand how much effort it takes. This would be a draft guidance that the FDA would be passing. It would still require public comment, and it is really -- it would be terrific if we could get this published before full implementation of the Creating Hope Act.

The second area I want to discuss beside guidances, is legislation. As I noted, we are asking Congress to permanently reauthorizing the Creating Hope Act to permanently establish the rare pediatric voucher program. And we hope the FDA will have a positive approach to this. We'll work constructively with advocates and the community to provide technical assistance and help us get this passed.

And the second piece of legislation I want to

address again is the RACE for Children Act. You know, I think it has been phenomenally successful. Before the passage of the RACE for Children Act, the problem that pediatric oncologists would pose is, how do we get access to novel and exciting therapies being developed for adult indications? And this was a significant limitation on pediatric oncologists' abilities to study new therapies in children. Now the problem they discuss is, how do we decide among all the opportunities we have to study different therapies, which ones should be our priorities and which ones we should consider first? I think it's going to result in significantly better health for kids with cancer. And I'd like kids without cancer to also benefit from the same improvements that we've had in cancer space.

So I hope that as a community we will think about extending the RACE for Children Act past cancer to noncancer drugs for the next PDUFA in 2022. I understand that there may be some interested from other advocacy groups and I really applaud and support

that. I think that the orphan exemption, which we closed for RACE Act, only for oncology drugs, there is no intellectual and rational reason why that shouldn't also be closed for non-oncology drugs. So I ask the FDA to work with advocates, industry, and Congress to close the orphan exemption of PREA for non-oncology drugs.

And finally, I just want to address, you know, FDA has played a very strong role as an intellectual leader in the area of pediatric cancer drug development. And I just want to touch upon a couple of areas that we as a community and academics as a community have to think about with respect to implementation of RACE. And I ask the FDA to work with us, to lend us your expertise and your intellectual leadership to figure out some of these problems.

So the first is, of course, how to pick and prioritize agents to study in children. Academics in the pediatric cancer community are building in vivo models and collaborative efforts. We also have the

Childhood Cancer Data Initiative to tie data sets together. With respect to the Childhood Cancer Data Initiative, I think we also need to think about how to create higher quality data sets that include, you know, whole genome sequencing matched with clinical data, RNA sequencing, and whatever other kinds of omics studies we can provide so that pediatric oncologists really have an opportunity to ask the question, what pediatric indications are relevant for a new drug that's being development for an adult oncology indication? And again, with in vivo models, I hope that, you know, we receive additional funding and, you know, I hope they're effective.

So the second area that we, as a community, are working on and that academics in particular in the cancer community are working on is the question of how do we study all of these novel agents as quickly as possible and how do we study as many of them as possible? So we have not introduced so many master protocols or basket protocols into our community although we have started. And I think we need to

double down and create many more master protocols so that really we have an efficient and robust way to test as many novel products as possible, as quickly as possible, and really get the best therapies available for kids.

And the third area that I want to just talk on is just academic studies in consortiums generally. It is my hope that the pediatric cancer community steps back from Phase III trials at this time. You know, Phase III trials are very time consuming. They take, you know, five to seven years on average for pediatric cancer studies. They take a lot of kids, and often times they're looking at old questions and old therapies.

Now that we have so many new agents to study, I hope that, as a community, we really focus more on Phase I and Phase II studies. And with this effort, I think we need to be very careful and start focusing on control arms. I really appreciate the FDA's real-world evidence guidance that was just published, and I think we need to think about how we can use historical

data in the children's oncology group or in other consortiums to create control arms so that we can do something. It's not a single-arm study and it's not a randomized control, but it still provides more data on the potential efficacy of a novel agent.

And then finally, it's come to my attention that many academics in the pediatric cancer space are now actually developing new drugs and testing new drugs without adult companion studies. And as a community, we have not done this very much. We have less expertise than we could have on what is the difference between an academic study and a registration study that the FDA would find acceptable for a BLA or NDA application. And so I would ask the FDA to think about hosting a series of panels, workshops, or articles to help our academic researchers understand what they need to do to meet the standards of the FDA for these new therapies that they are developing.

So I want to thank -- I want to take this opportunity to thank you all for giving me an

opportunity to speak here. I want to thank the FDA. You've absolutely been in the forefront of developing novel ways to consider new therapies for children's cancers and for rare children's diseases. And I want to thank academics who are here in the audience who've, you know, really been heroes for me, and the other advocates and industry. And I look forward to working with you as we figure out these and many other questions that we need to address. Thank you.

DR. MCCUNE: Another tall one. Thank you, Ms. Goodman.

All right. Our next speaker is Dr. Jonathan Davis. Dr. Davis is the Vice Chair of Pediatrics and the Chief of Newborn Medicine at the Floating Hospital for Children at Tufts Medical Center. He is a professor of pediatrics at the Tufts University School of Medicine.

Dr. Davis.

TUFTS/CTSA PRESENTATION

DR. DAVIS: Thanks very much, and it's a pleasure to be here. I first want to start by congratulating Dr. McCune who was just elected to the American Pediatric Society which is the oldest and most established academic pediatric organization in the United States, and you have to have made a significant impact on child health in order to be elected. So congratulations for that.

I also want to thank my colleague, Gerri Baer. Gerri is one of now several neonatologists in the Office of Pediatric Therapeutics. Gerri and I just wrote a chapter for the leading neonatal textbook on neonatal abstinence syndrome. We also had publications on standardizing safety reporting in pediatric and neonatal trials, on co-enrollment in trials, in multiple trials on bronchopulmonary dysplasia and several others, and I think leaders and participants from the FDA in a variety of these projects have been integral on helping us move things forward. No disclosures.

So I'm going to focus a little bit as a

neonatologist on some of the neonatal aspects and you've heard some of them already. Certainly, knowing that six percent of the approximately four million births we have each year in the United States end up in the neonatal intensive care unit. We have the highest rates of prematurity in the United States of any developed country in the world. We have the highest rates of maternal mortality during childbirth of any developed country in the world, and I can keep going on.

And yet, despite an enormous amount of money we're spending in this area, there's really only been marginal improvements in survival and outcome in the last 20 years with over 90 percent of the drugs that we use in the NICU not having been FDA approved and that's certainly something that I appreciate Dr. Benjamin and PTN, and we've participated in some of these trials to help move that process along. Our smallest babies that can weigh 14 or 15 ounces at birth can be exposed to over 60 drugs while they're in the NICU and almost none of them have been studied

adequately for safety and efficacy.

So why has this been so hard? Well, it's a small market, rare diseases and a lot of risk and liability. There aren't very good premature animal models. There's variable definitions of our neonatal diseases. It's complicated study designs as you've heard. Really, it's hard to agree on the outcome measures. What is the proper outcome measure that we should have for neonatal trial, and when do you determine that outcome? So is it just in the NICU? Do we wait until they get older? Do they go to school? It's very, very complicated and it's hard to establish safety and efficacy with everything that goes on and their multiple comorbidities that some of these small babies have.

So there's really unique challenges in studying neonates, and Dr. Benjamin mentioned their rapidly changing physiology. I take care of patients that range from 14 ounces at birth to 12 pounds at birth. They're totally different.

We need to follow these children long term,

and it's really the longer the better. And yet, if we're asking PhRMA to develop a drug for use in the NICU, we can't say to them, gee, we want to wait until these kids are two years old and get our Bayley exams and know that the kids are developing normally. Or other people say, well, we really should wait till five years of age till we see their speech and language and how they're starting to socialize. Other people say, well, shouldn't we really be waiting till they get into high school and see how they're doing and what their grades are? So you can keep going on this. So that makes it much more complicated.

The postnatal environmental exposures are important too. So as these kids get older, they're being exposed to a variety of environmental impact from their homes, from their schools, and that becomes important. There's a lot of confidentiality issues that are important, especially when you have things like substance abuse trials, and you have confidentiality issues with the parents and the baby.

Getting informed consent is very complicated,

and especially if we're going to do something in the delivery room and we don't know that that baby's going to come out and have that problem, how do we get informed consent with something like that? So can you waive informed consent in certain circumstances?

The other things is for many children's hospitals, we cover at Tufts about 150-mile radius. And so what we do is when we get the babies who are sick at other hospitals and bring them to Tufts, they can be separated from the mother. So we've actually started bringing the mothers in and keeping the mothers with their babies, but most hospitals, especially none of the children's hospitals, can do that because they don't have obstetric services.

And so there really has been a huge impact of all these different legislative efforts, but it hasn't been as great in the neonates. And yet, we're making a lot of progress that I'll talk to you about, but I still think we have a ways to go.

So the regulations have facilitated pediatric studies about neonates, and this is one study from

four or five years ago where they looked at 406 medicines studied in children in order to achieve exclusivity, but only 28 of them were studied in neonates. And of those 28 drugs, we didn't really use them. We don't use them on a routine basis.

There's also concerns about pediatric formulations and we're using a lot of adult formulations because we don't have neonatal formulations. So certainly, the extrinsics, the stabilizers, the preservatives, and Dr. McCune addressed some of that in her opening slides, for instance, the methadone that we use for treatment of neonatal abstinence syndrome has 15 percent alcohol in it. So that wine is nine percent, to give you a reference. Buprenorphine is 30 percent alcohol. Phenobarbital has 20 percent alcohol in the elixir. That's what we're treating babies with neurologic and brain injury and we're giving them drugs that have 15 or 20 percent alcohol in the elixir and if you use the IV form that we're treating acute seizures and brain injury, it's 60 percent propylene glycol and a number

of premature babies have died of propylene glycol toxicity in Europe over the last few years. So we need safer pediatric formulations as well.

And so I take this from my friend, Ed Conner, you know, where we talk about neonatal clinical trials, the demand is increasing, the trials are inefficient. Most trials fail due to inadequate enrollment, if a trial infrastructure is fragmented and lacks sustainability, the expertise in the workforce is limited, and there are significant opportunities for change and improvement. And you can see below from PhRMA how complicated many of these trials can be.

So moving forward, what's our pathway forward? As I've said, I think we're making a lot of progress. But can we enroll every neonate in the NICU in a study protocol to optimize outcomes? How can we do it for cancer? Why can't we do it in the NICU? Can we adopt uniform and better definitions? Can we collect standardized data? Can we examine global survival and outcomes because it's very, very different across the

world, and can we adopt best practices in both our clinical trials and in our clinical care? Can we establish even normal laboratory values based on birth weight, gestational age, and postnatal age?

And when I do global trials, I have to convert all the laboratory values because all the units of measure are different in Europe and in the U.S. and some are even different in Asia. Can we develop safer drug formulations for neonates? Can all of us as key stakeholders, especially the regulators, collaborate to develop the best protocols that we can run? And can we do that before we're approaching the Agency? We should be doing all the work first, and I'll talk about the Trial Innovation Network through the CTSA that Dr. Benjamin mentioned as one way of doing that.

The other thing that FDA has been very effective is recognizing this need in neonates and help us establish the International Neonatal Consortium. So we started with a prayer and a pipe dream and about four or five of us sitting around saying we should really do this. And four years

later, we have over 300 members in 35 countries, over 75 academic organizations and parent groups, nursing groups, and we're all meeting together and talking how we can move this process forward. And I'm happy to talk to folks about being engaged, but we really had all the key stakeholders in this room have participated in this process through the Critical Path Institute.

The Clinical Translational Science Award Program, I think that's important for people to recognize that it's having a significant impact, that interacting with the regulators in a positive way is helping to move this forward. It's a national consortium of over 60 research centers under the National Center for Advancing Translational Science, one of the 27 NIH institutes. And the mission is to really develop innovative solutions that will improve the efficiency, quality, and impact of the process for turning observation in the laboratory, clinic, and community into interventions that improve the health of individuals and the public.

And it's really as a research service organization and designed to provide infrastructure and support for the clinical trials process. We're conveners and connectors; we get investigators together with the people that help them and we're innovating in promoting change. How can we make all the processes involved in clinical trials, how can we make them better?

And this is what it looks like, and Dr. Benjamin is actually the director of the Trials Innovation Network. And this is the vision and partnerships that we have these 60 hubs that are parts of the Trial Innovation Network. We have a recruitment innovation center and trial innovation centers at Duke and Vanderbilt and at Tufts and Hopkins and Utah too. What we do is take investigators, help them build their protocols, help them write their grants, and get them in and get them funded much more quickly. And that's huge.

So I had a project. We were looking at whole genome sequencing and developing and targeted next-

generation sequencing platform and doing genetic testing in newborns, comparing multiple techniques. We did have a comprehensive evaluation, even myself as a seasoned investigator. The trial was made much, much better. It got funded on the first time. We actually are at a 150 percent of our projected enrollment already. It's the most impactful trial I've ever done in my career. We're taking babies in status epilepticus and getting a diagnosis of a rare genetic disorder in a day and instituting new treatments and watching the seizures disappear and the babies wake up and look normal. So these are things that are very important, but all that work upfront made it a much more feasible trial, and I think this is really important.

This is from our Tufts/CTSA. We were proud to have a perfect score on our grant, but this is very complicated, but it's just designed to show you the multiple touch points in different groups that we have to work with investigators up front, and this is all at Tufts before we approach the Trial Innovation

Network and the trial innovation centers. So this has really helped move things forward in a very, very positive way.

Dr. McCune showed a slide of this. This is even my more advanced pediatric clinical trials ecosystem. It really does take a village to do these trials and do them successfully and you can see a variety of different groups and networks, some of which we've heard from and some of which we will hear from, that are really making a difference and collaborating together in order to facilitate these clinical trials processes.

So from my favorite movie, the Wizard of Oz, how do we get to the Emerald City? Well, we need sustainable infrastructure. The days of coming to academic community, setting up a trial, and running the trial and they saying good-bye and shutting everything down and having the next company come by two or three months later and say we want to start it up, and we say, well, we just let our study coordinator go. We have to now hire someone new. We

have to set the process up. I think that's a bad approach and so that's why organizations like I-ACT, and Dr. Conner will talk about this later, are trying to establish sustainable infrastructures so we go from one trial to the next without stopping and keeping that research infrastructure available.

I think you need to have cooperative networks on a global basis all working together. I think you have to have a knowledgeable workforce, and I think that's something I that appreciate with PTN because certainly for the PTN studies, yes, I did make sure my junior investigator was doing the work, and I did that for free. Dr. Benjamin was quite correct, but it is a way of engaging young investigators and training them how to do clinical trials because I really do worry that we're pushing so much clinical work on them and these trials are getting increasingly complicated and complex for even established investigators like myself. So I worry about the future of it as they become more complicated. Instead of making it easier, will it be more difficult?

And, of course, I had to end with efficient regulatory processes. I've certainly been appreciative as long as we remain product agnostic of all the members of the FDA, the EMA, Health Canada, the PMDA who've participating in helping us organize our trials and looking at endpoints. I think that's made a huge difference.

So I think I'm going to stop there, right on time. And thanks very much.

DR. MCCUNE: Thank you, Dr. Davis.

And our final speaker for the morning is Dr. Bridget Jones who is the Associate Professor of Pediatrics at the University of Kansas School of Medicine and Children's Mercy in Kansas, and she is here representing as the Chair of the American Academy of Pediatrics Committee on Drugs.

AAP PRESENTATION

DR. JONES: Thank you, Susie, for that introduction. And thank you to the FDA for holding

this meeting and giving me this opportunity today to discuss the significant strides that we've made in pediatric drug development and also some areas that I think we can do a lot more.

I'd also like to thank all of my colleagues in the room. Thank Dr. Benjamin for those very warm comments regarding the AAP, but I really feel like all of the strides that we've made have only been possible because of all of the people in the room and the stakeholders and colleagues that are in the room. So I think all of us have a lot to be proud of today at this meeting.

So like I said, I'm going to talk about the progress that we've made in pediatric drug development, but also touch upon some of the challenges. So BPCA and PREA have revolutionized pediatric therapeutics. There's been more than 800 pediatric labels that have been made as a result of BPCA and PREA. In 2012, both of these laws were made permanent, so at that time, it gave children a permanent seat at the table, but we really need to

make sure moving forward that that table is really what all children need.

So orphan drugs is one area where we can do a lot more for children. So orphan drugs are currently exempt from PREA requirements. And as you can see, over the past several years there's been significant increases in the number of drugs that are approved that have an orphan designation. So there's also been an increase in the number of drugs that are exempt from PREA.

Data shows that last year over half of the drugs that were approved by CDER were designated as orphan drugs and so they're exempt from PREA.

In August of this year, FDA released a report titled Pediatric Labeling of Orphan Drugs, and the study examined all FDA approved orphan drugs that treat rare conditions that occur in children as well as in adults. In that study, it showed that over a third of orphan indications that were relevant for pediatrics was missing pediatric information, either no information at all or just incomplete information.

So of those 127 indications that are relevant to children, 81, the majority of them, had no information on pediatrics.

So the current law allows FDA to apply PREA to orphan drugs through rulemaking. So FDA should act quickly to remove the PREA orphan exemption. For pediatric cancer, the FDA Reauthorization Act was passed in 2017 which was a very important change to BPCA and PREA. It allowed FDA to require pediatric studies of cancer drugs based on a molecular target rather than limiting it to when the cancer indication is the same as in adults.

Going forward, the AAP would like the law to move towards a disease agnostic approach where allowing children that have conditions that could benefit that may be different from adults to also benefit from these innovations.

Another area of need is regarding noncompliance and enforcement tools for noncompliance. So the FDA has issued 31 PREA noncompliance letters since 2013. Eight of the sponsors have fulfilled or

been released from the PREA requirements, but 23 have not completed the PREA required studies or been released from requirements. Six of these requirements have been pending since 2013, and so the FDA needs stronger enforcement tools to ensure that critical pediatric studies are completed in a timely manner.

There also needs to be greater transparency regarding which studies are requested and which studies are being done. So there needs to be transparency around the BPCA studies in order to improve collaboration between industry researchers and patients. Details on BPCA are not made public until well after the studies are completed so often five to ten years after they are requested by the FDA, and the FDA can't share the specifics of the BPCA studies that are being requested with counterparts in other countries which hinders the ability to perform pediatric studies in those other countries. And the public is also not informed about which studies are declined BPCA study requests.

Other areas of challenges that we've heard

about also today include formulations, the lack of drugs available for neonates, and also the lack of certain populations not being included in clinical trials. So for formulations, many of the therapeutics that are currently manufactured are not manufactured in formulations that are easily administered to children or feasible to give in children. So many of these drugs have not been appropriately studied for routes of administration common in children.

In neonates, neonates we've previously heard from various speakers. They continue to lag behind those for other children. Progress has been made in FDA with creation of the permanent position for neonatologists in the office of pediatric therapeutics and the recent release of guidances, but still more must be done.

Children from racial and ethnic groups are often not adequately or not included at all in clinical trials. The study population for certain therapies used to treat given conditions must be reflective of that general population so that we can

ensure that all therapies that are approved are benefitting all children.

So with that, I thank you. Tremendous progress has been made in the recent years to ensure that drugs are safe and effective for children. Without the support of the FDA, none of this could be possible and we look forward to continuing to work with FDA and all of the colleagues in the room on making progress for children. Thank you.

DR. MCCUNE: Thank you, Dr. Jones. I want to thank all of our speakers from this morning that have given us a lot of information and good thoughts to consider. And I will say that we're right on schedule and so we will break for lunch and I will see everyone back here at 1. Thank you.

[BREAK]

DR. MCCUNE: All right. Welcome back from lunch and for those who are outside that want to come back in and take a seat, that would be great.

So we have one more session this afternoon with four speakers, and then we're going to kind of open the discussion up. We have one person who has put their name down to make comments at 2:00. If there's anyone else in the room that officially would like to do that, please, I guess at this point, see Terrie who's going to be sitting up at the front table. And otherwise, we're going to move right into the afternoon session. Our first speaker is Denise Schulz who is the Senior Director of Global Regulatory Strategy at AbbVie and she's going to get us started for the afternoon. Thank you very much.

BIO/ABBVIE PRESENTATION

MS. SCHULZ: Thank you Susan. I'm Denise Schulz from AbbVie, and I'm here to talk about a case study of Pediatric UC our ENVISION Adalimumab Trial and also touch on Adolescence in an Adult Risankizumab Trial.

I'm taking a different on twist what some

other people have presented today. And like I said, it's going to be a case study. This case study does reinforce several points that BIO and PhRMA and other people have presented today such as the need for more defined and agile mechanism for multi-regulatory authority, scientific advice, consideration for the use of innovative trial designs, as well as sufficient resources to support pediatric studies.

So AbbVie is committed to the research in pediatrics. I'll start off with some background of adalimumab and pediatrics. Humira adalimumab has been studied in seven pediatric indications globally, four of which are approved in the U.S. The study I'm here to talk about today is currently ongoing and that's the pediatric ulcerative colitis study.

The journey for this study began in 2011 when we first engaged FDA on this. The adult indication was currently under review when we engaged the FDA. FDA was still reviewing the proposed dosing and they told us to come back after the adult indication was approved because the proposed dosing hadn't been

decided yet.

In 2012, the adult indication was approved, and we did have a post-marketing requirement to study higher doses. In 2013, we had submitted a special protocol assessment for the pediatric trial of which we received a non-agreement letter. We followed that up with a Type A meeting. At the Type A meeting, we did finally get agreement on the dosing, the study design, and the endpoints after which we had to submit a request for PIP modification because our PIP measures were affected because of the endpoints and dosing.

The FDA and EMA agreed to study design after taking all the feedback from both EMA and FDA was very complex. FDA required the endpoint of Mayo rather than PUCAI. Mayo requires endoscopies, so there was two endoscopies within a 52-week period which is burdensome on pediatric patients, one at screening and one at week 52. We were successful in negotiation that at our week eight endpoint there was no endoscopy. Otherwise, that would have been three.

The EMA required mg per kg dosing as well as placebo within this trial. This was also the largest IBD trial ever proposed with 225 subjects and this is a very small population Pediatric UC.

Of note, our Pediatric Crohn's Disease Trial did not require placebo and the infliximab Pediatric UC trial did not require placebo as well. All subjects received active therapy at the beginning of the trial. This was one way around the fact that placebo was in this trial. After week eight, responders were removed from the trial -- non-responders were removed from the trial and responders either received one of two doses of adalimumab or a placebo.

We had significant recruitment issues into this trial. To boost enrollment, we talked to our investigators to get some ideas. They indicated at week 20 if you lost response to adalimumab or placebo, you were able to get active therapy, rescue therapy, to loosen the criteria. We loosened that criteria to be able to get rescue therapy. We still didn't get

the boost in enrollment we were looking for.

We then modified the protocol again to reduce that criteria for rescue therapy all the way down to week 12, just four weeks after you received induction therapy, we still had trouble enrolling this trial.

We identified several barriers to the conduct of this trial. Placebo was a significant barrier. Even if it was okay for investigators, it wasn't okay for parents and it was okay for the patients. Infliximab was already approved for pediatric ulcerative colitis. Adalimumab was approved in a pediatric formulation for both Crohn's disease as well as JIA in the United States as well as other indications outside of the U.S.

Where withdrawal of active treatment in UC patients with response, not remission, at week eight meant some patients could have residual disease. Worsening of UC can lead to serious complications, including hospitalization and colectomy. Interruption of a biologic has theoretical immunogenicity concerns. Additional barriers included the two endoscopies.

Rather than using the traditional PUCAI, we moved to that endpoint of Mayo as required by the authority.

The ENVISION experience. We approach 220 sites, 100 of them declined study participation of which many of the cited it was largely due to the placebo arm in this trial. Two of the top EU-5 countries declined participation. The coordinating investigators actually declined participation in this trial and in these EU countries when the coordinating investigator declines participation, that means no other investigators in these countries will participate in your trial.

Sixty-three (63) sites were activated across 15 countries; 6 countries never even enrolled a subject and 71 percent of the patients enrolled into this trial were from Eastern Europe. We amended the protocol three times to help boost enrollment which included reducing the criteria and time to qualify for active rescue therapy as well as reducing the procedural burden.

Our final amendment in 2017 to help boost

enrollment is where we removed the placebo arm. This took approximately two years of negotiation between both the EMA and the Pediatric Committee -- or the negotiation between FDA and the EMA of Pediatric Committee.

Other barriers were the mg per kg dosing as requested by the EU authority. It added additional complexity, study visits, and some at-home dosing errors throughout the study. While the study was ongoing because it took so long, we were globally submitting and launching a new adalimumab formulation, our citrate-free formulation, which has less pain on injection.

Global harmonization of our protocol amendments with FDA and EMA's pediatric committee took months, sometimes up to six to ten months for harmonization, and after harmonization, we had to submit clinical trial applications and submit to the ethics committee before we could actually implement these at our study sites.

The current status, finally last year in 2018,

we got agreement to cease enrollment into our trial and follow these subjects through completion of 52 weeks which is a reduced sample size from the 225 and to use an external placebo control. That external placebo control consists of all available adult and pediatric trials that we could find with a placebo rate that has a similar trial design and the same endpoints that we are using in our study. That placebo was based on the upper 95 percent competence interval using a meta-analysis.

We requested a type B meeting recently with the agency of which this type B meeting was granted 125 days from the meeting request date. Type B meetings should be granted 60 days. This has been a consistent theme with the gastro division. All our meetings have been granted delayed. So this study is still ongoing eight years after our first Agency interaction.

A known non-enrollment of adolescence in adult trials. For our Risankizumab Phase III Crohn's Disease Trial, AbbVie proposed to include 16- and 17-

year-olds into the trial where it was locally permissible. The EU CHMP requested full physical maturity for inclusion of the 16- and 17-year-olds. Some countries, as we were submitted the CTAs outright rejected the approval of these protocols citing the inclusion of the adolescence. This delayed study startup in many of the geographic regions.

Enrollment of these adolescence commenced about eight months ago and thus far, it's been challenging to enroll these adolescence.

In closing, placebo is a major barrier in pediatric IBD programs, even when it's acceptable to investigators, it's not for parents and patients. Extrapolation, trials with un-blinded comparators such as the Golimumab Trial from Pediatric UC that's currently ongoing, or external placebo controls such as the one we currently have in our trial deserves strong consideration as innovative trial designs by regulators to accelerate the conduct of pediatric trials.

Although AbbVie has been successful in the

removal of placebo in our ENVISION Pediatric UC Trial, other subsequent Pediatric IBD Trials have received comments back by agencies to include placebo yet again. Negotiation currently occurs separately by both EMA's Pediatric Committee and FDA. There's a need for more collaboration and lessons learned by agencies from previous trials such as our ENVISION Pediatric UC experience.

There's a need for an agile mechanism for multi-stakeholder regulatory authority scientific advice to facility global harmonization of clinical development programs.

We'd like to thank the investigators and study sites who have participated in our clinical trials and we'd also especially like to thank the parents and children who have been willing to participate or consider participation in our trials. Thank you.

DR. MCCUNE: Thank you, Ms. Schulz.

Our next speaker is Dr. Ed Conner. Dr. Conner is the Chairman and Interim Chief Medical Officer at the Institute for the Advanced Clinical Trials for

Children or I-ACT for Children. Dr. Conner.

I-ACT PRESENTATION

DR. CONNER: Thanks. Thanks for the opportunity to be here and to talk a bit about I-ACT for Children and some of the issues that we're tackling over the course of doing product development for kids.

So I have the privilege of actually being on the founders and the chairman of the board of I-ACT for Children which is an independent 501(c)(3). It's a public-private partnership and it was launched in 2017 to advance innovative medicines and device development in labeling to improve child's health. As Danny talked about previously in the off-patent space with BPCA, I-ACT focuses almost exclusively on the on-patent drug development through primarily PREA.

The momentum for I-ACT came from an initiative that was started AAP in thinking about different ways of doing product development for kids and then

ultimately incubated at the Critical Path Institute for a couple of years and then launched in 2017. And the question is -- and what it focuses on really is development science, innovation, and efficiency and primarily child health impact. The goal is to have continuous early engagement of all the stakeholders in the process including parents and patients and it's funded by membership support, partially from an FDA U18 grant, and from donations and philanthropy, and it really focuses on four main areas. One of them is in strategy and planning which includes innovative trial design, feasibility of studies that are being proposed, et cetera, and pediatric program development. So this is in the mode of trying to get it right the first time and by doing that early in the process.

It also focuses on infrastructure development that specifically brings the lens of product development. So currently there are 60 centers primarily in the U.S., although now starting to branch out into the international community, and it partners

with other public-private partnerships in the space also. And then we also focus on doing best practices and thought leadership, bringing a sense of urgency to issue of addressing of the challenges in pediatric development as early and much as possible.

So the goal is that I-ACT brings together a variety of different stakeholders that are instrumental in moving innovative product development forward. Those are all listed here. They come as part of the network that we've developed and external collaborators which bring the essential elements for understanding regulatory product developments around the table.

We partner with lots of people. This is just some examples of the partnerships in various research organizations, folks have mentioned conect4children, which is a European initiative that also is a public-private partnership, a variety of other places around the world, a number of advocacy and care communities, and examples of certain research alliances that include access to real-world data, to regulatory

science, to develop development, to a continuous quality improvement program, the Tufts CTSA and digital health technology that, obviously, is an important part of building the infrastructure.

We work with a variety of biopharmaceutical partners including many of them that are listed here as well as some of the bio and pharmacy trade communities.

The organization itself, as I mentioned, has about 60 built-in sites current. The goal is for those sites to have -- they are disease agnostic trials, so we operate across therapeutic areas. There is in each of one those a site champion and operational lead and then a variety of in-house processes and central processes to make the startup and the conduct of trials most efficient.

We think that it's very important to build infrastructure, as somebody was mentioning earlier, that is sustainable. Our, you know, history and product development has really been that we sort of -- I guess people have used the analogy of an airport

lately. You know, if you basically traveled in airport to get here, you went to the airport, you took the flight to D.C. and you came to the meeting. If that airport went away and then the next time you wanted to come here to build the airport before you actually go to D.C. again, that causes a little bit of inefficiency in the system. And we should really have a sustainable infrastructure supporting the efforts for developing products in kids and that's generally what we're trying to do here.

Right now, most of the sites are in the U.S. As I mentioned, there are some sites now in Australia and in the Middle East, and then there are partnerships with a whole variety of the international community and with specialty networks to bring those resources to the table.

As I mentioned, I-ACT was in the planning stages for several years and then was launched in 2017, and by 2019, we've really now gotten engaged in operating in a number of the places that we've talked about today. So we work both in the precompetitive

space and in the proprietary space with individual companies who often will engage us in thinking about the development of their pipeline as partners. I think AJ mentioned this in some of his remarks.

We've now engaged in multiple areas of therapeutic development in innovative trial designs where we've provided advice and guidance about extrapolation, simulation, master protocols. Particularly in master protocols we've created a sort of incubator for folks that are thinking about and then operationalizing master trials and have taken forward master protocols in the neuromuscular space where we actually have been now the regulatory sponsor for the master trial and are developing master trials in inflammatory bowel disease and in other spaces.

Innovative methodology and trial design where we've made independent assessments of the application of Bayesian and adaptive methods to programs and then used those reports, those separate independent reports, to be able to submit to regulators as a separate view of these innovative methodologies.

There's a lot of activity in the landscape for infeasibility assessments for trials, for providing independent expert position papers in a variety of places. Folks have mentioned the difficulties sometimes in the goal to include adolescence into clinical trials. We recently held a large stakeholder meeting in which the guidance that's been provided hopefully will help through these kind of interactions in translating into operational activities.

Implementation science, digital tools for endpoints, et cetera, this is the list of current activities in which we're providing either pre-competitive support or direct proprietary but independent support in assisting in the development of pediatric programs.

We talked a lot about some of the challenges in the past and I-ACT was really created in some ways to try and address some of these issues. We have spoken about the advances that have happened through PREA and BPCA and the fact that we've made substantial inroads in changing labels for pediatric patients.

But at the end of the day, we're still left with a significant amount of work in the case that while the numbers are being reduced a bit, there's still a little less than half of the drugs that are used in kids and, as you've heard earlier, maybe 90 percent of the drugs that are used in the NICU that are not labeled for kids.

And importantly when we actually are able, historically, to label for children, it's taken in the order of about nine years to go from an adult program to a pediatric label. And we did some work a couple of years ago to look at that over the course of about a decade and unfortunately, we actually haven't made that much inroad. It still takes about nine years to go from an adult label to a pediatric label, and we really need to address those issues.

So we know that there's an increasing demand for pediatric trials. There's a high infrastructure demand. Trials generally are taking quite a long time and many of the trials, although again, we're making some progress at addressing this, either stall or

fail. And you've heard some of the examples of how it can be quite difficult to get through this whole process.

I think we've made significant progress in reducing the gap in labeling for BPCA drugs and stimulating pediatric studies for labeling through PREA. And we have made some progress in reducing both the number of unlabeled drugs as well as the number of trials and activities that fail, but we really have still a long way to go. And so I just want to mention a few things that are relevant to the meeting and the topic from today.

So first of all, I think everybody has acknowledged that pediatric regulations continue to be essential for catalyzing drug and device development. It is not -- while we have made significant advances, there is still more work to do, but we cannot be, you know, move away from the fact that we need the incentive and the requirements that are in place in the regulations in order to be able to drive pediatric development.

Permanent pediatric legislation that happened through FDASIA has resulted in pediatric development moving in the sponsor world often from a real afterthought to at least some forethought. It's not totally moving the direction of where very early consideration of pediatric projects are quite as early as we'd like them to be, but the making permanent of PREA and BPCA have been really significant in moving the culture to thinking about pediatric trials earlier on in the progress. And that's been a major advance.

We also have scientific advancement. This has really created a pipeline in the biopharmaceutical industry that's really quite unprecedented over the last decades. And it's been estimated that about 30 percent of the current pipeline for biopharma have some pediatric applications. So the work that's going to need to be done in order to be able to have pediatric considerations of all of that pipeline is quite substantial and given the challenges that are associated with the development of those products important for us to pay attention to. So shame on us

also if we now have the opportunity to do this and we are not prepared from both a planning and an infrastructure perspective to make those things happen.

I think FDA's leadership in advancing both innovative trial methodologies and in scientific and community engagement has really been foundational. I think it's been very clear in our experience as we've moved forward putting in place platform trials or the work in adolescent inclusion in adult trials that FDA and multiple FDA components have been present in the conversations in order to be able to advance the dialogue. And I think both the leadership in advancing innovative trial designs for pediatrics as well as the FDA's engagement actively in the scientific community has really been very, very important in advancing pediatric programs.

Public-private partnerships have emerged as a mainstay in pediatric development. Critical path institutes started with a critical path initiative that happened over 10 years ago and ultimately has

developed, and other public-private partnerships like I-ACT and c4c, the network in Europe, have been really critical in making things happen and in providing yet another method for there being both public-private engagements as well as infrastructure that can be sustainable over time.

Regulatory and development science are really essential to reduced development risk and applications are advancing to practice. What I mean by that is that in order to be able to have folks pay attention to advancing pediatric trials with the alacrity that we actually want them to be paying attention to, we have an obligation of de-risking some of those programs and it's really through the scientific investment into understanding how to get from the bench to development that really make a difference. And programs like the CTSA and other programs as well as other activities that are developing these sort of innovative methodologies from a scientific perspective are really key to being able to advance programs in these spaces. And trial networks skilled in pediatric

produce development and implementation science are creating needed global sustainable infrastructure.

You heard about the decade-plus experience of PTN in this space which has made really substantial contributions. The foundation of the global Pediatric Trials Network through engagement of networks in Europe and in the U.S. is really critical and I think that we really need to be sure that we have the capability of taking forward the pipeline that's coming through the biopharmaceutical development programs.

We do, on the other hand, still have a way to go. First of all, the culture change that we talk about in changing from thinking about protecting vulnerable patients from research to protecting children through research and applying the principle of justice which basically says that we shouldn't really summarily exclude children from research, that overprotecting children is harmful as well as under protecting children, but that that culture and the integration of research into clinical care really has

a way still to develop. We believe that. We have made significant progress in it, and yet at the same time, we need to embrace it more than we have currently and be able to move forward under those principles.

I think the other issue is really how early we consider pediatric development in the process. I mentioned that we've moved from a real afterthought to a beginning forethought, but the fact of the matter is that the earlier the pediatric development is considered in development programs of innovative product development and the more it becomes routine, the more of the tools that are necessary at the end of the development program or to incorporate pediatrics early can be applicable.

I think there are many examples of where adult programs can facilitate pediatric programs by doing additional PK that's necessary to be able to do simulation where the adult programs themselves can include endpoints and outcomes that are useful in pediatric development, et cetera. And whether or not

those choices are made, it's important to consider those things very early in the process. And without consideration, then they're left at the end to sort of catch up at a time that is almost times too late.

I think we've begun to think about our history of thinking about age as a sort of arbitrary cutoff in pediatrics and that we've moved a bit to thinking more about science versus age as the driver of product development. So there are many times that we've spent talking about children are not like little adults, but sometimes children are actually like little adults and there are times when science should drive us to actually manage patients in a way that gets development to go a bit faster.

I think this closing the gap of the nine years that we're talking about is really quite important. I think there was just some discussion around the fact that this nine year off-patent drug development allows for trials to become more and more difficult to conduct. And really, our goal should be to have pediatric indications at the time of adult, but at

least if not that being possible, at least to have it happen within the couple of years after an adult indication.

Once we get past two or three years, then off label use of the drug become another significant obstacle to actually getting trials done. And what that means is that we then need to move back to the pediatric consideration to a time that allows us to get the drug approved if not at the time of adult approval, at least soon after adult approval while there's a window of opportunity to make that happen. And we're actually not doing a service if we don't do all of the things that we can do to move that up as much as possible.

I think the evolution of models and regulations and policy to address underserved populations, we've talked a bit about including newborns, but also other rare and orphan disease and devices for pediatrics are another area that needs some attention. We've spent some time talking about workforce development. The focus of thinking about

product development as a specific set of skills and the development of individuals who are experienced in that is really an important element.

I think the trials of the future are beginning to look very different than trials of the past. So we're going to need infrastructure that basically can use the innovations that we've talked about in the infrastructure and that incorporate digital methodologies and other aspects of ongoing care into adaptive platform methodology that can be used in the long term for pediatric patients. That activity, which really both incorporate studying multiple drugs at the same time but then also following patients for a long time after that is a new kind of infrastructure that we have to design for fit for purpose. And so it's extraordinarily important to have use consider to support those efforts to be able to do that.

I think this has been a time of significant progress and we're all very grateful for all the work that's been done by decades of folks to bring us to this point in time. And while there's a lot of

opportunity to identify where the issues are that still have to be addressed, I think there's a lot of substantial optimism that those things can, in fact, be overcome.

So I've being doing this for 40 years almost at this point and there's been a lot of times when we've sort of struggled along that time to get pediatric development at the forefront. I actually probably could not be more optimistic in that time than now about the opportunity to do what is right for kids. And I think that by continuing to pursue, to build on what's been done so far, we can really make that difference happen. So thank you.

DR. MCCUNE: Thank you, Dr. Conner.

Our next speaker is going to be Dr. Brenda Weigel, who is the Chair of the Pediatric Early Phase Trial Network and Developmental Therapeutics from the Children's Oncology Group. Dr. Weigel.

COG PRESENTATION

DR. WEIGEL: Thank you, Dr. McCune, and thank you for what's been a really stimulating day and wonderful and I'm really going to build on some of the introductory comments made this morning by yourself and also by Ms. Nancy Goodman who presented earlier today.

To really paint the landscape in pediatric cancer, we have sort of three big challenges in drug development. And the first one we think about a lot which is improving cure rates, but we also are in an era of trying to decrease the side effects of what we do in the acute setting as well as the late effects. And that's something that we are learning more and more in pediatric oncology is creating a population of survivors, but it's survivors with significant long-term complications. So we have really a three-pronged mission for developing drugs in children.

In childhood cancer, we have worked collaboratively for well over three decades now in mechanisms of doing organized clinical trials that have increased the cure rates for children with cancer

upwards of about just over 80 percent. But that's not been because we've had lackluster drugs that we have FDA approval and labeling for children that have been targeted to childhood cancer; it's using very old drugs and getting really good at supportive care.

But we do have cancers in children where even over the last 30, 40 decades we have not made the bar or the grade, so we do have cancers where the cure rates are dismal, and the need is tremendous for cure.

But as I said, a big, big challenge in pediatric cancer is our standard of care accepts life-threatening toxicities and side effects, and we've done this to accept a cure. But this is going to become a big question as we develop drugs that are less and less toxic, how do we ask the questions of decreasing toxicity at the expense of survival. A big question, that I think we don't know how to answer and maintain the current cure rates.

We also have long term complications that affect every organ system in children and these questions require the potential for very novel trial

designs, novel questions, novel endpoints, but very long-term follow-up. So really stretching the bar for what we need when we looked at this three-pronged approach to pediatric drug development.

What has been raised by, I think, everyone here this morning is most of what we do is in rare and ultra-rare conditions. Pediatric cancer is really a rare and ultra-rare disease that's becoming even more ultra-rare. For every approximately 150 cancers diagnosed in adults, there's 1 in children. So what drives and has historically driven the drug development industry in cancer are the big adult cancer diagnoses, breast, colon, lung, prostate, et cetera. It's not pediatric cancers. And we are dealing with roughly about 1500 newly diagnosed children a year in the United States, not a huge population when you start splitting that down.

So what are the realities of doing pediatric cancer drug research? We have a relatively low incidence, i.e. a small study population. That study population is becoming smaller and smaller and

smaller. As we learn more about the specifics of childhood cancer, we're subclassifying patients and risk stratifying patients. This has mandated and very successfully as has been highlighted by many other groups this morning, the mandate for multicenter, multidisciplinary clinical trials. That has improved, as I showed you the outcome, across the board in very large trials using old drugs and standardized supportive care with the integration of biology and we have advanced the science through the National Cancer Institute's cooperative group program, the Children's Oncology Group, and the COG Pediatric Early Phase Clinical Trials Network.

The Children's Oncology Group really is a large network that incorporates over 200 sites in the United States with the real goal of having a clinical trial access point for over 90 percent of children diagnosed with cancer in the United States. This serves as a wonderful platform for integrating new drugs as well as standard questions across the country.

The Children's Oncology Group also has an international reach with Australia, New Zealand, and sites as well now in Asia as well. So it really, there is the potential for also inclusion of Canada, I should say international, within these studies.

But we do have an evolving and changing landscape. This has really resulted from, I would say, the explosion of genetic and molecular understandings of cancer across the board over the last decades. We are doing across all cancer research extensive genomic profiling of human cancers that have identified very specific targets in cancers that have not necessarily followed the traditional here's lung cancer, here's colon cancer, but are becoming more and more tissue agnostic and more pathway and target specific.

We are now looking for, and I will show you one example, with some of these treatments because they're very specific targets looking for very large treatment effects in very small subsets of patients. This really begs the question of what several other

speakers have said is the need for seamless, very adaptive designs that allow us to quickly make decisions quickly, stratify patients, and quickly answer questions in very small subsets of patients. And really, this area of precision cancer medicine is becoming more the norm, and there are examples that are transformative in the adult cancer space.

At lot of these target vulnerabilities are extending now into pediatric cancers and this is an example of a group that published in Nature last year that estimated that in this group of pediatric tumors that are in the yellow boxes, you can find just over 50 percent of targetable druggable events, it's just whether you have a drug or a mechanism to actually administer an effective agent to those children and are they necessarily independent as a single drug to achieve a viable response. But it is possible now that we will be able to identify targets in the majority of children with cancer.

This has led to a variety of what are now looked at as precision medicine trials or trials that

have incorporated new drugs in these master protocol type or master screening type of studies. But these are still far and few between and a challenge to administer.

A key example that led to very rapid FDA approval is a drug developed by Loxo Oncology, larotrectinib. This is the first drug that was approved in pediatrics that is tissue agnostic. It was approved from the treatment of NTRK fusion-positive tumors. And as you can see on the top, the tumors -- this is what's called a swimmer's plot where the farther you swim down the lane, the greater your survival. At the top are the patients who had this NTRK fusion marker and the ones on the bottom didn't. It is not subtle that the ones who did better had the target, but what is key is that the company developing this knew that this was an important target in children with certain types of cancer and from the time of drug development they started with a liquid formulation that was able to be administered to very small children including infants. So the reason we

were able to detect this signal was because the formulation was something that we were actually able to give children and biologically knew that the target was of relevance in children.

So we have many challenges applying this precision medicine approach in pediatric oncology. We have a very limited understanding of the spectrum of the biology in these pediatric tumors and what are actually clinically relevant alterations. We can find these changes, but do they actually mean anything and if we actually have a drug that targets them, is it actually going to make a difference?

We have very limited preclinical models, so models in the lab to say we actually know how to target some of these and actually demonstrate a clinical benefit before we get to the clinic. We have limited experience with the application of the actual technology to do these sequences and trial design, as has been mentioned by many others day, really becomes limiting because of small numbers and for us, as we get into very specific tumor types and very specific

markers, becomes a real issue. And very few biopsies are performed in children at a time when tumors progress or change which limits our ability to truly understand the target or the biology of the disease.

The other which has been a major limitation has been, and still continues to be, the limited number of available drugs, but that spectrum is changing. And this is data recently published in the European Journal of Cancer that shows that in the decade from 1997 to 2017, a 10-year span, there were just over 120 drugs, FDA-approved, for cancer. Period. Not pediatric specific.

From the time of the first patient started in adults to the time the first pediatric patient was dosed, the median in that 10-year span was 6-1/2 years, which is way too long as has been identified in many other talks today is we're looking at just even to start that trial is 6-1/2 years.

So as you have heard earlier today, the RACE for Children Act is really trying to change that and really requires now the evaluation of new molecular-

targeted drugs and biologics intended for treatment of adult cancers and directed at a molecular target substantially relevant -- and I'll come back to this -- to the growth or progression of a pediatric cancer. And that you have to use appropriate formulations and, as Ms. Goodman mentioned this morning, the elimination of the orphan exemption.

So factors related to relevance, and this is a key question that comes up a lot. How do you know that something is relevant? Well, if you can identify the target in a pediatric cancer, it's potentially relevant. It doesn't prove relevance, but it's potentially relevant. The target function is related to the cause of the cancer or development of drug resistance, if you can demonstrate that. The effect of the target by changing it in mouse models in the lab, in cell lines, either independently or in some type of combination does garner relevance. Probably one of the things that is most relevance is if the same target occurs in adults and you demonstrate an actual effect and the same target is in children, that

adult data is incredibly relevant. And if there are markers that are predictive of response, that is also of relevance.

So this really puts us in a situation of looking at an awful lot of targets and an awful lot of potential targets and how do we now switch, as Ms. Goodman mentioned this morning, from an era of lack of availability of the drugs to a prioritization of drugs and drug development in smaller and smaller populations? So we really have to base that on biology and preclinical data, but that assumes that we have relevant and valid cell lines and models to study and that is still truly limited in pediatric oncology.

Many targets are identified very late, so they initially are identified in the adult cancers and it's an afterthought to actually look for some of those targets in the pediatric cancers. And there's very limited human tumor data because the tumors in children are very different than the tumors in adults. They're biologically not the same and they're rare.

So then how do we select these? It puts us in

a position of saying what's all the available preclinical data to suggest a possible role. This allows us, likely, to be able to move more drugs into early phase, Phase I or II, or in appropriate trials for expansion cohorts based on minimally relevant data, based on the cell lines, pathway knowledge, and broad mechanisms of action.

Another big factor that has been raised is formulation and the ability to deliver the drug. So it's not just enough to say we know this is kind of a potential drug of benefit in a child with cancer. If we can't actually deliver the drug, it doesn't matter, and that may be limited, most importantly in the oral setting. And that is limited by tablet size, but also solubility of many of these agents. They do not go into solution very well. So there is a significant issue of formulation that needs to be addressed much, much earlier in the process and encouraged and incentivized much earlier in the process. This has historically been an afterthought and left very late and certainly with the new requirements of the RACE

Act, we hope that this changes.

So key considerations. Pediatric formulation requirement. This is key. It does us no good to identify a target if we can't get the drug. The evidence from larotrectinib example, where from the get-go there was consideration of a pediatric-friendly formulation demonstrates that if you know the target and if you have a drug that you can deliver that's biologically effective, you can actually show a significant difference in a small number of patients.

We absolutely need formulations that allow for accurate dosing. We cannot estimate or guesstimate based on available, particularly tablet sizes, how to administer these drugs to children. Also the diluent that was mentioned for very small children, especially in the neonatal intensive care setting, is an issue for some of the pediatric oncology drugs as well.

And I would say we need to encourage early investigation of drugs, even if the formulation is still under development to expand into smaller ages, but we start with the existing formulations and work

collaboratively to develop the formulations as data emerges, not to delay until all of it is in place but work with what we have and move forward.

We still definitely need to manage and appreciate and understand risk benefit. We have to understand toxicities. We have to understand how these drugs affect growth and development and particularly in the oncology space, short and long-term toxicities over time.

Other key considerations, we have a rare target population. This absolutely requires collaboration. It may require international collaboration and coordination of regulatory requirements. There is a need by many pharma companies to meet regulatory requirements, both in the EU and in North America as has been addressed by others. And there needs to be a recognition and coordination of these requirements and moving past unrealistic requirements that cannot be met in very rare populations.

We need adequate safety in dosing of children

and adolescents. That is the minimum. We have to actually know how to dose these drugs in children and this really allows us to utilize variables of age and appropriate formulations and really for adolescents, utilize the FDA guidance for incorporation of adolescents in any and all trials as potentially possible.

We have a big impact on trial design as has been mentioned by others. We really are moving into an area of master protocols where we can more nimbly and effectively study multiple drugs in a single platform. We have in the early phase trials tried to use strategies that enroll patients in a much more efficient and rapid rate for Phase I/II studies using a rolling-six design.

We really, for drugs with limited toxicity, need to move more quickly to limited does finding and really starting at what is considered the adult recommended Phase II dose unless there's real toxicity reasons to consider otherwise.

We really need to move, and this is a lovely

picture from a recent publication by Dr. Dubois. We have to move from a past where we started the pediatric studies and the pediatric oncology studies, decades, sometimes, later than the first in-human studies in adults to a future where we are much closer to studying the drugs in children and adolescents. This is really possible through concurrent enrollment of adolescents and for planning for pediatric trials much, much, much earlier in the drug development pathway.

We are very optimistic, and I share that optimism that we are really at a really amazing time of pediatric drug development. We are really on the precipice of, I think, bringing more drugs to children with cancer. This will, however, require tremendous coordination of the preclinical data, clinical data, and biology resources to prioritize what we study in very rare populations. We absolutely have to improve our understanding in oncology of the tumor host and drug factors that impact the potential for not only tumor response, but toxicity. We have to develop more

robust biomarkers and standardized testing so that select the patients for the most benefit whenever possible. And we have to have access to the agents of interest, all which we hope will be immensely enhanced through the RACE Act and we are very grateful to the FDA for the work done in this regard.

We absolutely need collaboration with federal funding agencies, such as the National Cancer Institute, academia, and industry. This is really a partnership and will absolutely require internal collaboration. Thank you for your attention.

DR. MCCUNE: Thank you, Dr. Weigel.

And our final official speaker for the day is Ms. Katie Coester, and I apologize if I just -- I got it right. All right, and I learned grammar -- who is the Policy Advisor for the Elizabeth Glaser Pediatric AIDS Foundation. Thank you so much.

EGPAF PRESENTATION

MS. COESTER: Thank you so much again to the

FDA for inviting the Elizabeth Glaser Pediatric AIDS Foundation, or EGPAF as we refer to ourselves, to speak to you all today. Just a little bit about our history. We have a long-standing history in advocating for pediatric drug development through law changes at the FDA. This is a picture of Elizabeth, our founder, and her husband, Paul, testifying on the Hill after Elizabeth's daughter, Ariel passed away from HIV. Elizabeth started the foundation really in response to the fact that AZT, the initial ARV was being studied in adults and she couldn't get it for her child who was dying of HIV.

So it's really something that goes to our roots and, you know, a little bit of emotional connection to the organization, but now as a global organization, we really understand how U.S. policies here, the FDA obviously, being the gold standard, impact children's lives around the world.

So we are -- I always say we have sort of an old-fashioned foundation name, but we are a global organization with a 30-year history. We have a

presence in 19 countries. We are working about 5,000 medical sites with having enrolled over 1.6 million adults and children on antiretroviral therapy. And we focus mostly on the clinical setting, so getting children and their families on treatment, but also focusing on helping HIV-positive pregnant women prevent transmission to their children.

This expansive experience obviously really informs how we look at treating children and what the challenges are in treating children with HIV and other comorbidities like tuberculosis, and we think about ways that the FDA can use existing mechanisms to speed up the availability of new and exciting ARVs for children.

So just a little bit overview, there are still 1.7 million children living with HIV around the world, about 500 new infections each day. Only half of them are accessing treatment and without treatment, half die by the age of two and 80 percent die by the age of five. The smallest children, neonates -- we talked a lot about neonates today and we talk a lot about

neonates at EGPAF -- are still using AZT, the medicine that I mentioned before which was approved 32 years ago. Now, obviously, it's okay to use medicines that are old. As one of my colleagues said, we will use ibuprofen, aspirin, et cetera, if they're effective. The issue is that AZT is no longer seen as anywhere near a gold standard for an adult medicine, but it is still something that we're using for the smallest children.

In the last 20-ish years, and I use that because children under 25 kilograms are still using medicines that are around 20 years old and older. About 14 new individual ARV compounds have been approved for adults and many are still not available for children. You know, HIV, I think, has been moving sometimes at a breakneck pace for adults with lots of new and exciting medicines, but children just really are not benefitting from those advances.

The medicines that we do have are often sub-optimal. We heard folks talk about dosing administer. Obviously, in the developing world we're not using

IVs, so taste-masking is very, very important for children under 25 kilograms. One of the medicines tastes horrific, I am told, that once you taste it, you will never forget it, and we're seeing through some public-private partnerships and other efforts rolling out new formulations of those medicines, but it's taking a long time and again, there's been a lot of these advancements for adults but not for children.

We have seen improvements. Raltegravir, which is one of the three ARVs used for neonates which was recently labeled for neonates in 2017, and the World Health Organization whose guidelines are generally considered gold standard, changed their guidelines to include raltegravir for neonates, took about 10 years from FDA approval to when it was labeled for neonates. And dolutegravir, which is a very exciting new ARV the FDA approved in 2013 is expected to be labeled for children down to four-weeks-old, so not the smallest, but still a pretty good subset next year, so seven years. So we're seeing some of those timelines shorten, but we think that those could be shortened

even further with some additional reforms and implementing some guidance by the FDA.

So we're really lucky in terms of looking at children with HIV because we have a rather expansive natural history of the disease. HIV research has been generously funded over the years and HIV impacts children not so differently than it impacts adults, and so we have a good understanding of how it works.

And there's several classes of drugs. Obviously, folks understand that you generally give more than one medicine to treat HIV and there's lots of different classes that you can chose from and so that's why we have neonates on three different medicines that you might give children under 25 kilograms and then children over 25 kilograms, so we do have lots of choices. And we also have expansive research networks through our friends at NICHD and others through the NIH. There are lots of opportunities for industry to study medicines in children to build on existing networks.

Additionally, I think there's a lot of lessons

that we can learn from HIV, and one of the points I really want to make today is not that we're so lucky with HIV, but how can FDA use the lessons learned from pediatric HIV and maybe apply those to some other diseases.

So there's new guidance released earlier this year on pediatric HIV infection drug development. It's a really clear articulation. It's only seven pages long. I am not a scientist or a doctor and I could very clearly understand it so it wasn't too technical of a document, but from what I understand, it really just cleared up questions that industry had around pediatric drug development in HIV, put it in one place so we don't have to have that back and forth with industry and FDA asking questions about study design or weight bans versus age bans or whether you should concurrently study drugs in adolescents and adults. It put it all out there very clearly and so FDA can say look, here you go. Don't ask us questions. When you come in with your pediatric study plan, take this under consideration.

This document in part came out of meetings that the Vatican actually held. The Vatican convened a group of stakeholders including the FDA, the EMA, the President's Emergency Plan for AIDS Relief, or part of the federal funding program for HIV in the developing world, as well as NGOs like EGPAF and faith-based organizations to really say we have a very serious issue with pediatric HIV treatment. How can we improve it?

And FDA came to this meeting and one of the pieces that I think had been in development, but it was spurred in part by this meeting was this guidance. And we really saw that as when you bring the right people to the table and you're willing to have an open conversation about moving things forward, change can happen. And so just we encourage everybody to have that willingness to come to the table because we've seen advancements through that willingness.

We also really encourage FDA to use the existing formal processes through the end of Phase I and end of Phase II meetings to make sure that they're

continuing to encourage industry to think about children as early in the process as possible when thinking about HIV and other pediatric drug development.

And then lastly, sort of continuing on this theme of folks talking about the orphan exemption for PREA, we just really encourage FDA to strongly consider applying PREA to orphan drugs. It's not relevant to HIV specifically, but it is to a lot of the comorbidities and other issues that affect children around the world, specifically tuberculosis.

Many people have talked about the recent report. I'm not going to repeat the statistics, but one of example that I wanted to talk about is the bedaquiline which is the first tuberculosis medicine from a new drug class in 50 years. Very, very exciting. It's still under pediatric studies, but it's not expected to be labeled for children for 13 years after adult approval. I think as we know, tuberculosis is now the largest infectious disease killer world-wide. It impacts, I think, a million

children a year, so this is specifically for MDR TB, but we want to make sure we have all the options for children available.

So I just want to wrap up very quickly and say, again, we're really focused on today really what FDA can do. Again, using those end of Phase I and end of Phase II meetings to ensure that industry is on track when looking at pediatric study designs and making sure that timelines are moving very quickly, applying PREA to orphan drugs. Again, taking the lessons of HIV, how can we apply really the incredible advancements we've seen with HIV and apply them to other disease groups? We know, I think tuberculosis is a similar one, but I know that there's other disease groups out there where the lessons from HIV can be applied to.

And lastly, I just want end with even with supportive policies, even though we've seen amazing word done because of BPCA and PREA, children are still being left behind and I think we can't just sort of say, like rah-rah, great, things are really doing well

because they're not. There are still millions of children out there on suboptimal medicines for HIV and other diseases and we want to make sure that they are getting the advantages of new medicines just as quickly as adults are. And that's it. Thank you.

DR. MCCUNE: So thank you, Ms. Coester.

First off, I want to thank everybody who spoke today. I really want to thank you for coming and for speaking. And so now we're going to kind of open this up to more discussion. We have one person who has formally requested to speak, and I will introduce him, sort of, in just a second.

I wanted to tell the folks online to remind you if you have a question or want to make a comment, please shoot the information in the discussion tab of the online. And I think folks have generated quite a bit of interesting discussion today and so if you spoke earlier or you didn't speak but you would like to speak again or speak for the first time, please kind of think about it. We have time for open discussion.

So with that, I understand that Douglas Fishman is the one person that we have who has requested to speak, so I will let him introduce himself and then we'll open it up again.

NASPGHAN COMMENTS

DR. FISHMAN: Great. Thank you so much for the opportunity. My name is Doug Fishman. I am a pediatric gastroenterologist and I stand here to comment today on behalf of over 2,000 pediatric gastroenterologists, hepatologists, pancreatologists, endoscopists, and advanced practice providers from NASPGHAN, the North American Society of Pediatric Gastroenterology, Hepatology, Nutrition.

We aim to provide optimal care, improving and adapting with innovation, with medication and devices. We are doing this in the clinic, hospitals, and operating rooms. In pediatric GI and liver disease, we continue to struggle with treating a range of conditions with medications and devices lacking a

pediatric label or indication, often with significant delays and without pediatric studies.

We also care for a litany of disorders within the rare disease category such as progressive familial cholestasis or PFIC as an example. In terms of medications, we heard it several times with an average of eight years post adult approval before pediatric studies and usage. As you also heard, adalimumab, for example, is being used for pediatric ulcerative colitis on an active basis; however, with challenges, without FDA label in pediatrics.

However, a great example of progress since the last guidance is the study of hepatitis. Hepatitis B and C studies ongoing have now decreased to 18 months post adult approval. And as we move to potential cures, at least in hepatitis C for adults, the FDA guidance has been critical within our unique pediatric population. Proton pump inhibitors labeling with pediatric indication and pharmacokinetics has also been important.

But when we think about developing studies, we

definitely need pharmacokinetics as noted earlier today, specifically in IBD therapies, but we need to perform pharmacokinetics of a new or even old drug in children during trials. The major difference in IBD and many conditions is not the biology of the disease so much, but rather the metabolism of drugs in children compared to adults. And this probably could be paralleled in any of the conditions that we're talking about.

We must balance the need for this without hindering the pediatric studies. Can this be done in parallel or utilizing European network data or even existing data or registry data? We know that placebo is problematic in children, at least in IBD, as an entry requirement for both pre- and post-study colonoscopies are also required.

What is the current standard of care and can we compare that new drug to our standard as a comparator? And that should be sufficient, at least, in certain populations, or at least for drugs that are already approved in adults.

We want to encourage federal support for development of pediatric clinical outcomes in needed areas and consider enrollment of late adolescents to adult studies when appropriate as has been discussed today.

We need to improve our post marketing adverse event tracking, perhaps with industry collaboration or with red cap among centers that have it. We have great appreciation of the Create working group which was supported by the FDA as a registry and things such as this may help to provide this.

In inflammatory bowel diseases, one area of concern is the role and approval of biosimilars. Biosimilars are unique when compared to typical generic drugs. These products were processed and purified from a living specimen. The impact is such that there may be significant variability which is possible even in the original biologic medication.

The main concern is that once the FDA approves, insurance companies may require usage over the standard medication. In a joint grade level

recommendation provided by the Canadian Association of Gastroenterology and the Crohn's Colitis of Canada, they suggested there's insufficient data to recommend the use of biosimilars in patients with active ulcerative colitis that are naive to standard medications. They recommended against non-medical switching from the originator medication to a biosimilar in patients that were stable and doing well, and also suggested that switching in that setting may lead to an increase or worsening of disease.

In all medications, we need to improve post-marketing adverse tracking -- I did that already.

In hearing the comments today, we should consider the FDA recommending new phase trials to involve a pediatric needs assessment including both patient and potential investigators and include recommendations for study involvement which might enhance industry's ability to move forward with studies in adults in areas where there is a pediatric need.

As an aside as was just mentioned, having a palatable liquid or other formulation or ODT that are pediatric-friendly should be development at the onset. The need to compound medications is often a significant expense to our patients and not always covered by insurance.

The last guidance did not include pediatric devices and these two are critical to our mission. There have been great strides in device development. We appreciate the work of Dr. Varum Paris (phonetic) from the from the FDA who has been active with the Center for Devices and Radiological Health. Novel devices have been designed and approved for pediatrics, but only account for about a quarter of those as in adults. This was reported in 2018 by the FDA commissioner, Dr. Gottlieb. From the Gottlieb session it was also relayed in 2017 more than 60 percent of approved devices were labeled for use in adults but could be applicable for pediatrics.

We also struggle in GI with the available equipment to perform procedures for liver and biliary

obstruction with ERCP. Many of us are using outdated equipment that will no longer be serviced by the three primary companies, Pentax, Olympus, or Fujian. When the CRE infection issue arose a few years ago, several endoscopes were removed from market leaving only endoscopes normally used on adults for those down to one years of age.

Because the volume of certain procedures is less in adult patients, the incentive to tailor equipment for children is limited beyond making smaller endoscopes. Devices to go through endoscopes and other measuring equipment are often limited by their size leaving limited options, specifically in children under two years of age. Children do get gallstones, ulcers, and related problems, typically in sicker patients with cancer or severe cardiac disease, so we get really good at working in small spaces with small tools. Unfortunately, for the smallest endoscopes, often two times smaller than the standard adult equipment, the choice of approved device is almost as small as the total available devices. So

just making the device smaller but designing with pediatric use in size and mind is important.

Several companies will sell equipment and devices but limit marketing and training due to lack of FDA approval. So even as experts, we are asked to wing it in children with life-threatening bleeding or other conditions with non-FDA approved devices and equipment. This unfortunately is not the exception.

Identifying companies who are willing to develop equipment and devices needs some opportunities to fast track and offer appropriate development and studies in children while maintaining the highest standards.

In summary, we appreciate in GI all that the FDA has done and will continue to do. We would like to see fast tracking of current devices, post-market studies, and continued innovation and on the medication side, to improve time to study and final approval with appropriate study design. On behalf of the North American Society for Pediatric GI, Hepatology, and Nutrition, we thank you.

DR. MCCUNE: Thank you, Dr. Fishman.

OPEN DISCUSSION

All right. So I'm going to open this up for discussion. We have a microphone there, and I believe Terrie, you have a microphone here. Anyone who would like to make a comment or -- and I would just ask that before you make the comment, you introduce yourself because we do have a transcriptionist at the back.

So anybody want to jump to the microphone? I don't think -- and we haven't heard anything online. We don't have any online comments yet so.

If you would like to. Is that mic live, Terrie? Do you know. Do we know.

MS. CRESCENZI: It should be.

DR. MCCUNE: It sounds like you might need to get close to it.

MR. BIRCH: Okay. Can you hear me okay?

DR. MCCUNE: Yes.

MR. BIRCH: My name is John Birch. I'm an

angel investor from Kansas City. I find this fascinating and full of unmet needs that I think digital health entrepreneurs can meet.

I want to ask one very specific question though, because there are a thousand that I could ask and that is, is there any interest in this space in monitoring more systemically off label prescribing and the outcomes? Simple question. Hope there's an answer.

DR. MCCUNE: The floor is open to anyone who wants to answer the question.

MR. BIRCH: No interest at all?

DR. WEIGEL: I can talk about it.

DR. MCCUNE: Okay.

DR. WEIGEL: So, Brenda Weigel. It is a huge question, and I will say in the pediatric cancer space, one of the things that becomes very challenging for us is if a drug is approved in adults, there becomes a very quick exodus from a participation in a clinical trial because they have access to the drug and if there is an indication, most insurers you can

argue well enough to actually get it covered in the cancer space. So it is a very fine line for us between enrolling someone in a trial in this space before there is lots of approvals.

We have talked a lot about how could we collect some of that data. It's a very difficult thing to imagine how you would do, and I think the problem is probably there's probably more off label use than we actually understand, I think. It's how would actually collect that data and I think the data systems you'd need to do that would be really challenging, and what would be the data footprint that you would collect. And I think -- so there's toxicity, there's efficacy, there's lots of things, and the heterogeneity of the patient population would also be challenging, and then what would the data be used for.

I think it's an incredibly interesting question because we have often thought there's a lot more out there than we have access to actually be able to collect. So I think there would be challenges, but

it is an interesting question.

MR. BIRCH: I'll just elaborate a little bit. Bear with me for the moment in thinking that it is possible to collect a higher degree, a higher-level quality of data on all newborns. Just assume for a moment that that's possible. Dream with me if that's the dream, and to monitor them to some extent for the rest of their lives, mining EHR data, mining personal health records, mining a whole variety of sources in the real-world data space that are increasingly now available.

So just imaging that that's possible. What opportunities would that create? And one of the first ones that comes to mind when I talk to the people about this is the idea of off label monitoring. You used the word that most gastroenterologists are winging it and indeed, 40 percent, I think someone said, of all prescribing for young children is off label. Did I get that number right? Something like that. In any event, something can be learned. We're talking about a learning health system. We could

learn simply from monitoring the outcomes of the prescribing that's going on today, whether they're best practices or not, we could at least learn something. So I guess that was suggested as maybe a starting point. So that's the basis for my question.

DR. MCCUNE: Oh, good. Dr. Jones is coming to the microphone.

DR. JONES: Yes. So I just have an add-on comment to that just in regard to data in general because I think having access to large data sets is another area that I think we could take better advantage of, especially with the multiple EHRs that hospitals and institutions use. For example, as within the Pediatric Advisory Committee for the FDA, one of the things that we look at is post-marketing safety and a lot of times those data sets are limited in the data that we have available.

So I think, you know, if FDA could take advantage of the current EHR data sets that we have to provide more comprehensive data as well as thinking about some of the long terms outcomes that we really

should be looking at in children. So earlier today was mentioned antipsychotic medications and how we're not looking at the long-term effects of children that are placed on these medications for years and years. And so using EHR type data sets might be one way that we could start to do that.

MS. SCHULZ: I'd like to add, you know, during our pediatric UC engagements with the agency, we've been asked to supplement data with our application eventually with real world data and we've been finding difficulties trying to find quality data to supplement out there. We have located some, but it's been not of quality. It's been difficulty to locate so, you know, if there's a way to get quality data to be able to supplement it. You know, I see use even in the future with the 21st Century Cures Act with real world data, conducting smaller trials, and being able to supplement that with quality data, and maybe trying to progress pediatric indications even faster. So, you know, if there's a way hypothetically to do this, I see a lot of benefits from it.

DR. MCCUNE: And I know -- since you're talking about kind of the off-label world, I know that Dr. Benjamin and Dr. Zimmerman probably would have been jumping to the microphone already. I don't know if Dr. Taylor-Zapata wanted to mention anything in that space, or not. I don't mean to put you on the spot, but --

DR. TAYLOR-ZAPATA: I was going to jump up, I was.

DR. MCCUNE: Okay.

DR. TAYLOR-ZAPATA: Actually, as you were all were talking it reminded me -- I'm representing Dr. Benjamin and Dr. Zimmerman and myself.

So we, actually within the Pediatric Trials Network have delved into this issue of trying to gather quality data from EHR to support some of our studies, and it definitely is a challenge. Remember, EHRs were built primarily for billing and not for research, and so the infrastructure of the way electronic health records in general don't support quality regulatory rigorous trials.

So some things we thought about are, is there a way to have a platform that's in between the EHR and what we need for data for FDA where we actually can collate that data to make it of good quality and across multiple EHRs to be able to submit that to FDA? So is there an interim platform, for lack of a better word, where we can actually have that data? Or is there a way to do an experiment within EHRs where Epic at Hopkins would talk to Epic at Children's would talk to Epic in Indiana which are all three different Epics, if they could all sort of talk to each other and actually have a platform to put quality data into. That may be another option.

So it's been a challenge and we're looking at different ways to do this. And so we're going to start small within one institution as our first pilot study and it's just starting in this year. So we'll let you know how that goes.

DR. MCCUNE: Excellent. Thank you very much. And I know, I can't speak for the Office of Surveillance and Epidemiology in CDER, but I know that

the recent Sentinel contracts have expanded a lot of the data analytics. But I think that the challenges that have been raised are clearly ones that need to be addressed.

Okay. You should sit closer to the microphone.

MR. BIRCH: There's -- in the last several years, I'm aware there's huge growth in the number of registries so I guess my question is, although -- I'm not sure I've heard the word registry mentioned here today, but there is a huge growth in rare disease registries, in registries in general, and certainly, I believe there's a hundred and some pediatric registries according to the registry of registries that ARC maintains, and I believe the number is growing. But yet, I'm surprised that it hasn't been mentioned here as a source of data.

My understanding of pediatric trials or, I guess, clinical research with vulnerable populations in general is that one should first look at all possible other sources of information before doing a

clinical trial, and I would think that that would include registries. And so I guess I'm just wondering out loud here why has there been no discussion of registries today?

DR. MCCUNE: I'm surprised I'm not seeing anybody jump up because I know there are a lot of folks in the audience who are involved with registries. So I don't know if anyone wants to make a comment about that experience.

Dr. Weigel's going to help us.

DR. WEIGEL: So to your point, it's an incredibly powerful tool in the pediatric oncology space. So we actually have master databases and actually Ms. Nancy Goodman mentioned this morning that there's actually a big effort right now in pediatric cancer to try and merge a lot of the data because we have data -- and so there's a real recognition of the power of that database. I think for us, one of the big drivers in the drug development space for databases is really the identification of targets, for use, or targets, or actual, something that the drug

can affect. And unless we pool a lot of these resources, it's very difficult in very large data sets to pull out sort of those ultra-rare populations.

So it is an incredibly powerful tool. It is something of tremendous need in the pediatric cancer space to be able to start to prioritize and to your point, optimize the potential for benefit to the children who we can identify that would benefit most. But it's going to require -- and some of too in the cancer space, it's an evolving changing landscape as the science evolves and develops and so it's going back to the database re-querying it, saying what do we know about this patient population. So it's actual critical to what we do.

DR. FISHMAN: I touched on it briefly, but there is the Create registry which has CDER approval. The FDA functions as a liaison for this project. Interestingly, my society, NASPGHAN, submitted congressional testimony for funding in 2016 for an IBD registry Phase IV that mimicked the CARRA registry for pediatric rheumatology. There was no funding offered.

As I mentioned, CDER -- sorry, Create has approval from the FDA.

There's also the 21st Century Act for drug approval and being able to use surveillance registries for that. And then there are models like PEDSnet.com or ImproveCareNow which is used for inflammatory bowel disease which could be utilized for some of these other studies.

I'm also involved in Inspire Network which is currently part of a U01 through NIH for evaluating recurrent and chronic pancreatitis and using some of these data centers that, you know, after five years, the data is owned by NIH, but there's multiple registries involved that have the potential to be utilized both in this instance for recurrent pancreatitis, but also later for pancreatic cancer.

DR. MCCUNE: Dr. Conner.

DR. CONNER: Thanks. I think just to build on that a little bit, there's a lot of effort in thinking about registries as a starting place for actually what becomes an underlying master trial or platform trial,

that the concept and Create is a good example of that where a lot of people have come together to try to create a registry as the beginning building block for creating real world data. But then wrapping around that, the possibility of generating -- using that same platform to also create the platform for master protocols, and ultimately that's what the landscape is going to look like, I think, is that there's going to be an opportunity to put together infrastructure that will ultimately follow kids for the long haul. Not just follow for safety after we do an investigational trial, but actually use that platform for the conduct of the investigational trial and begin to standardize some of the things that need to be standardized to draw inferences from them.

So the IBD is a good example of that. There are other examples in neuromuscular disease and in other places where the same thing is happening and were CARRA, which has been used in the rheumatology space very effectively, is also sort of having conversations about how to adapt that trial, that

registry into other further purposes. It's a timely question that I think will ultimately become how things look in the future.

DR. MCCUNE: And with the ADEPT meeting that we had last week, we talked with all of the pediatric patients and the majority of them either were in registries or at least, everyone was aware of registries. They may not have been available for their particular disease, but when there were registries available, they were actively participating in them.

DR. CONNER: I guess the other thing is to be sure that we use that resource also to leverage information around things like disease progression. So in addition to using registries for sources of real world data to be able to capitalize on that real world data, a lot of the data that comes from either the control groups and trials or other longitudinal sources can then be used to model disease progression and then that model of disease progression can be used to enhance the trial program for drug development.

But it may not substitute for doing the study itself, but it certainly can be used.

So for example, in the neuromuscular space, Critical Path Institute also is doing the Create trial, the Create registry has established a Duchenne's muscular dystrophy program for modeling disease progress in Duchenne and that is being utilized as part of the information that's fed back into what actually has now been in development which is a platform study for Duchenne and will help inform both the endpoints for the trial as well as -- picking endpoints for the trial as well as designing the study. So --

DR. MCCUNE: Dr. Taylor-Zapata.

DR. TAYLOR-ZAPATA: Okay. More discussion about utilizing data resources. So for one of the label changes that I mentioned for ampicillin, we actually utilized the Pediatrix, with an X, data warehouse to supplement the PK data that we had acquired through the network. And with the collation of that data, we were able to actually submit that for

label change and actually was successful. So it can work, but that sort of data warehouse has to have the forefront of drug development in that model for it to really be work of good quality.

DR. MCCUNE: Okay. Anyone -- thank you very much. Anyone else want to jump to the microphone?

All right. I'm not seeing jumping, so I'm going to let you think for a minute while I thank some folks for their help in this putting together the workshop for today, and you'll get one last chance. Let me just make sure, Terrie, anybody online?

MS. CRESCENZI: No.

DR. MCCUNE: Okay.

MS. CRESCENZI: There are people online, but --

CLOSING REMARKS

DR. MCCUNE: Well, yeah. Nobody that wanted -- no jumping online, I should say. Okay.

So first actually, I want to thank Terrie

Crescenzi for all of her help in managing all of the logistics for this meeting. This involved a tremendous amount of work over the past few months and I really want to thank her for all of those efforts.

I would also -- they're not in the room with me right now, but I want to thank Betsy Sanford and Sheila Reese for doing all the registration work outside in the lobby today.

I'd like to thank behind the scenes that you all didn't really see, Kathy Lee and Maryanne Nune for all the IT support today.

But once again, I really want to thank Captain Terrie Crescenzi because the meeting would really not have been possible without her dedication and support in the office. So thank you.

All right. I'm not seeing any jumping, so with that in mind, I will let you go 15 minutes early today. Thank you all for coming.

[MEETING ADJOURNED]