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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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PEDIATRIC MEDICAL DEVICE DEVELOPMENT

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Silver Spring, MD 20993

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M E E T I N G

(8:35 a.m.)

DR. PEIRIS: Good morning, everybody. How is everybody doing today? Good. Excited for Day number 2 hopefully? I know there are a few of you that didn't have a chance to join us yesterday, so thank you very much for joining us today.

I'll do a quick recap of some of the housekeeping things, just so that everyone that's joining us today, both in person and on the web, will know what the process is. And for those that didn't get a chance to have my introduction yesterday, my name is Vasum. I'm the Chief Medical Officer for Pediatrics and Special Populations with CDRH.

So, once again, for anyone that hasn't downloaded CrowdCompass, please go ahead and download CrowdCompass. For people both on the web and in person, you can ask questions through CrowdCompass. The entire schedule is on CrowdCompass, all the speaker bios are on CrowdCompass, so please take a look at that. And, if you use the #Devices4Kids, there is a social page on CrowdCompass also that hopefully will populate. So feel free to use that. And we'll go through some instructions, but if you haven't done it yet, please go ahead and try to do it now because we'd like for you to participate in the audience poll questions that also will be conducted through CrowdCompass.

As I mentioned the question, Q&As, and when you do question and answer, work through CrowdCompass, you can just hit the area of the schedule that says Question and Answer, and that'll take you to the option to file a question with us. Even if you're in person and you'd like to submit a question through CrowdCompass, feel free to do that if you don't want to come to the mic. But we definitely want to encourage everyone to come up to the mic.

Another piece of housekeeping, and I'll just read this out loud again as I did yesterday, so participation in a public meeting by an individual or organization does not

imply any endorsement by the Food and Drug Administration. As all of you know, we try to maintain a neutral forum here for the exchange of ideas and education. So, I definitely welcome all of the ideas and thoughts that we'll be going through today.

Let me highlight the point that if you do have comments to submit to the docket, please feel free to take a look at this website and submit comments as you'd like. If there are any questions or issues that you haven't had answered, you can definitely let our Webex and CrowdCompass team know specifically when you write in the comments to them through the question process. Or you can go ahead and submit officially through the docket.

Important stuff: Food, hopefully everybody had a chance. If you'd like to preorder your lunch, please go ahead and preorder outside. Depending on how the schedule goes today, and because I know some people have early flights, we might consider a little bit of truncation of lunchtime, just so that we can end a little bit earlier, just to ensure that everybody has an opportunity to stay with us for the entire day. But we'll get a sense of how people feel about that as we move forward.

So, the first section for today is a section on Creating Regulatory Value and Simplicity. For those of you that weren't able to join us yesterday, we had a section on Optimizing Evidence Generation and an introductory session that really were topics that applied across the board. So hopefully we'll be able to address issues or we should be able to address issues today focusing specifically on the regulatory issues that impact pediatric medical device development, and also on the marketplace and economic issues that impact medical device development in pediatrics. And the marketplace session will be the afternoon session.

I'll start with our first audience polling question. And then I'm going to hand it over to Eric Chen, our Director for the HUD Program and the Pediatric Device Consortia Program.

So, if everybody has your mobile devices out, we'll go to Audience Poll Number 7, from the list.

So the question reads, in your opinion, what legislation/regulatory action has been most beneficial for pediatric medical device development? Regulatory guidance on pediatric medical devices; pediatric user fee exemptions; lifting the HDE pediatric profit restriction; increasing HDE exemption criteria to 8,000 patients per year; tracking and reporting pediatric device approvals; establishing the Pediatric Device Consortia; or you just don't know and that's what you're here to learn.

So go ahead and take a second to answer, and we'll see what everyone is thinking this morning.

All right, that's quick. Well, hopefully, everyone had a chance to answer. It looks like we still have some answers coming in. And it looks like people feel that the PDC program definitely is one of the significant regulatory benefits. And the guidance on pediatric medical devices is number 2.

So it's good to know that the PDCs have definitely made an influence. There's definitely a lot of positives that have come out from the PDC program. And we'll have an opportunity to discuss the PDC program today as well. And it's always good to know that people are reading guidances. I know I read them every night before I go to bed, so it helps.

(Laughter.)

DR. PEIRIS: I joke, but it's very important because guidances truly offer the opportunity for us to clarify concepts and issues relevant to different areas with all of the stakeholders and our internal partners.

So, without further ado, I will hand things over to Eric to get the session started.

MR. CHEN: Thanks for that, Vasum. I'll wait to get the clicker.

Great. So as Vasum talked about, you know, and we talked a little about yesterday,

FDARA had asked the Agency to put on this workshop, and its title for this session is Creating Regulatory Value and Simplicity. We're going to talk about three of the topics that were listed in FDARA, especially for this, is postmarket registry usage, FDA insistence to pediatric device innovators, and then the current barriers and incentives.

So, today we have key speakers that are going to highlight some of the topics that we have today. We're going to start with James Baumberger to go through a highlight of the history and existence of some of the work that we have, that we work with at the Agency with regards to medical device legislation and development, as well as talking about some of the programs that we have.

We have Dr. Lynne Yao that's going to give us a presentation focusing on some of the legislation that the Agency has and works with, with regards to pediatric drug marketing lessons.

And, lastly, we'll talk about some of the opportunities for improvement and redesign of some of the incentives that we might be able to have for children. And then we'll also focus on some presentations that we have from our colleagues outside the United States to determine whether or not there are some incentives that we can take from in the European regulatory aspect and bring to the United States.

So, I'd like to introduce our first speaker, James Baumberger, he's a Senior Director in Federal Advocacy of the AAP. He's going to give us an overview of the pediatric medical device legislation history.

MR. BAUMBERGER: Thank you, Eric, and good morning, everybody. So, yes, I'm James Baumberger. I'm a Senior Director in Federal Advocacy for the American Academy of Pediatrics here in our Washington, D.C. office. And so that means one of my jobs is to lobby Congress on pediatric drug and device policy. I came to AAP in 2007, so right as AAP was advocating on Capitol Hill for the initial passage of the Pediatric Medical Device Safety and

Improvement Act, so I've really been able to have a front row seat throughout the legislative history of pediatric device policy at FDA and have been able to witness, you know, the creation and the development of CDRH's pediatric program.

So, what I'm going to do today is kind of go over some of the history of how the pediatric device legislation came about. And so, this is a brief timeline of what I'm going to cover from sort of the initial discussions that led to the legislation as well as the subsequent reauthorizations of it in 2012 and 2017.

But I want to start with a couple of things before 2004, when this timeline starts, and take you back a little further, which started in 1977, when the American Academy of Pediatrics Committee on Drugs established our first policy statement that said not only is it ethical to study drugs in children but it's unethical not to. And we're beginning to try to change the paradigm of researching therapeutics in children.

So that began decades worth of advocacy regarding pediatric drug policy. And that culminated then in the passage of the Best Pharmaceuticals for Children Act in 1997. BPCA created an incentive of 6 months of marketing exclusivity if companies do FDA-requested pediatric studies.

Then in 2003 Congress followed up BPCA with the passage of PREA, the Pediatric Research Equity Act, which is a requirement for certain new drug applications to do certain pediatric studies in kids. And so, as Mark Del Monte from AAP yesterday spoke about the importance of BPCA and PREA, and really the historic success they've had together, that sort of carrot-and-stick approach has resulted in over 700 drug labels studied.

So, after those big congressional innovations, Congress was then looking to us to see what the next big thing was and wanted to wade into the issue of medical devices. And that's what brought us down this path.

The other sort of point in time I would just also mention here is 1990, which is the

passage of the Safe Medical Devices Act, and that created the Humanitarian Device Exemption pathway, which as we discussed yesterday, but just to review, the Humanitarian Device pathway allows FDA to approve devices based on probable benefit rather than a full demonstration of efficacy, with two caveats: one, that it's for a disease to treat fewer than 4,000 individuals per year; and two, at least initially in 1990 when it was passed, there was a restriction on being able to make profit on those devices. So, if you got one, a manufacturer got an HDE approved, they were allowed to recoup their R&D costs but not actually make any profit on those devices.

So that's just to sort of lay the groundwork as we move ahead to 2004. So, again, this is a year after the passage of the Pediatric Research Equity Act. Members of Congress, in particular, Senator Chris Dodd from Connecticut, were asking, were very interested in doing something else for children, particularly in the area of pediatric devices. AAP, at this point, was beginning to hear from our members about concerns with medical device safety. And so, we wanted to try to get together with other interested stakeholders and have some initial discussions and maybe get some recommendations about what's next.

So, the AAP, along with the Elizabeth Glaser Pediatric AIDS Foundation, the National Organization for Rare Disorders, what's now the Children's Hospital Association, and AdvaMed, the five organizations hosted a series of stakeholder meetings on pediatric devices. So, FDA and NIH as well as other stakeholders were also present. And it was a series of four meetings. There was one introductory kickoff meeting and then three additional meetings with the topics listed there.

Data collection information sharing was the first meeting. The second meeting was administrative and regulatory issues; third meeting, market capacity and incentives. Interestingly enough, those three categories track very closely to the categories of things that we're talking about at this meeting. So it shows you that what's old is new, and we're

still obviously dealing with all the same issues that we were, but now 14, 15 years later.

So out of these meetings came a series of recommendations. And those recommendations went on to form the basis of what was in the initial 2007 Pediatric Medical Device Safety and Improvement Act.

Also in 2005, the Institute of Medicine put out it's report, Safe Medical Devices for Children. If you remember, in the early 2000s, there were some high-profile issues with medical device safety. And so, Congress was very interested and looking legislatively at the issue of medical devices and ensuring that they're safe. IOM put this report together on Safe Medical Devices for Children, which made some recommendations around increased postmarket surveillance devices for children, in addition to many others.

So that sort of led up to the context with which Congress approached this issue in 2007. For those of you who are not, you know, FDA lobbyists, what happens is that Congress, every 5 years, needs to pass a user fee, user fee legislation that funds much of FDA's activities. That every 5 year piece of legislation becomes a vehicle for passing a lot of FDA-related legislation.

So, in 2007, as Congress was working on its FDA user fee package, we worked with champions on the House and the Senate side to put a package together to hopefully ride along on that bill, which become the Food and Drug Administration's Amendments Act of 2007, or FDAAA. We worked with our champions to put a package together on pediatric medical devices.

So, our champions in the Senate were Chris Dodd and Mike DeWine from Ohio, in the House, Ed Markey and Mike Rogers. As you can see, and you will see through the entire history of this medical device legislation, it's always been a very bipartisan issue.

So, what was actually in the Medical Device Safety and Improvement Act of 2007? Much of what you just voted on in the poll was initially innovated in 2007. So, first, it

improved pediatric device tracking. In the 2004 stakeholder meetings, one of the things we determined was that FDA actually couldn't really tell us how many devices it approved every year that were labeled for children. So that seemed like a low-hanging fruit, to be able to figure out how to address that problem, to make sure that FDA is doing the appropriate tracking to be able to tell us, give us a sense of what's actually happening.

And so this was paired with a requirement for industry to submit readily available information to FDA on pediatric populations that could benefit by the devices that they're trying to bring to market, so much of the data that Mary Clare shared with us yesterday as a result of this legislation of this provision that requires now FDA to report annually to Congress on the number of medical devices that are approved for kids.

It also created, well, one bullet that's actually not on here that is important is that this legislation also gave FDA the explicit statutory authority to use extrapolation. So, the authority for FDA to extrapolate adult data to use, to label, in pediatric devices was granted in this law in 2007.

It also created the pediatric HUD incentive. So, as I talked about, the Humanitarian Device Exemption prohibited companies from making profit on their devices. So this provision said now allowed manufacturers to make profit on devices so long as those devices are labeled in kids. So, they could either be designed specifically for kids, or for kids and adults. And then those companies would be allowed to profit. So the idea here was to give an additional incentive, at least to those devices coming through the HDE pathway, to try to stimulate device development.

So this is also the law that initially established the Pediatric Device Consortia Program. The idea here was to give grants to nonprofits to help stimulate medical device development and hopefully approval. The way Congress does this is that they authorize a program, which essentially creates it, and then they have to come back later, and another

group of congressmen, called appropriators, actually have to fund the program, and so that was a whole other issue. But this at least established the program for the next 5 years.

This law also expanded postmarket surveillance authority. So this was one of the recommendations from the IOM report. The idea here is that, particularly for implantable devices that you're going to put in a kid, and the kid's going to grow and have that device maybe for many years, you want the authority to be able to require, as a condition of approval for Class II and Class III devices, companies to do postmarket surveillance.

So that was a provision in the 2007 law as well. And then it also required FDA and NIH and ARP to all put together plans within 180 days on how they can increase their activities around pediatric medical devices.

So, then after the passage in September of 2007 came the implementation, where FDA began to implement these provisions. One thing that was not required by the law but was done by Center Director Dr. Shuren, who I see in the back there, is he created a Chief Pediatric Medical Officer in CDRH, which is not a requirement of the law but was really essential to have one sort of focal point for pediatric activities within the Center, and that's the position that Vasum now holds. So we are really excited about that.

And then we have had since 2007, had to encourage Congress to actually fund the Pediatric Device Consortia Program. It was initially authorized, which is sort of considered more or less a ceiling, it was initially authorized at $6 million. And we got initial funding at $2 million, the first year it was funded, were able to raise that up to $3 million. FDA, over the years, was able to add some supplemental funding, but Congress was giving $3 million a year. And then just last year, we were very excited to double that number in congressional appropriations to $6 million. So now the program is up to the initially fully authorized level of $6 million, so we're really excited about that.

Okay. So two of the provisions in the initial law were just 5-year provisions and then

sunset after 5 years and needed to be reauthorized. So that's the Pediatric Device Consortia Program as well as the HUD incentive. So, in 2012 when Congress came to do its next user fee program, we needed to make sure that at the very least those programs were extended.

Congress was also keeping tabs on the implementation of the 2007 law at this point, noting that FDA had yet to issue final rulemaking on device tracking and submission of readily available information. Congress required FDA to promulgate that final rule. It renewed the Pediatric Device Consortia for another 5 years. And it also expanded the HUD incentive. But there was some discussion in 2012, if this is a good thing for kids, why don't we expand the profit incentive for HDEs for everybody? If it's good for kids, it's good for adults.

So we had to work to educate Congress that if companies could get the same incentive for just doing studies in adults and not kids, then we're going to dilute the importance and the impact of the pediatric incentive. So there was ultimately a compromise made that allowed adult devices to receive the profit incentive through the HDE program but only if labeling for kids in those devices would not be beneficial for them. So if it would be beneficial for that drug or that sort of device to have pediatric labeling, then a company will have to pursue that labeling in order to get the incentive.

So, again, we have 5-year extensions of the PDC program and the HDE profit incentive. So just last year, when Congress again looked at their user fee packages, we had to again extend the HDE incentive and again extend the PDC program. So we were successful in doing that. We also were able to kind of change some of the reporting requirements for FDA. They had this quirk in the law which because pediatrics, under device law, is defined as up until your 22nd birthday, the report that FDA was required to submit to Congress was basically giving Congress lots of information about pediatric devices

that may have only been approved for 21 and up, 18 and up.

And so we wanted the report to be more clear to Congress about what devices are actually have really meaningful pediatric labeling. Not that labeling in sort of the transitional adolescence period is not important, but we wanted to be sure that Congress is getting clear information about really how many devices are actually labeled in younger kids as well.

And, finally, the 2007 law is the reason that you all are sitting here today. So the law required FDA, within 1 year of enactment, and you'll see that the bill was enacted on August 18th, so FDA is getting in right under the radar, with the 1-year requirement to have, convene a meeting on pediatric device development.

So we are really excited about this meeting and about the discussions that we're all having. And sort of as we look to what's next, we think that this meeting is really hopefully going to be a great catalyzing moment for coming up with some recommendations that can really help move the ball. So FDA is required, after this meeting, to report to Congress with a summary of, and responses to, recommendations raised in this meeting. So as you all are thinking today and making recommendations, know that FDA is listening, and Congress will be as well.

So, at a minimum, next time, Congress has to come back and renew the FDA user fee packages in 2022; Congress will also have to figure out and extend the HUD incentive, will also have to reauthorize the PDC Consortia, but there's also the opportunity to do more. The FDA user fee packages have always been vehicles to move FDA policy. So now really is the time to start thinking about what we might be able to do 4 years from now legislatively. Certainly, there are things that we will have recommendations for FDA. There's a limit to what FDA's going to be able to do on its own, and so there may be things that we can, that Congress can help out with, to try to help us all move the ball for kids here.

So I will end there, end with a picture of my children, Ella and John. And I look forward to continuing the conversation today. Thanks a lot.

(Applause.)

MR. CHEN: Thanks for that, James.

So our next talk is going to be from Dr. Lynne Yao. She's the Director of the Division of Pediatric and Maternal Health in the Center for Drug Evaluation and Research. She's going to give an overview of what can we learn from the pediatric drug development legislation. I think we all know that there's differences between drugs and devices, but there could be incentives that we might consider, and hopefully Lynne can talk about those today.

DR. YAO: Thank you, Eric. Thanks, Vasum. Thanks, everybody. I'm glad you were able to make it this morning.

I hope to provide you some perspectives and maybe tell a little story about where we got to where we are on the drugs and biological products side. It's, I think, a success story, so I'm happy to tell it. And it's also maybe there are some cautionary tales or two in the story as well.

One of the things I will say, from the top, is that this is a relatively new audience for me, working on the drug side. Many of the faces here are not familiar. I do spot a couple of faces here and there that are familiar, and I think that's a good sign. So, you know, I think, as we talk about collaborations, I think, you know, the device people have always been the device people, and the biologic people have always been the biologics, and the drug people always the drug people. And I think that if we come together a little bit and learn from each other, that perhaps we'll learn a thing or two from each other that can help all of us.

So to start, let's see, advance? Oh, that's backward. Okay. This is my disclosure statement, which of course is standard.

I do want to talk a little bit, and I haven't heard other people talk about this yet, so I'm going to go a little bit further back than 1977, James had described. That back in 1963 was a gentleman, a physician, clinical pharmacologist pediatrician by the name of Harry Shirkey, and he was the first person to coin the term "therapeutic orphan." Now we use "orphan" and "orphan product development" like we know exactly what it was, but when Dr. Shirkey first described this in 1963, he was really referring to children, that this increase in development of drugs, the safety of drugs, this is right around the time of Kefauver-Harris, that children were being left behind. And so he coined this term "therapeutic orphan."

And what has developed over that last 50, 55 years, or so is that we've come to really push the concept across the drug development space that pediatric patients should have access to products that have been appropriately evaluated. And if you're going to develop a drug or a device that's going to be used in children, then you ought to include pediatric studies when you think there's going to be use. That is described in guidances that have been adopted internationally, including the E11, International Conference on Harmonisation E11 document.

Well, I don't really want to spend a lot of time on this because suffice to say that the evidentiary standard for approval of new drugs differs slightly with the evidentiary standard for the approval of a device. And all I've put this here is for you to reflect on that and the differences and how that might affect the development of policies. But I'm not going to really go into this in great detail.

What I do want to point out is, is regardless of whether you're studying a device in children or a drug in children, that there are special developmental considerations, developmental as in pediatric and developmental as in development of the product considerations, that really fall into two large and very important categories, ethical

considerations and feasibility considerations.

And many of you who are already in this space know this very well, but I also put this up for your reference. You know, clearly there are ethical considerations that must be in place because children, as a population that again is a vulnerable population or potentially vulnerable population, needs to have special protections. In addition, as we've heard throughout yesterday and I think will hear today, that there are feasibility considerations that really require us to think innovatively and differently about how to get these studies done if we're really serious about developing products for children.

So what about these U.S. drug development laws? James already described them, and I think it's important just to briefly review how these two laws work together to come to where we are today in drugs and biological products. So BPCA, which is the Best Pharmaceuticals for Children Act, you've heard James describe it, first passed as an incentive provision not called BPCA in 1997, but really as BPCA in 2002, and shortly after, the Pediatric Research Equity Act passed in 2003.

Now these two programs work together, BPCA as the incentive program and PREA, Pediatric Research Equity Act, as the requirement, if you will, the carrot and the stick as we describe it often, to increase the number of approved therapies in children. So what about these two laws, and how have they worked to increase the availability of approved drugs and biological products in children?

So here's a picture over time. And I was telling Mary Clare that I need to have her work in our shop for a while because this is the best I could do. And her slides and her analyses were much more elegant. But I think this slide tells a pretty important story, and that is that over the course of the first incentive provision until through the end of last year, we can see really a steady increase in the number of pediatric-specific labeling changes in drugs and biological products approved in the United States. And this is really, I think, a

success.

Now, you say, okay, this looks like a pretty good slide, Lynne. Tell me about what was the contribution? Why do you think that BPCA and PREA did work? Well, I can tell you that pre-1998 or pre-1997, before the first incentive provision was passed, we had no drugs. We had virtually, you know, over 80% of the drugs that were approved in the United States without labeling and with pediatric information in labeling.

And you can see that it took a while for us to figure out how to do it and for companies to figure out how to do it. But I think, over the last 20 years, it's really been clear that not only have companies figured out how to do it, FDA's figured out innovative ways to get the job done. And so prior to 1997 we had nothing. Okay. And I think that's an important point to make. It wasn't as though we were doing great before 1997.

So if you look at 1998 to now, this is the breakdown of what contributed to the labeling changes. So how many labeling changes are related to PREA, how many related to BPCA, to both, and then the rule, which is I'm not even going to talk about. That's a very interesting cautionary tale, I would say, on the FDA side. But that pediatric rule information, if you would, is sort of analogous to what we call PREA now.

So if you look at the relative contribution of these two laws, you can see that really, about 70% of the approval, or sorry, approved labeling changes with pediatric information are related to either a combination of BPCA and PREA or PREA alone, and that about 30% are related to the incentive alone, which is BPCA.

I'm going to change gears a little bit now and talk about another incentive provision, and then I'll bring it back to the end. So the Pediatric Rare Disease Priority Review Voucher program was passed under FDASIA, you've heard James talk about FDASIA a little bit, in July 2013. And it was amended just a couple of years ago with the Advancing Hope Act. And so this voucher program is intended to spur development in pediatric rare diseases. And

there's a whole list of ways that are described in the statute about how a rare disease must be defined.

Suffice to say that the intent is to spur development. And if you qualify for or receive a voucher, the voucher can be sold to a buyer, and there's no limit to the number of times. And we keep track. Keep in mind that these vouchers, the reason that vouchers are attractive is that it gives the owner of the voucher a priority review, whether or not that drug deserves to have a priority review from a public health perspective. It doesn't necessarily need to be for a life-threatening or serious condition, where no therapies exist, or a substantial improvement on an existing therapy. You just have to have the voucher. So it's like a coupon for a quick review.

Here are some of the vouchers awarded to date. And you can see on this slide that they're all for very rare pediatric diseases, including genetic disorders and cancers. And you can see that the price of the sales of these vouchers has fluctuated, initially from 68 million up to 350 million, and appears to be settling somewhere around 100 to 130 million dollars.

So what are my take-home points for you this morning and maybe my challenges to you this morning? Number one, I strongly believe that children are protected through research and not from it. I think we have an obligation to study pediatric patients for both devices and drugs when we believe that they'll be used in children, because the consequence to not is that they'll get treated anyway because prescribers and practitioners have to do something for their ill patients. And to not have the appropriate information to treat is really, I think, really a situation that we can do better with.

The BPCA and PREA have increased the availability. It's still a little bit early, in my view, to conclude that the voucher program has been successful in incentivizing, but I think that over the next couple of years will tell.

Now, if I'm going to tell you something, I think that all the things we've talked about

yesterday, which include, you know, innovative trial designs, use of big data, real world evidence, how to use extrapolation, bringing in networks, and international collaborations, which I'm very excited to have Eliane speak about next, those are all important. And I do think that incentives will get us somewhere, as we hoped to in the last 10 years with the HUD and HDEs. But I'm really going to challenge you to think about is there a way that we can, in some way, provide some form of requirement for device manufacturers, coupled with an incentive, because if I look at my data, those data tell me that the requirement piece was necessary to move forward and incentives only may not do it alone.

So I'll leave you with that provocative question, and thank you for your attention.

(Applause.)

MR. CHEN: Thanks for that, Lynne.

So I have the honor of presenting Eliane Schutte. She's the Chief Development Officer for Xeltis. She's going to give us a brief overview of the regulatory landscape on the international stage.

MS. SCHUTTE: Thank you.

Congenital heart defects are the most common defects, at birth, in both the U.S. and in Europe. And what that means, that means serious problems to the structure of the heart that are present at birth.

I'm Eliane Schutte. I'm working at Xeltis. I'm the Chief Development Officer. And what Xeltis is trying to do is solving one of the problems that surgeons and cardiologists and also the patients are facing today, which is limited solutions for these patients today. These patients are seriously facing issues, as today there are no suitable solutions that will help these kids avoid suffering through their life.

Xeltis is a venture capital-backed company, a clinical stage company, and we're focusing on reinventing the heart valve. And we're doing that by using a novel technology.

We're using the body's own ability restorer, and we're using that capability to restore a valve in a natural way. And that has been a novel technology that we hope will be successful in children, as well in the future, also in adults.

The content of my talk today will be also focusing on what is happening outside of the U.S., and how does pediatric device development work outside of the U.S., and what has been our experience coming from the industry, developing a true device for pediatrics, what has been our experience today. I will explain to you a little bit about the regulatory requirements in Europe and also again tell you some of the challenges that we have been facing through that whole journey.

The most common birth defect today at birth, actually 1% of children are facing congenital heart defects. It's really a serious, serious disease. And about 15 to 20% of those children are really having a defect on what we call the right ventricular outflow tract. And, basically, you might be familiar with conditions such as tetralogy of Fallot, pulmonary atresia, truncus arteriosus, pulmonary stenosis, all conditions that these children are facing. That all means, at a very early stage, at the time that they're born, children are facing an intervention or an operation.

Children are suffering. They're facing multiple open-heart operations today. And all of these replacements are unavoidable today. The problem is not only that some of the solutions today are not sustainable, they're not durable enough because they create problems such as degeneration; the biggest problem is also the children, as they're growing, they're outgrowing their own implants as they grow up.

So what could be the potential solution for these children that Xeltis is working on? We're using a technology which is based around a polymer, a polymer construct that has only polymer as a constituent, so there's no active ingredients in there. It basically acts a heart valve in the pulmonary space, so we're focusing on the pulmonary heart valve

indication. And as the valve gets implanted, the body starts to bring the blood through the scaffold. Fibering is being formed, and the first tissue restoration occurs. And at the time where the tissue is being built up, at the same time, degradation occurs, and the polymer slowly degrades and healing occurs.

So, eventually, the purpose of Xeltis is to truly create a novel technology that will allow these implants to remain in place and also to grow as children grow up. That should overcome some of the limitation of today's products out there, that there's not really truly novel innovation happening today, as for all good reasons as we heard yesterday. Animal tissue and homografts really present still some severe limitation and drawbacks.

So our indication for today is we're still working on two sizes which represents the pediatric population. Ultimately, we'll target for the full pediatric population and eventually also the adult.

As you see here on the right side of the picture, it's a pure polymer construct, which is around 70 to 80% porous. And this resembles a little bit what happens in vivo, in the body, in the patient's own body as the material gets implanted. Blood cells are infiltrated, and then the first steps of true healing occurs as the material slowly absorbs.

So where do we stand today with Xeltis? We have our first demand study ongoing. We have 12 patients that have been implanted with the pulmonary valve, in Europe as well as in Malaysia. We're very happy to have some very excellent centers in the U.S. that work with us on an early feasibility study, so we have actually some implants here in the U.S. as well, with a patient age range of 2 to 12 years.

Now, what is the situation in Europe? So what have we been facing as we started this clinical trial in Europe? Well, first of all, we ask you, what is the general regulatory pathway in Europe? And, really, it's not for pediatric, there's nothing special in place in Europe. If you want to bring a pediatric device to the market in Europe, you just face the

general medical device regulation as is today existing, which is the Medical Device Directive. And some of you might know that are more familiar with the changes in Europe, we have a challenging situation as the Device Directive is changing into a medical device regulation, which is much more stringent but also brings a lot of unclarities.

And that type of regulation will be enforced mid-2020, but also, reading that very thick document, you will notice there's nothing specific regulated for pediatric population. There is only the very obvious elements there, such as clinical studies on minors to do a proper risk-benefit analysis and have a proper informed consent and have general safety and performance requirement being analyzed. There is no specific guidance towards support of regulatory roots for pediatric devices in Europe today, nor will there be now in the near future, as we have seen.

In Europe, we don't have systems like Humanitarian Use Designation and Humanitarian Device Exception routes that at least encourage to bring safety data and get the device earlier to the market. So in some of that regard, we're slightly behind versus where we stand in the U.S.

Now, for the approval of studies, it's basically the same as how you go about for adult devices. You have to have a CE mark in order to really get a pediatric device to the market. And for a clinical trial, you need to get ethics committee at the hospital and go to the local member state competent authority to get approvals.

Now, in Europe, because of all the member states and the spread of that, and as you've heard, the scale of pediatric studies is really an issue, we are facing the situation that we really need to target multiple member states to do clinical trials. And at all these member states, there's very limited pediatric device experience. Usually, if they have pediatric experience, they have drug pediatric experience. They don't have usually, and especially in the smaller countries, device experience.

Also, in the hospitals, the pediatric hospitals, what you see that sometimes ethics committee lack the experience of really truly doing device studies. And sometimes even in countries in Europe, they have a central ethics committee to really try to solve it.

Now, the differences that we have seen is, in facing this, is it varies a lot about what one country requires versus the other, in terms of preclinical package but also in terms of informed consent. The infrastructure in some of these European countries is really limited. They don't usually have specific research departments in hospitals that have dealt with doing research. So, really, they have to be educated to perform studies.

So the response that we've had with some of these, going through this experience is that in some countries they said, well, you can forget about doing trials in our country; you first obtain a CE mark. Well, okay. Then you just closed the door. I mean, that's very easy.

And in some of the countries, we've also seen a pretty much pharma approach; let's first test it out in adults, and then you go back into pediatrics. Well, in our situation, it has been extremely challenging because specifically, as I explained, our technology is so unique for children as they're growing up, so the benefits are particularly there for pediatrics. So to first test this in adult doesn't make really sense.

So we've had some struggles with the Swiss authorities as also they said you have to use different type of bench models that they're more familiar with in the specific space for adults, and as well, they basically said, okay, you can do this, but you have to be risk adverse. Let's try to use the age range above 16 years. So, therefore, we also did not use Switzerland as a country to participate.

So, all in all, we are facing some struggles in Europe. We face the problem that there is no specific knowledge. We do see the lack of experience sometimes, but in some countries it's much better, so it varies from country to country. So, as industry, you really need to pick your country really carefully. But we also want to say, there is also some

opportunity in Europe.

What we have also seen, as opposed to the U.S., that where we had a very efficient process with the FDA for the early feasibility study, we are also facing the problems with the general things of the administration in hospitals, getting contracts lined up, getting the budgets in place, which is very expensive and dragging. At the same time, also the speed of enrollment is challenging for us, especially in the early feasibility phase where we've been able to tackle that problem in Europe faster.

So I just want to close with that remark. Although it's very, very challenging and it's complex, we're here still, and we believe that this will ultimately help children and help alleviate the suffering of the children. And that's why I think it's very rewarding to still be in this place and to continue pushing this forward.

Thank you.

(Applause.)

MR. CHEN: Thanks for our presenters this morning.

So now we're going to move into the question and answer session. So, for the folks that are in the room, if you have a question, please come to the mic. And then folks who are connecting with us on Adobe Connect, if you put in your questions, we'll be able to have those that people can read out.

So, first question?

DR. WALL: Hi. James Wall from Stanford. Question for Dr. Yao.

I'm stunned by the economic value of the vouchers. What is the time frame that those offer? Generally speaking, do you have numbers on the sort of time benefit that those offer and the scale of that versus devices?

DR. YAO: Sure. I didn't get into it, but thank you for asking that question. So once once the drug for the rare disease is approved, the voucher is awarded. At any point after

the voucher is awarded, the sponsor may use it on their own, or they may sell it. And what we've found is that the value of the voucher is really in the selling, right, because these guys were developing drugs for rare diseases, serious, life-threatening, you see the list. So, they were getting priority review, and they had to be eligible for priority review already in order to receive the voucher.

So selling that to a company who's maybe developing the next "me too" or something that's similar, or trying to get to the market first, but it's not for a rare or life-threatening disease, that shortens the review clock from 9 or 10 months, really 10 months to 6 months. And that added advantage of that 4 months shorter review can sometimes make a big difference in terms of getting to the market first and beating a competitor.

So you can see that that value is apparent to many companies who have decided to purchase them. What is not clear yet is, and that's why I'm not sure about how successful this will be, is, you know, the voucher is valuable if there are a limited number. So the more that FDA issues, you know, obviously the supply is greater, the less expensive it might be. And it's also not clear that if the incentive is intended to increase the number of approved rare disease products in children, this prize is all the way at the end of the line, you get that payoff with the approval.

Well, we've heard, in many situations, for startup companies who are looking at going into the rare disease spaces, they need the money up front. So it's hard to say. We haven't, you know, quite figured that out. Time will tell. And we're certainly keeping an open mind about whether this program's working. But, you know, I think we're going to hear, and I think my colleague and friend Sam Maldonado's going to talk a little bit, the right incentive for the right market. You know, if you're going to create an incentive, it's really got to address the issue, the problem that we're having.

And so I think that's what we're trying to figure out still. Is the voucher really addressing the problem that we have with rare disease development in children?

MR. CHEN: Dr. Nelson?

DR. NELSON: Hi. Skip Nelson, Johnson & Johnson.

Lynne, some of the proposals that are on the table, such as tax credits, are modeled after the Orphan Drug Act as opposed to BPCA or PREA. I'm wondering if you could provide some general comments about those incentives and the extent to which those could be used as a model in the device space?

DR. YAO: Sure. So as Skip points out, you know, tax credits, you know, waiving of user fee, those are all things that can help earlier in development, certainly the tax credits, right, and then the waiver of the PDUFA fees, you know, before you even, you know, get a ruling on or a decision by FDA about approval or not. So these kind of things, I think, are intended to help earlier in the process. BPCA and PREA, really BPCA, you know, gives you extra exclusivity for that product. And I'm not sure how exclusivity works in the devices market, if that's the kind of incentive that would really work for devices.

And, of course, PREA is the requirement. So BPCA doesn't have any tax credits or user fee waivers at all. It's really just you get extra exclusivity attached at the end of whatever exclusivity or patent that you have. So I think that depending, again, the theme being what's the need, what's the problem, what incentive will really work, it could very well be the tax credits and waiver fees and consortia grant money is the way to go in pediatric devices as opposed to, you know, added exclusivity at the end, as we have for drugs.

MR. CHEN: Let me come back to you. I believe we have a question from online.

DR. GOLDBERG: Thanks, Eric.

MS. CHOWDHURY: So there was a question online as specifically what allowed the

sale of the vouchers; why were they able to be sold?

DR. YAO: Well, that's an easy question because the statute says they're allowed to be sold. So sold or transferred.

MR. CHEN: Dr. del Nido.

DR. del NIDO: Yeah, I want to explore that, the concept of the incentive a little bit more, because I think there's important differences between the drug pharmaceutical world and the device. The lifespan of a drug is very different from the lifespan of most devices. And so the incentive kind of tends to be, needs to be, at the front, particularly for small companies.

So maybe I can ask Eliane to comment. You've got a small to medium size entity, an SME. And what would help you the most as far as getting off the ground? Is it 3 months or 6 months of earlier entry into the market? Or is it the actual dollar amount from selling a voucher?

MS. SCHUTTE: Yeah. It's an interesting question. And I think we probably want to see both. But I think the struggle with the SMEs is, indeed, we want to get all those incentives earlier on. It really doesn't help us to bring that, you know, pot of money at the end of the row. I mean, we're already facing the problems earlier on in development. So what would help us most is bringing some, indeed, reduced timelines for reviews, bringing some other type of incentives there, as well as, you know, looking at easier ways to get approvals.

DR. del NIDO: You know, I think for pediatric devices, it's mostly been small, startup companies. I mean, there are very few large device manufacturers that have really delved into the pediatric space. On and off, they have. But I think the incentives are going to have to be totally different.

MR. CHEN: Dr. Pantalos.

DR. PANTALOS: Yeah. George Pantalos from University of Louisville. I have a comment and a question for James.

First of all, thanks to the AAP for being a champion for pediatric devices.

Question, actually two questions: One is in your presentation you used the word both "advocate" and "lobby." Does AAP do one, the other, or both? And how can developers and clinicians become active in your efforts to influence legislation?

MR. BAUMBERGER: Sure, absolutely. Both one and the same, I think. There are legal definitions of lobbying, so we have a number, I think about 10 registered lobbyists on staff. But I think, what we consider what we do advocacy. We're advocating for kids. And all of you can also do the same. So regardless of your own position, you can, in your own personal capacity, talk to your members of Congress about the importance of these programs. If you haven't talked to your member of Congress about the importance of the Pediatric Device Consortia Program, for instance, you can talk to them and encourage them to make that a funding priority every year.

So I would just encourage everybody to get involved, because I think, regardless of what we come up with, you know, maybe there's some big lifts and some small lifts, that in terms of what we want to ask Congress to do, we're overall going to need to come together and be pushing this on Capitol Hill if we want to actually make some progress.

DR. PANTALOS: So in my ignorance, and I'm not familiar with your website, do you have a tab for federal advocacy work and talking points and guidelines, if a piece of legislation is coming up, to help folks who want to go advocate?

MR. BAUMBERGER: Yeah. So one of the key functions that we do is help our members lobby and, you know, advocate for on behalf of children to Congress. So we routinely put together fact sheets and briefs and talking points so that people can have the materials they need to speak with the policymakers about, you know, what's important for

kids. So that's something that we routinely do on a lot of issues, including pediatric device policy as well.

DR. PANTALOS: Thanks very much.

MR. CHEN: Steve.

STEVE: Hi, Eric.

I'd like to go back and explore again the incentives and how these might differ between pharma and device companies. I thought the other questions were and the comments that were made were right on. But even a more important issue is not how this would affect companies that are going after pediatric device development, but the ones that aren't, right. And as we talked about yesterday here, I mean, these are really tough times for device startup companies in getting started raising capital.

I'm in Minneapolis, Saint Paul, you know, which we always thought was a hotbed of medical device development. We do not have one VC doing early stage device investment, not a single one. I don't know what that means in the next 5 to 10 years for the device space and for our ecosystem, but it can't be good. And, you know, I'm afraid we're going to be 5 to 8 years down the line in Minneapolis, going whatever happened to this thriving industry that we had?

And so the question is, as difficult as it is right now to raise capital, what kind of effect would having a legal requirement to also do a pediatric study? That would really, really be difficult. It would make it harder to raise money, raise capital. It may not double your clinical costs, but it's certainly going to increase your clinical costs. It would very interesting, we have a number of representatives from J&J, Medtronic, be interesting from the big companies to see how they would react to this also. But I think the question of incentives is one that needs to be explored in much more detail. I don't believe that a legal requirement can possibly work.

We used to have a number, that 90% of the device companies were under 10 people. I don't think that number is quite that high still, but it's still, you know, it's still small in scale compared to the pharma companies. But what really are the correct incentives to make this happen?

MR. CHEN: Thoughts from the panel, or other folks?

DR. PEIRIS: I just want to say thank you once again. It's always a pleasure when people are setting up our upcoming talks. So, thank you.

The second session for this afternoon will certainly focus on some of the economic issues, including the VC and finance perspective and what types of perhaps novel finance systems could make a difference for both the small companies and the large companies. So I just wanted to point that out.

And I've also had a few requests from people on Webex, if everybody can speak directly into the mics so that everybody could hear clearly, that would be great, because these questions are very valuable. Thank you.

MR. BAUMBERGER: I just have a couple of comments. I think there is a limit, as others have said, to what we can learn from the drug context. I think neither BPCA nor PREA could you take and move to the device context and have that be a successful policy, right. But I think what we can learn from BPCA and PREA is that they work together well as both an incentive and a requirement. I think that has proven as a successful model. I see the points about not wanting to only put additional requirements on device companies without giving them financial incentives, and so I think whatever moves forward, you know, should be a balanced approach and figure out what exactly do we want to do to ensure that companies are, as much as possible, developing devices for kids. And that may be some sort of combination of incentives and possibly requirements, if we can figure out ones that work as well.

DR. YAO: Just one quick comment, and again, I threw this out there to be, you know, to challenge the group and to provide the experience that we've had on the drug side. Any kind of program, whether it's incentive or requirement, related device is going to have to be really carefully considered. And, again, in the context of is this the right strategy to get to the end game, what is the problem, when I hear the problem across, you know, across the room is that we have no devices that are getting approved for children. So how do we do that?

And I've heard, this is an anecdote, so I don't want people to take it too much to heart. But, you know, I've had people from industry come to me and tell me that they're pediatric champions when they're within their own companies. And I get that some of these companies are small enough that there's not even a person who's got one job. They're doing 10 things because it's such a small company.

But in these companies where they have pediatric dedicated folks, they're saying listen, the existence of PREA and BPCA, actually the requirement helps us because we have to tell our, you know, R&D, not our R&D, but our business folks that you can't just ignore this. This is going to be a requirement, so we've got to figure out how this is going to fit into the business plan.

So while I'm not saying at all, suggesting at all that requirement is absolutely the way to go, I'm throwing out that for, hopefully, for some discussion, perhaps here or in the future.

MR. CHEN: Great. And just to add to that, I think we have an upcoming break. And so we'll have a break now, and then we'll have our audience poll at 9:55. And I would encourage folks that we do have a panel discussion in the afternoon, and I hope a lot of you can stay to that because I think that's where we will be able to dive into some of the things that we want to focus on for the next 5 to 10 years.

And so for now we'll break, and then we'll reconvene at 9:55.

(Off the record at 9:40 a.m.)

(On the record at 9:57 a.m.)

MR. CHEN: So we will continue the session that we started today already, the Creating Regulatory Value and Simplicity. And we'll be ready for our audience poll question. So this will be Questions 8 and 9. And so Poll Question Number 8, I'll give you guys time to bring up your phones and go through the app: If you were to develop a medical device, what would motivate or encourage you to develop and test the medical device in the pediatric population?

So give folks a little time to vote on that, and I'll read the responses that we have. Tax credit incentives, expedited regulatory review, guaranteed insurance coverage or reimbursement, post-approval medical device government, reimbursement for development, user fee waiver, regulatory submission review by a pediatric specialist team, no incentives needed, or don't know.

So I'll give folks about 30 seconds to enter your responses, and then we'll go show what you guys voted on.

(Audience poll.)

MR. CHEN: Okay. So as we have our responses here, it appears that for now guaranteed insurance coverage and reimbursement is winning. And then we have expedited regulatory review coming into the second. So I think these will be very interesting results and some of the things that we can also discuss in the afternoon session to see what additional thoughts people may have on how this can be accomplished.

Okay. We can go to, we'll go back to the Question Number 9. So Poll Question Number 9, so folks if you want to into that poll question, it'll be up now: Is clinical testing of medical devices required in adults before pediatric patients? So four answers: yes, no,

no but it should be, or don't know. I'll give you guys about 30 seconds.

(Audience poll.)

MR. CHEN: Okay. So we can bring the responses over. So an overwhelming response of 80% is no, being no, clinical testing of devices should not be required in adults before pediatric patients. So thank you for that.

So the second half of our session, we're going to focus on a little more about what we heard a little earlier today about some international harmonization. So we have Declan Dineen from Medtronic. He's a Senior Regulatory Affairs Director in the Structural Heart Division at Medtronic. He's going to give us a presentation on the importance of international regulation harmonization between the U.S. Food and Drug Administration and the Japanese PMDA agency partnership.

MR. DINEEN: Hi. I want to thank FDA for organizing this important event and allowing me the opportunity to speak.

My name is Declan Dineen. I'm responsible for regulation of our heart valve products in our Medtronic Structural Heart Division. And I was asked to speak on the importance of international regulation harmonization and share some of our experience with the Harmonization by Doing initiative.

That's my conflicts of interest. I am a full-time employee of Medtronic, which I think for the purposes of this audience makes me completely conflicted.

This image was shared yesterday during one of the presentations discussing the evolution of pacemaker development. And this shows the first battery-operated pacemaker, which was a challenge given to our founder, Earl Bakken, by Dr. Walt Lillehei, who's pictured here, after the pacemaker that one of his pediatric patients was connected to failed during a power outage in the University of Minnesota. So Dr. Lillehei challenged Earl Bakken to come up with a pacemaker that was independently powered, and that led to

the foundation of Medtronic.

So treatment of pediatric patients is something that's inherent in our foundation and remains very important to us today. However, as we're hearing throughout this conference, commercialization of pediatric products is very, very challenging. Pediatric patients are typically small, heterogeneous patient populations that are widely dispersed and difficult to accrue in studies, leading to protracted enrollment periods during clinical investigations.

Treatment practices also vary depending on the regions that the clinical evaluation is being conducted in, which leads to complications in developing a uniform protocol that's going to be accepted by global regulatory agencies. Many times, we're developing products to address an unmet medical need; however, the therapies are being held to standards for well-established therapies, which doesn't always make sense.

And perhaps a good example of that is with heart valve products. We're currently required to conduct animal testing to 150 days. However, there is no good animal model to evaluate a transcatheter heart valve, and this typically leads to complications and confounding results that, in essence, are due to the animal model as opposed to generating any useful information on the product itself.

And then, of course, clearing regulatory hurdles is a consistent theme throughout the conference as well. The reality is there is limited alignment amongst global regulators as to what constitutes adequate clinical evidence to support safety and efficacy of a given product. And even within the U.S., there's no clear pathway to PMA, either going the HDE route or going directly the PMA route. And that's something I can give an example of. And then, of course, reimbursement challenges also remains a continuing theme.

So Eliane covered this quite well during her presentation, so I won't repeat it here. But in the structural heart space, we're also focused on treatment of pulmonary valve dysfunction. And perhaps I'll just speak a little bit to the treatment options that are

available today. So the treatment options include watchful waiting, basically doing nothing if the patient is asymptomatic. However, the problem is that many patients are lost to follow-up. North of 70% of patients are lost to follow-up, due to waitful watching.

Surgical options include replacement through a bio-prosthetic valve implant or a conduit repair in 23% of patients or non-conduit surgical repair such as patch repair in 77% of patients. The problem here is that, of course, these patients are growing, so surgical valves have to be replaced as the patient gets bigger. And conduits fail over time. All conduits become stenosed for one reason or another to fibrous tissue ingrowth or other factors. So these patients are going to be subjected to multiple open-heart surgeries through the course of their life, which of course is quite traumatic for the patient, but it's also quite stressful on the family.

So, at Medtronic, we've developed two minimally invasive treatment options for these patient populations. One is the Melody product that's approved in the U.S. And the other one is the Harmony device. And both of these have taken different regulatory pathways. The Melody product was successfully converted from HDE to PMA, and I'll talk about that in a bit more detail. And Harmony was actually the first product that qualified under FDA's early feasibility study program and just last year qualified by Harmonization by Doing for children, which I'll talk about in a bit more detail.

It's important to point out that these minimally invasive treatment options don't necessarily cure the disease, but they hopefully will minimize the number of surgeries the patients have to endure over their lifetime, and patients can recover in a matter of days or weeks as opposed to months, which makes an enormous difference to the patient and to the family.

I'm going to skip over this because it's really already been covered.

So this is the Melody product. So Melody consists of a bovine jugular vein that's

sewn into a platinum iridium frame. It's then compressed onto a delivery catheter and delivered transfemorally. It was actually the world's very first transcatheter valve. So the first transcatheter valve was developed in the pediatric space. The first implant occurred in Paris in 2000, and CE mark followed in 2006 following clinical evaluation in Europe. The first U.S. implant occurred in 2007, and commercialization began with HDE approval in 2010.

After accruing a substantial body of evidence of over 300 patients in clinical studies in the IDE and in European trials, and with support of long-term clinical evidence published through peer-reviewed journals, we were able to work with FDA to have that HDE approval converted to a PMA in 2015. And that really was very important in removing a number of barriers that have been touched on today, including reimbursement barriers, because payers really view HDE as still being experimental because efficacy has not been established.

It also eliminates the burden of IRB approvals and annual PAC meetings, and it also allows us to communicate our clinical efficacy data, which we cannot do under HDE. And that's quite important for uptake of this therapy by new centers, because it's an evidence-driven field, and if physicians can't see the evidence, they're unlikely to uptake the new therapy.

This is the Harmony product, and it differs quite a bit from Melody because this product's implanted into the native anatomy. Melody's implanted into a surgical conduit, so it's got a more uniform implant zone. Harmony has to contend with a wide variety of anatomies in this patient population. And it was an ideal candidate for FDA's early feasibility study.

If you're not familiar with the early feasibility studies, these are typically small-scale studies, typically evaluating 10 to 20 patients. And it's really intended for situations where

safety data cannot be reasonably generated on the bench or in animal models. In the case of Harmony, we wanted to evaluate the boundary conditions that the product is being exposed to so we could ensure structural integrity of the product over the course of time.

But what that allowed us to do then was move from early feasibility to pivotal studies. So after generation of data on 20 patients, the FDA really viewed that data as a very positive dataset. And that allowed us to move into a pivotal study in October of 2016. So we're currently evaluating 40 subjects in the U.S. and Japan, with a primary safety endpoint of freedom from procedure or device-related mortality at 30 days.

And during the course of the pivotal study development and approval, FDA highlighted to us that Harmony could be a good candidate for Harmonization by Doing for children. So if you're not familiar with the Harmonization by Doing effort, it's a cooperative effort between academia, industry, FDA, and PMDA. It's actually been in place since 2003, but the Harmonization by Doing for children is kind of an offshoot of that. And it really focuses on mechanisms to address device lag in both U.S. and Japanese approvals, focusing on solutions for implementation of global clinical trials, etc.

So this is an overview of the Harmonization by Doing experience. The top line gives the experience in the United States, and the bottom line gives the experience in Japan. And just to highlight a few things here, so the U.S. obviously came in ahead of Japan, but the only reason for this is because Japan were not brought to the table until after the pivotal study approval was already in place in the U.S. If we had approached PMDA and FDA at the same time under Harmonization by Doing, those timelines would be closer together.

We moved from a formal consultation meeting with PMDA, where they review all of the available safety data on the product and any available clinical evidence, to formal clinical trial application and approval within a month, which is really, you know, light speed by Japan's standards, compared to our typical experience. So this allowed us to use the

pivotal study design that we had agreed with the FDA to also support eventual commercialization in Japan.

And one of the great advantages of this Harmonization by Doing effort is that it almost allows FDA to act as an independent consultant for Japan, PMDA, because of course FDA have a lot of experience with this product through the early feasibility development and then through the pivotal trial development. And they understand the concerns and questions of regulators, so they can share their perspective on the risk-benefit profile and how they arrived at certain conclusions. And I've no doubt that that really helped facilitate a very efficient process.

So some of the key learnings here, so I guess my challenge to FDA would be is if we can expand the positive experience of the Harmonization by Doing effort to other global regulators, either under IMDRF or under HBD or under some other initiative. As we've seen with PMDA, it's a lot easier for global regulators to buy into a study design if they're at the table at the time of the study design development. And the reason that that's important is that, you know, the CHD is prevalent in many countries across the globe. It's not just a U.S. issue; it's a global issue. And we have an ability to accrue clinical evidence in a much more timely manner if we conduct clinical trials and cast that net wider to include global clinical patients.

It also allows us the opportunity to develop an understanding of global patient populations, treatment practices, training, and treatment options. And the fact of the matter is, is that a global product really presents a long-term, a more viable product from a business perspective and allows for more investment and iteration of the device.

So I'll stop there. Thank you very much.

(Applause.)

MR. CHEN: Thanks for that, Declan.

So we'll move into the next presentation. So we have two presentations from the corporate standpoint, and we'll start with the first one from Bob Kroslowitz. He's the CEO of Berlin Heart. He's going to give us the company perspective that he had, has gone through with his device.

DR. PEIRIS: And, Bob, while you're walking up there, I just want to help encourage all the speakers to speak directly into the mic so everybody online can also hear.

MR. KROSLOWITZ: Sure. Thanks very much. Again, thanks for inviting us to participate in this meeting.

My name again is Bob Kroslowitz. I'm the CEO of Berlin Heart. I've been asked to talk about the regulatory challenges and solutions of getting a pediatric device to market. You'll see we're still in the process, through the regulatory process. We've been at this for some time, but it takes time to bring a Class III pediatric device through the full, through approvals process.

In any case, Berlin Heart is the only company worldwide, for those of you who don't know us, covering all areas of VAD applications for patients with chronic heart disease of every size and age. In the United States we treat only the pediatric population with our device. We're the only company worldwide that has a VAD that is specifically designed and approved for the pediatric population. The device is intended to provide mechanical circulatory support as a bridge to transplant for patients who require circulatory support while they're waiting for an organ to become available.

So the first implant of the device was in 2000. We received, and applied for, HUD designation and had one implant under the compassionate use regulations. Between 2000 and 2004, we had only three implants in the U.S. The company the device is designed or was developed in Berlin, Germany. That's our headquarters, Berlin Heart. And they really had no intention of coming to the U.S. They had no plans to be here until they started

receiving these compassionate use requests.

In 2004 we implanted a patient at Stanford University. The story was placed on the front page of the *New York Times*, and the phone started ringing, ringing, ringing. Between 2000 and 2004 we implanted 30 patients under the compassionate use regulations. And then the FDA came to us and said we need to discuss a way for you guys to get approval of the device here.

So I will be the last person, for those person who know me, to ever take credit for somebody's success, but Eric Chen, I think, between 2003 and 2007 about, worked full time nearly on compassionate use approvals for Berlin Heart. And I don't know if that had anything to do with the success now in the Humanitarian Use Device division, but in any case, we received conditional approval to start an IDE. But it's now probably called an early feasibility study.

In 2007 we had an approval to start with 10 patients at 5 centers. After we enrolled those 10 patients, then we expanded. We had two cohorts of patients. I'll talk about that a little bit longer later. Because we were studying a large group of patients, we split them into two groups based on age or size of the patients and designed the study so that when either cohort was enrolled, we could split them out, get approval for that cohort, and continue studying the other cohort.

We, in 2010, then finished enrollment of Cohort 2. We submitted our application to the FDA in 2011, and they convened a panel. We were granted to HDE approval, with the condition that we conduct a small post-approval study to assess the commercial use of the device.

In 2014 we completed enrollment in the post-approval study. In 2015 we discussed again with, similar to what was just presented from Medtronic, the FDA of converting to a PMA based on the additional data that we had collected in the post-approval study and in

the commercial setting and then received PMA approval. It was granted in 2017, again, with the condition that we do a post-approval surveillance. And that's where we are now. We just finally, in June of this year, settled with the protocol on the FDA, and we are now collecting data on patients for post-approval surveillance.

The initial experience with our device was really quite complicated. The compassionate use regulations required that a patient had to be identified, and the site had to then petition the FDA for approval of use of the device on an individual basis. There were a number of things that had to happen, letters, documents that had to be collected. The IRB, local IRB had to approve. And then the information all had to be sent to the FDA.

This device, our device, we always ran into problems with urgency of the need versus the reality, right. I mean, these were children that were dying, that required circulatory support to be bridged to a transplant and really with not many other options or viable options available. And all of this took time. So what ended up happening is often these compassionate use requests escalated to emergency use, where the centers went ahead and implanted the device without receiving compassionate use approval and then had to notify the FDA within 5 days they had done so.

One of the biggest things that came back to bite us later on with the number of patients that we had done under the compassionate use regulations was that we're not able to collect any data, right. You can't consider compassionate use, emergency use patients research patients. We're not allowed to collect any data on those patients. So we had a whole big group of patients that we had implanted but were not able to use any of the data on those patients in the initial approval process.

The guidance and some of the incentives that are recently available, we were not able to take advantage. However, when we started the study, we were able to take advantage of the, issued in 1995, the FDA's Paper Reduction Act. And this is what we felt

like when we were just starting our study.

In any case, the IDE study design was for HDE approval. We wanted to prove probable benefit of the device and safety of the device. There was really no comparative device for us to compare to. The therapy that was available to these patients before our device was here was ECMO and had really a dismal outcome for patients being bridged to cardiac transplantation, somewhere around 40% or less survival at 20 days.

So, in the end, we had to enroll 24 patients in each cohort, 48 patients based on the size of the patient. However, during the study, we wrote into the study an arm, a compassionate use arm, where we were able to, at the study sites, collect data on patients that were not eligible to be enrolled, who did not meet the inclusion-exclusion criteria. And by the time we finished the IDE study, which required data on 48 patients, we actually were able to present data on 204 patients. And the compassionate use patients served as supporting, a supportive cohort for the HDE approval. In December of 2016 we were finally granted HDE approval of the device.

Yesterday there was a talk on these, Michelle Tarver on the Collaborative Community Initiative, and I tell you, we had a collaborative community before anyone even knew what it was, I think. I can tell you, absolutely, there's no way we would have ever, ever been able to get through this if it wasn't for the support of the medical community and the FDA. We really worked all very effectively together in order to get this done.

So the FDA required a small post-approval study to assess the use of the device in the commercial setting. We had argued with the FDA that we had already done that by enrolling more than 100 patients under the compassionate use regulations, but they still required us to go on, which we did. It was a little challenging. In the IDE study, we had 12 IDE center studies that participated in the trial. We limited the number of centers that we were working with just due to the cost, the nature of the cost, the nature of the study. In

the post-approval study, we had to open it up to all the sites that had been using the device under the compassionate use regulations, which included 23, sorry, 43 centers in North America.

The objective of the post-approval study was to compare to the best outcomes of the IDE study, and also then compare to the adjudicated events, adverse events that we had collected during the IDE study. In the end, the data from the study was published in the *New York Times*, but really, did we make a difference, right? That's what we wanted to know, after we had done all of this. And there was an article that was published by the group in Cincinnati, where they looked at patients supported to transplant before VADs were available, in the pre-VAD era, and then in the post-VAD era, after the advent of the EXCOR Pediatric in the United States, and found that there was a 50% reduction mortality wait list, irrespective of other factors. The patients with our VAD were four times more likely to survive to transplant than patients who did not.

So some of the issues, I mean, we've talked about a lot of these here today and a number of them yesterday. I mean, we're talking about the same things, I think, over and over in the pediatric population. I think these are issues that we're going to continue to deal with. But we had, you know, a diverse group of high-risk patients, right. We included the whole pediatric population, from newborns up to 18 years of age. And dealing with the heterogeneity of the population and the disease and diagnosis, we had some patients with cardiomyopathy, some patients with myocarditis, some patients with congenital heart disease. They were all critically ill children with rare conditions and limited options.

I'm just going to move forward because I'm out of time here.

Again, the lack of comparative and a control group, this was a big issue for us. Initially, we talked to the FDA about a randomized study, and the clinician said, absolutely will not do that. It's not ethical for us to do that with the option that's available. And we

had issues with the lack of pediatric assessment tools. There just aren't, for the exams, neurological exams, quality of life exams, there just aren't tools that were, at the time, available for us to assess these individuals.

So it was a challenge for us. Again, I think the biggest message that I can leave with you is that, you know, work early with the FDA. We really, in the end, were able to find solutions to most of our issues with them and to get the device through the approval process.

Thanks.

(Applause.)

MR. CHEN: Thanks, Bob.

Our next presenter will be Lee Grant. He's a Distinguished Regulatory Affairs Advisor for Medtronic, and he'll be talking about from a larger company perspective.

MR. GRANT: Okay, great. Disclosures, you know that I work for Medtronic Spine. The other disclosure is I'm not a public speaker, and that will become painfully apparent further on in my talk. Also, I'm a user of the Medtronic MiniMed, and I can tell you that another that's not a claim that you'll find in the package insert, that you can actually measure your stress by this because it'll tell you how much your blood sugar is going up. It's really pretty good. So there you go.

So my talk today is about getting pediatric devices to market and the challenges that incur along the way. And to me, the most significant date was September 27th, 2010, not necessarily because it was my wife's birthday, but that was important, but it was also the day that FDA cleared pedicle screws for pediatric AIS patients. And it was the very first pediatric clearance that we'd received for pedicle screws for ILS and idiopathic scoliosis.

And this is how it happened. FDA was participating in a panel discussion in a society in 2009 during which Dr. David Marks, a spinal surgeon from Birmingham, England, initiated

a discussion on the absence of U.S. approvals and clearances for pedicle screws in pediatric patients. He raised the question, how come devices invented in this country, used around the world, used off-label in this country, had never been cleared by the FDA for the patients which they were invented.

So, inspired by that, I looked at more than 300 peer reviewed journals and documented the clinical outcomes of more than 5,000 children treated in the U.S. and around the world with pedicle screws. And based on these published outcomes, the FDA granted us the clearance for pedicle screws for pediatric patients. And it's kind of like what we discussed yesterday in that you provide all the data, and then FDA may give you some but not give you everything. We presented data on all the indications that pedicle screws had. They came back and said, well, we'll give you AIS, but come back for later for others.

And we did that. We came back for fracture repair. We came back for other deformities, to the point where FDA said, okay, we've got enough. You don't have to come back and present us the same articles again and again.

But at the same time that this was going on, if you went to any Scoliosis Research Society meeting or International Congress of Early Onset Scoliosis, you saw other kids that were having more severe problems than the kids with AIS. And the problem that they had was that these were kids, 6, 7, 5 years old, that had 70, 80, 90-degree curves. And fusion wasn't an option for these kids because if you fused the spine, yes, you would correct the curve, but you would also limit their ability for the hearts and lungs to grow. And so you would be basically reducing their mortality.

And so what to do? There was no predicate device. There was no implants that were being made specifically for this population. And so, fortunately, we found out about Dr. Paul Harrington, who had actually created a growth rod system in the 1950s, working with Zimmer. This was not part of a research grant. This was not a custom device. This was

something that he created on his own.

And so through the Harrington Archives at the University of Kansas Medical Center, we were able to show that this was, in fact, a pre-amendment device. And the important thing about pre-amendment devices, they have to be before May of 1976. So think about that. That was 42 years ago. How many surgeons from 1976 are still alive? How many are still practicing? Part of the pre-amendment process is that you have to get affidavits from surgeons that were practicing, showing that these devices were being used in their normal practice. So pre-amendment devices, in the next decade or so, are going to go away because there's going to be no evidence.

But based on that, FDA granted us our very first clearance for traditional growing rods. And I want to thank FDA for that because I remember a Friday night, at 8 o'clock Memphis time, 9 o'clock Maryland time, and I was working interactively with Zane Wyatt, the reviewer. I was working with him all night long just trying to get that thing done. And it was amazing to me that they would do that. But they understood the importance of getting these devices cleared. And I want to thank Mark Melkerson and Dr. Vincent Devlin and Ron Jean for being encouraging and trying to help us do this.

And through that, we were able to get things like the SHILLA Growth Modulation System, because traditional growth rods, you had to lengthen the rod every 6 months. With SHILLA, you didn't have to do that. It was self-lengthening. Ellipse was able to get their MAGEC device, now it's NuVasive MAGEC device, where you use magnets to lengthen the rod. So the technology has come a long way. And thanks to FDA, we've done that.

But there are still challenges ahead. There are still children with AIS that you don't want to fuse. They have small curves between 30 and 60 degrees. So now we're coming to FDA, got a HUD designation for the device that we're trying to get cleared. We're going to come back to them later this year for HDE. But we run into the same problems. What's

going to be, is there going to be a control? Is there going to be some type of cohort required?

Because right now there's two options for these kids: There's bracing, which you think about that, being a 12-year-old girl, being told you have to wear a brace 20 hours a day, going to school with that brace, when you're self-conscious anyway. And so kids don't do it, and they don't want to do it. So you can see here, the average non-monitored brace patient wears the brace between 50% and 65% of the recommended time.

So this is an example of a kid with a 43-degree curve. And now they've been tethered, anterior tethering. There's companies around the world that are creating these devices, Medtronic included, where they go ahead and they fixate the convex out of the curve, that allows the concave side to try to catch up with the convex and correct the deformity as the child grows.

And this is, if I can get this to play, let's see, will it work? Okay. Okay. This Lena, and she's a failed brace patient. And instead of fusion, her mom took her to Canada and had Dr. Steven Pratt do a tether procedure on her. And this is 3 months after her surgery. Instead of doing an 8 to 10-level fusion, they did this tethering, and so she was able to recover faster. And think about that. It's kind of like what we talked about with pedicle screws: going outside the country in order to have a device implanted that was developed inside the country.

And so, you know, Vasum had asked that we bring long-term obstacle or objects to us, and along short-term. And I know that tether is a long-term. We're hoping that FDA will say we don't need a large patient population for this, we do not need long-term follow-up for this, we can do postmarket surveillance. That's what we're hopeful for. But I think there's also low-hanging fruit out there. There's a fracture repair without fusion, something that I've been trying to get cleared now for 10 years. And I first started out with adults, but

now I'm finding that pediatric patients are doing the same thing.

So pedicle screws fall under the regulation 888.3070. They say they serve as a adjunct to fusion. Well, pediatric fracture repair clearance came in 2011. But fusion is not always a desired outcome, particularly with pediatric patients. We have the same obstacle, no predicate devices. Same reality, these patients are being treated all around the world without fusion.

We have the same desire, to create a new product code, just like they did with AIS, the OSH code, for allowing for pedicle screw fixation stabilization for trauma, and remains silent on fusion, because what's happening is, this is a case of a 16-year-old girl in Israel who fell from a great height, had an L2 fracture caused by the fall. Dr. Rabinov went in, built a short construct, used as an internal brace, and then after the fracture had healed, he went back in and removed all the implants. She didn't lose any of her mobility. She has no metal in her body, and she's completely healed.

And that is what we can do right now. Not worried about being an adjunct to fusion. Just concentrate on the words "stabilization" and "fixation," because if you think about it, 888.3070 still says that these are implants are for skeletally mature patients. And these pediatric patients are, of course, not skeletally mature.

And so there's an opportunity, I think, there to massage the language and allow us to make this more available for pediatric patients, which would be very helpful to them and to their parents. And, oh, it's also interesting, if you think about it, the package inserts for these pedicle screws back in the day said that after fusion occurs, they serve no purpose and should be removed. That's exactly what they're doing with these fracture repair cases. They're removing the implants after healing occurs.

So that's all I've got to say, and thank you. I'll give my minute to somebody else.

(Applause.)

MR. CHEN: Thanks for that, Lee.

Our next speaker will be Dr. Chester Koh. He was the co-founder and co-PI of the Southern California Consortium for Technology and Innovation in Pediatrics. He's also at the Texas Children's Heart, Baylor College of Medicine. And he's going to give us a presentation about the Pediatric Device Consortium, its role in the pediatric medical device ecosystem.

DR. KOH: Well, I want to say thank you to Vasum and Eric and to all the organizers at the FDA for this excellent meeting and the opportunity to speak in front of you on behalf of the Consortia.

I think that we all agree that we've seen many positive changes at the FDA recently and hope that you all can join me in advocating to the FDA leadership that the staff should be able to continue to have a high level of support and flexibility, to continue the great work that they're doing, and throw in a raise if you can.

So we've been discussing this public health problem over the past 2 days, or during these 2 days, but I'd like to share a happy story with you, and that really is of the AAP, Congress, the FDA, as well as the pediatric and device communities to work together successfully via the PDC program.

We know that pediatric devices lag adult devices by 10 years, and this is in part due to the inadequate market-based approach. But as noted by James Baumberger today and Mark Del Monte yesterday, advocacy by the AAP Washington, D.C. office, as others, led to the 2007 act that led to the FDA PDC program via P50 grants.

This is a map of past and current consortia, several children's hospitals across the U.S., and the next five consortia who'll be funded over the next 5-year cycle will be announced soon. And they will continue the efforts of the PDC program and work with the orphan products division as well as CDRH to identify strategies that will enhance the

availability of safe and effective medical devices that serve the unique and complex needs of children.

I've had the privilege of starting two consortia. This is one example of the consortia. The Southern California PDC called CTIP was started with university seed funding and joined a children's hospital, the medical school, and an engineering school, as well as multiple stakeholders. And at this point I want to do, send a thank you to Jessica Rousset, Dr. Yaniv Bar-Cohen, and more recently Dr. Juan Espinoza for continuing CTIP after I moved to Texas Children's 5 years ago.

This is another example that was based on the CTIP model, and that's our PDC in Houston. The Southwest PDC is based at Texas Children's and Baylor College of Medicine and includes other Texas medical center partners, Rice, Texas A&M, University of Houston, Fannin Innovation Studio, Biotex, as well as hubs in Dallas, San Antonio, Austin, as well as Phoenix. And we're hopefully building on the long history of device innovation in Houston, especially in the cardiac field where Dr. DeBakey, Dr. Cooley, as well as Dr. Chuck Fraser and Bob Kroslowitz with Berlin Heart.

We even have a pediatric device which is also adult device, Visualase, is out of Biotex and Texas A&M, which is a MRI-safe ablation device for epilepsy that was sold to Medtronic in 2014 for $100 million.

So we are working together with the FDA to assist pediatric innovators. As Mark Del Monte noted yesterday, there are actually over 1,000 pediatric device projects that have been assisted so far, and there are over 25 devices used currently.

There has been continued evolution of the PDC. Each has a unique pathway to help pediatric device innovators. And I anticipate that we'll have, we'll continue to share best practices among us. I've always been an advocate for pediatric surgeons and clinicians. I believe we are an untapped resource. We see the unmet needs and inadequate current

devices in the ORs and the clinics. We eventually also will be the clinical champions for those clinical trials in the real-world data.

It is of note that device development is not learned or experienced by many of us as we go through medical school and through our training. If you're wondering where the pediatric unmet needs are, we had a previous call for needs at Jones LA, and these are the areas; surgery, the ER, the NICU and the PICUs, radiology and diabetes were just some of the areas where there are unmet device needs.

Now, we know that pediatric devices probably have to stay within academics a little bit longer, but there actually are established current academic programs, such as capstone programs, and we published this paper that came out earlier this year, but it's been available online for the past year, where we turned an education program, which were the capstone engineering design programs, we turned it into a prototype development program. Now, these programs exist at every accredited engineering school, and this could take place theoretically at every children's hospital across the nation.

You talk about the funding; how do we move these projects forward? I think that's where the NIH funding, such as the SBIR and the STTR grants, we've formed partnerships within children's hospital and the medical school, the engineering school, and local device development firms for these grants, as these development firms have SBIR expertise. And these are just some of the examples they have worked from the capstone program projects, as well as those that have obtained funding outside of the capstone program.

Now, if you need some help convincing your clinical colleagues, should they spend time in basic science grants, which we all know is definitely still needed to help move medical science forward, but if you're a busy commission, I would say, try to encourage them to think about engineering device projects. There is a mechanism, which are these SBIR, STTR grants, or R43, R44 grants, and you can utilize this when you advocate for them

to spend their time here.

I just want to point out a couple of things. It doesn't require a lot of high startup costs as a big science lab. The pay lines for these grants are much higher than the current ones for basic science grants. And the turnover, in terms of amount of time you need, you can find an answer whether it's going to work or not within a year, instead of 5 years, 10 years.

Now, there are some realities of pediatric device projects, and we know that many ideas will fail. But I think that's a good thing. I think each time around, we're going to have lessons learned to help us with the next project. And we find that the cycles are shorter, that you'll know within a year or two whether you should be spending that time on something else.

I would say that even successful pediatric devices may not be associated with large projects. I think it's well known. I know I'm keeping my day job. But I think there is a different value proposition here, that we have to think that these are mission-based projects in a lot of cases. Our pediatric patients need it. And keep in mind that also we have different customers. And this makes sense, because they're the ones that are going to support it because it's part of their mission.

So, in conclusion, pediatric device development may be challenging, and that's what we've been discussing over the past 2 days, but we know that there are nationwide progress being made via the FDA PDC program. We know that children's hospitals and academics as well as philanthropy do need to play larger roles than they do in the adult devices. And there also needs to be continued coordination among stakeholders. That includes the federal agencies, FDA, NIH, NSF, as well as advocacy groups, industry, professional societies such as AAP, and patient groups, as well as Congress, to keep us moving forward.

And with that, thank you very much.

(Applause.)

MR. CHEN: Thanks, Chester, for that.

So we'll move on to our question and answer session. So, again, folks, if you have questions, please come to the mic, and then as well as those who are on the Webex, please send in your response, or your questions, and we will get to them.

So maybe I'll start off with the first question. I'll gear it towards Bob.

You know, as you noted, being on the pediatric chair lead for AdvaMed, you guys have come up with some ideas on incentives for pediatric device development. Some of the ones you've discussed a little before was, you know, possibly designating pediatric devices for priority review as well as talking about a PEDs team and as well as some of the incentives. I wondered if you could elaborate a little more about your thoughts as to where industry might be seeing some priorities that you would like to see.

MR. KROSLOWITZ: Sure, Eric. I mean, I presented these yesterday in our talk. We think that it would be very useful. I mean, you guys have started with the PEDs team for the extrapolation. I think that's a big step forward. But one of the big challenges we had early on was just trying to have people in the Agency understand really the population that we were dealing with and what was going on with them. And I think that would be tremendously helpful, both to the Agency and to industry, if we could somehow develop a pediatric review team within the FDA that would, you know, when pediatric applications came in, you'd have, you know, specialists in different areas that would be able to review those applications and really understand the population and what the study was about, the device, and what they were trying to get at, I think would be tremendously helpful, both to the Agency and to industry. I think that would solve some problems, and it would certainly cut down on the review time.

MR. CHEN: Okay. Go ahead.

DR. WALL: James Wall from Stanford. This is really for Chester and maybe others from industry.

We've been a huge fan of the PDC program, find it very helpful, early stage, to develop prototypes, as Chester laid out. We've also had some success with similar strategies of using grant funding to kind of keep stuff in university and minimize development costs. But there's a reality you hit at some point where you need a quality system, run a clinical trial. And those things cost a lot more than 50K seed grants, or even the level of SBIR funding.

So there really, you know, I think there is a huge gap there that everyone's identified. You know, the question for you or others is how do we solve that potentially through either financial resources and/or other resources that can help us with commercialization beyond prototyping and testing?

DR. KOH: Right, James. That's a great question. You know, we know that there's a ceiling to the PDC program, so if we're going to advocate for the next round, what to do, I mean, the ceiling should be raised. But I think that's where actually industry can provide the quicker solution, I would hope, that we need to have large amount of fundings for the PDC, or even have a pediatric device consortia graduates program, where it can give out larger amounts.

I mean, I sit on an advisory committee for the Texas Medical Center Venture Fund, and we're giving out 250,000 grants or more. And I think that's where you need to go. The 50,000 early grants are really geared toward early stage projects. And so, it's not surprising that we see a lot of early stage projects. But as we move with those projects forward and if we hope to attract other device projects, we need larger amounts. So we just need to have ways to fund them. So I 100 percent agree with you.

MR. CHEN: Go ahead.

MS. STRASBURGER: Janette Strasburger from Milwaukee.

I had a question for the panel as to what value you saw in the pilot studies, going back and redoing studies for the benefit of having data that is more acceptable to the FDA? And was there value other than that? And, also, how did you fund that?

MR. CHEN: Any of our industry colleagues want to chime in?

MR. DINEEN: So if I could comment, perhaps, on the Harmony early feasibility study that was really pilot phase, we found that extremely valuable from a number of perspectives, and perhaps some of those values weren't initially obvious. In addition to answering the study question that was posed around the structural integrity of the product, we also gathered a large amount of safety data that then supported kind of smooth transition into the pivotal study phase.

But in addition to that, it also allowed FDA to learn more about the product, learn about the data as it became available. And because they were familiar with the product and familiar with the data, I think it really smoothed that transition into the pivotal study phase. It also kept clinical trial sites, you know, primed if you will. We didn't have to go back and train a number of centers on the use of the product for the pivotal study because they were already familiar with it through the early feasibility phase. So I actually think the early feasibility program is an incredible tool at FDA, and I really applaud them for putting it into effect.

MS. STRASBURGER: And you funded that internally then?

MR. DINEEN: Yes. Correct.

MS. STRASBURGER: But you're a large company, though. And how would you advise a small company to do that?

MR. DINEEN: I don't necessarily have the perspective of a smaller device company. I

think the benefits from a regulatory, I mean, we're kind of hearing a consistent theme that in addition to maybe the funding challenges, it's really the regulatory requirements in getting into study and having fast enrollment times or reasonable enrollment times, because the longer that gets dragged out, the more those costs go up. So I think the early feasibility program, at least I think that reduces some of those hurdles and perhaps incentivizes enrollment. At least that's been our experience.

MS. STRASBURGER: And were you able to use those pilot patients in the pivotal trial?

MR. DINEEN: Yes, yes. Yeah. Well, they're not incorporated into the pivotal study, but the data from the early feasibility will count as supportive data towards the PMA application.

MS. STRASBURGER: Thank you.

MR. KROSLOWITZ: Yeah. I mean, we've heard over the last couple of days that, you know, money is an issue, right. Funding is an issue. How do you support these things? We were in a very unique position. We're a privately held company. And we were supported through the whole process and continue to be supported. But that is very uncommon, right. That's not the scenario. And we were able to take advantage of an orphan product grant that's administered through the FDA, division of Humanitarian Use Device.

And that helped some with defray the costs of the study. But, yeah, it's an issue, how to fund these things. I recently was at a VC meeting, and there was a discussion about pediatric devices. And somebody said, don't ever say pediatric device to a VC company. You'll lose them; after that, they won't listen to you. Talk about pediatric and you're done; they don't want to hear you. So it's a challenge.

You know, this is really interesting. Dr. Wearden, who's here, a friend of mine, always reminds me, you know, what happened to us, right. What happened? If you look

back at some of the very early devices that were developed, cardiopulmonary bypass was developed in the 1950s, right, for what? To fix holes in a child's heart. That is what it was developed for, right. It wasn't till the '60s that surgeons realized they could use it for coronary bypass grafting, right. And now it's used every day in almost every single hospital in the United States.

Same things with pacemakers. The first pacemaker was designed for a pediatric patient, not for adults. And, I mean, we were then, right, at that time were able to overcome all these challenges, and these devices were developed for the pediatric population and then extrapolated into the adult population. I think there's tremendous value there that we need to revisit that again. I am convinced, if you can make a device work in a child, it certainly will work in the adult population.

The other way around, we've learned, does not work. It doesn't work to try and take a device, make it smaller and squeeze it into a child. It doesn't work. But to make a pediatric device, prove the technology in the pediatric population and then extrapolate that to the adult population, I think there's great value there.

MS. STRASBURGER: Thank you.

MR. CHEN: Great. Let's go to, we have one online question.

I'll get to Dr. del Nido, I'll have you right after that.

MS. CHOWDHURY: Thanks, Eric. This question was for Chester, but anyone's free to answer: What is the process for involving the PDC for getting moderate-risk devices to market? As was pointed out, most of the commercialization devices were for the low/moderate risk.

DR. KOH: So I guess my answer, as with always, would be it depends. I think each of the consortia have examples of going through that process. And I think it would probably be a good case study for each of them, that each consortia should share how those devices

go through that process. And so that's my short answer.

MR. KROSLOWITZ: I think the burden, you know, for commercial II and commercial III devices is much larger than it is for the lower, you know, Class I devices. And I think that that's, you know, again, you can, I think fund with the PDCs much more in a Class I device, get them a lot further than you probably could with a Class III device.

DR. KOH: Right. And I think, I mean, there are many children's hospitals where you fund it now. I would hopefully envision that every children's hospital has a program like this, hopefully not just dependent on federal funding, that's either funded by the children's hospital, by industry, or a combination. This is something that can happen in every city.

MR. CHEN: We only have time for one more question.

Dr. del Nido.

DR. del NIDO: Just a comment and a question. I'm the PI of the Boston Pediatric Device Consortium, and we've taken a different approach, primarily because we saw the need for some mechanism for Class II and Class III devices, and actually partner with industry, so large corporations actually, to come in and listen to the pitches of the devices that look promising. We preselect them. They actually look at them. They're not interested in all of them. They're interested in probably a small percentage of them. But at least it encourages the inventor to try to bridge that gap, to try to bridge the gap between showing a prototype, that the concept works, the technology looks promising, to an end in mind.

I think that that's, you know, a promising approach because I think government isn't going to be able to get these kinds of devices. It's just too expensive, and it's too high risk. And I wanted to hear your comments on that, because that's a potential separate role for a BPDC to do, or a PDC to do.

MR. KROSLOWITZ: I think that we need to do more to promote the approval of Class

II and III, Class III devices in the pediatric population. Those sort of therapies, right, are the ones that are probably the most often today being used by off-label use devices, right. And if we continue to allow or promote off-label use of devices, or adult devices in the pediatric population, why would anybody do this? Why? Why would you go through this and be in a study for 13 years and do a post-approval study and flip to a PMA? I mean it's just why would you do it?

That's what we need to change, is that we need to sort of really figure out how to get these, and the Class III and II devices, get them approved for the pediatric population.

MR. GRANT: Yeah. I would agree with what Bob said in that for years, you know, physicians were using pedicle screws off-label for peds. I would venture to say that they probably were trained on how to do that in medical school and came out of medical school not even realizing they were off-label for peds. And so we've got to be able to find ways to make pediatric devices available.

And to Bob's earlier comment about making them for children first and then adults later, you know, I think that's important so that our children can become adults, because without these devices, they're not going to be there.

MR. CHEN: Great. I think we've had some good discussions, and I want to encourage folks to continue to have those thoughts as we move into the afternoon session. But the next session we have a public comment section that Dr. Peiris is going to oversee.

So the folks who have registered to provide public comments, I would encourage you to move to the side of the room. That way, when your order comes up, we'll be able to have you guys provide your comments. Thank you.

DR. PEIRIS: Thank you, Eric. I want to just highlight the importance of the public comment period. When we have public meetings of this nature, we certainly do our best to ensure that we are collaborating with a number stakeholders throughout the ecosystem

and have expertise in the areas that we're discussing. It's difficult and challenging sometimes to ensure that there is representation from all perspectives.

The public comment period certainly provides the opportunity for individuals whom we've been unable to connect with or that we were unaware of to actually provide insights to the public meeting and to all of us. So I do appreciate the time that all the public commenters have taken to register and provide their comments.

We'll start with Dr. Peter Armstrong.

DR. ARMSTRONG: Thank you, Vasum. I'm a pediatric orthopedic surgeon. I currently serve as the Chief Medical Officer for OrthoPediatrics and previously served as the Chief Medical Officer for the 22 Shriners Hospitals.

Louis Pasteur once said, "When I look upon a child, I'm filled with admiration for that child, not so much for what it is today as for what it may become." I believe that last part really defined my calling and that my responsibility was to help children with orthopedic disorders and injuries overcome the obstacles and limitations they might have to maximizing their potential. For some children, these obstacles are life threatening. I would hope that everyone in this room, including the regulators, can identify with this calling.

In my capacity as CMO of OrthoPediatrics, I've sat in on interactions with FDA engineers as they conduct their review process for 510(k) approvals. I don't have time to share all my observations, but I will share a few.

I don't think anyone would disagree that industry needs oversight. I understand, as part of that oversight, that elaborate rules and regulations have been created and testing standards developed. However, it is my observation that the rules, regulations, and expectations are not always clear, understandable, and transparent. In fact, it's like guess what I'm thinking. No, no, you didn't get it yet; try again.

The testing standards that are applied are not often clinically relevant. The most

frustrating area is where an innovative device has no available predicate. One device comes to mind that took 10 years to finally get approved. Use of that device now has saved countless children's lives. I shudder when I think of the number of children who died during that 10-year period that could have been saved.

I'll skip this little quote on bureaucracy.

(Laughter.)

DR. ARMSTRONG: In my humble opinion, what we need is a well-structured, collaborative entity in each critical pediatric clinical area that has the following characteristics: led by the FDA but has knowledge experts from clinicians and industries; everyone shares a passion for helping children; the relevant perspective of each is clearly understood; all are clearly focused on quality, safety, and value.

The end result would be a truly informed decision made expediently and efficiently. My strong recommendation is the creation of expert panels in each of the major pediatric disciplines. In other words, have the people who know what they're talking about be involved in the decisions that are being made. We need to remember, for those who will really benefit from this.

Thank you.

(Applause.)

DR. PEIRIS: Thank you very much, Peter. I think we all share the sentiment of clarifying the process forward. We do quite a bit to ensure that the stakeholders have information regarding what's going on. And I appreciate your point significantly. We'll continue to work on ensuring that information is available and our guidance documents are also all available.

So thank you.

Our next public commenter is Tara Federici.

MS. FEDERICI: Thank you, Vasum.

My name is Tara Federici, and I'm the Vice President of Technology and Regulatory Affairs at AdvaMed. I understand my slides are going to be available online, so I'm just going to focus on a few high-level points.

As already noted, we've talked about it a lot already, the primary challenge is that the annual device market, for most pediatric diseases, is not commercially viable. AdvaMed's Pediatric Working Group brainstormed innovative solutions to create incentives and reduce costs by recommending federal tax incentives, coverage and reimbursement during device development, and reducing the burden associated with FDA review while maintaining FDA's strong safety and effectiveness bar.

We've talked a little bit already about that one way to solve this problem might be to create a stick or a requirement that companies must develop pediatric devices. The vast majority of pediatric device companies are very small. Even the large device companies, as my colleagues at large companies will tell me, are comprised of a collection of small device companies. And each of those divisions within a larger company has to be independently viable.

A mandate, even combined with an incentive of one stripe or another, is unlikely to result in successful development of pediatric devices. But it could successfully drive some companies out of business. And when you combine that with the structural issues and the small markets that we've talked about, it's not the right way to go.

I do want to kind of tag onto what Dr. Armstrong just said. We have talked about, at AdvaMed, the need to collect information and prioritize data on unmet pediatric device needs. FDA started this process with its pediatric rare diseases report on unmet device needs, but we think NICHD could facilitate this. I think what we'll find is that some high-priority devices need individualized approaches to determine the appropriate clinical

or surrogate endpoints, and collaborative communities could be the way to address those issues.

In closing, in my 18 years working on pediatric device issues, I've attended many workshops just like this one, and the goal is to somehow address this very challenging problem. What will make this workshop different from others, I believe the answer to that is that everyone in this room has to leave with the objective of advocating for change. The consensus proposals and FDA's report to Congress can be leveraged by all the stakeholders in this room to advocate for real change on behalf of pediatric patients.

Thank you.

(Applause.)

DR. PEIRIS: Thank you very much, Tara. I think you bring up some very important concepts, especially issues regarding the right level or the right balance of incentives and perhaps sticks. Those were things that we certainly need to work on. The bringing in collaboration from our other government partners and other agencies, that can assist here. And as you mentioned very clearly, ensuring that the summary report to Congress that we file from this public meeting includes perspectives from all stakeholders. And perhaps people will have an opportunity to bring their comments that are most important into the docket so that we can take a look at that.

Thank you.

Our next public speaker is Dr. Claudia Hoyen.

DR. HOYEN: Thank you so much for allowing me to join this esteemed group and to all of you who advocate. For those of us who take care of patients each day, I can't tell you how much we appreciate all of your hard work.

I am a practicing pediatrician as well as the Director of Innovation at Rainbow Babies and Children's Hospital. And, actually, our frontline neonatologist asked that I come and

speak on their behalf.

I know that there are many amazing things that this group has been doing in terms of bringing new products to market. But I just wanted to have a gentle reminder that where we struggle most, especially as Chester said, we need more devices in the area of PICU and NICUs, is really with our very smallest patients. So I just wanted to give you a brief example. I figured this would maybe lighten the day as we're heading towards lunch, but just to show you the struggles that we live with each day and to hopefully collaborate as a group and think differently as we are working with different companies, incentivizing them to get to do what we really need them to do, which is to make products in all ranges.

So, my first patient is this is a normal newborn. And oftentimes, oh, sorry. I'm too short.

Thank you, Chester.

So this is a normal newborn. And sometimes normal newborns have things called pneumothoraces, where there is air between their lungs and their chest wall. And what happens is your lung collapses. Depending on how quickly this happens, you may actually arrest and die. But there are things that we can do as clinicians to help our patients.

This is a pediatric chest tube. Imagine it with a metal trocar in it. Having gone through the TSA in Cleveland, they now have a metal trocar for this chest tube.

(Laughter.)

DR. HOYEN: Hadn't thought of that when I wasn't checking my bag. So what we do as clinicians is we put this in, and it needs to go in at least this far. So in a big patient, you can see, it's really fantastic. We're going to be exactly where we need to be. We'll hook this up to suction, and we'll get the air out.

Imagine now, though, that you're born at 25 weeks. You can see that there's a significant size difference. And this is not our smallest patient. At Rainbow, we care for

children who are 22 weeks. So imagine maybe this three-quarters as big. Again, we have a 10 French, and we need to put this chest tube in the baby to get the air out between their lungs and their chest wall.

Now, as we're going in, you can see that we're putting the chest tube in, but we're very near critical organs. And we see complications from misusing or using things off label or using things that are too big for our patients. So my ask to this group is let's think collaboratively, innovatively. How can we get companies that are already making these devices to make them in the right size? I can tell you, we've asked pediatric-specific companies, and they say the market is too small.

So I think if we work together, we'll be able to solve these problems for things that are already on the market and make it safer for all babies.

Thanks.

DR. PEIRIS: Thank you very much, Claudia. I think, as a pediatric cardiologist and somebody who works in intensive care units all the time, I appreciate your advocacy for some of our smallest patients.

Thank you.

Our next speaker is Henri Justino. I believe Henri will be speaking to us from Texas, if the system is set up.

Are we ready?

DR. JUSTINO: Yes. Good morning. Can you hear me?

DR. PEIRIS: Yeah, Henri. Go ahead.

DR. JUSTINO: Wonderful. I think my slides are up? Great. So I'm coming to you to give the perspective of a practicing interventional pediatric cardiologist. I work at Texas Children's Hospital. I'm also a father, but I'm also an entrepreneur. And I've created a startup company to develop heart valves for children. And I'd like to share with you the

journey that we've had so far and the challenges that lie ahead.

So if you can advance to the next slide, please.

So the most common of all birth defects is congenital heart disease, and it's the number one cause of infant mortality in the developed world.

Next slide.

What we're trying to do is help children who have a serious heart problem caused by a defective heart valve. These children need replacement heart valves every few years. And to this day, the most commonly used valve to give to them is a human cadaveric valve. So another child has to die and donate one of their valves for this child to be able to receive a heart valve in the majority of cases, especially for young children.

Next slide.

So this is what we've been working on. This is our polymeric heart valve, made entirely without any human or animal tissues. It's made in any size that we wish. We're already in animal studies, having passed all the benchtop testing. This is now the valve being expanded inside the pulmonary artery of a sheep. And this is an immediately functional valve as soon as the catheter is withdrawn. And then the following day, the sheep is up and about, and that's the kind of recovery we want to be able to provide to children as well.

Next slide.

This is our team, and we've been involved in a variety of competitions, *Shark Tank* style competitions, and have received support from the CTIP.

Next slide.

And that was really instrumental to us. The challenges ahead.

Next click, please.

So we have a Class III device, and it's an implantable device, which is a longer road to

FDA approval because it's a high-risk device. Next point, it's a small market size, and it's therefore less appealing to investors, everything we've already heard.

Next slide.

So what are potential solutions that we would see? Next, pediatric-specific funding opportunity announcements. We received our break through one of these pediatric-specific SBIR, STTR funding opportunities, but those have expired. And now if we want to apply for the next Phase II grant, we need to go through the omnibus application and compete with everyone else. We really need to bring back those pediatric-specific FOAs, and I would love to know if that is something that's in the docket.

Next point.

Expanding the funding of PDCs, Chester mentioned that earlier. The Pediatric Device Consortia need more money to be able to do things that are more than just simple device testing on a benchtop or very small grants, for us to then go to clinical trials, pay for patient costs, freedom to operate search. Licensing even our technology from our academic institutions is incredibly expensive, and we need to have solutions for that.

The next point.

We need to boost incentives for manufacturers to develop pediatric devices. And that should include things like tax incentives, and this was raised yesterday as well. We need to develop other creative funding strategies. For example, in Texas, there was something, and there is still something called CPRIT, which is the Cancer Prevention and Research Institute of Texas. This was created with $3 billion in state bonds that were issued to address an unmet need in cancer research. Why can't we do that at a federal level to treat children with unmet needs?

And then the last point I'd like to make, manufacturers really need to create a pediatric expert panel to review products in their pipelines for any potential pediatric

applications. This was raised yesterday. When a manufacturer comes to the FDA to have a device approved, it is fair for the FDA to be proactive in saying, do you have any potential pediatric applications for this? Can we extend this to children?

But let me give you an example on the next slide of how that may not go far enough. This is a real-life example. Drug-eluting stents are used to treat coronary artery disease in adults. We have discovered that pulmonary vein stenosis is a very serious condition affecting infants, it's a lethal condition, very often. But it seems to also respond to the use of drug-eluting stents.

If a manufacturer comes to the FDA with a new drug-eluting stent for use in adults, even if the FDA is proactive in saying, do you see any potential pediatric applications, they have no idea about pulmonary vein stenosis. It's a completely different disorder that is not even on their radar. And a case in point, a manufacturer recently released a larger diameter drug-eluting stent that could have transformed the treatment of pulmonary vein stenosis in babies. But if you look at the next point.

If you click the next slide, right there.

The very sizes that we would have needed, a 4.5 and a 5 mL diameter stent, they just left out the shortest length out of their portfolio of stents. And that makes all the difference. We cannot use a 12 or a 15 mL stent in most babies. It would stick out way too far into the atrium and be a hazard for future interventions.

So, if a pediatric expert panel existed at every company, so that any device that they are producing, even if they have no idea what other diseases are out there, they would bring this before every panel and say, can you look at this and think outside the box, could this be useful for something else? They would have proactively said, you know what, let's include in the portfolio the shorter length. We'll still set it up as an adult device for coronary artery disease. Maybe that shorter length and those larger diameters will not get

much use. It'll be a relatively less used product in the portfolio, but it's out there, available for trials, available for then approval for children or at least off-label use.

Right now, to then go back and ask the manufacturer to retool their pipeline to manufacture this smaller length device is a big step for them, and it's very hard for them to want to do this at this stage.

Next slide.

This is my final slide. I just want to acknowledge Vasum for really putting this on and driving this very important conversation for these 2 days. And, really, I was in Europe just a couple of months ago at a meeting there, and people are calling this the new FDA. Really, literally, just an acknowledgement of a real awareness of the need to develop devices for children and the greater ease of the pathways that are being put forth by the FDA. So thank you to everyone who works in this area at the FDA.

And I want to thank all the pediatric healthcare workers that are representing this important cause, and the entrepreneurs that are trying very hard to make this work out there, and patients and their families for their willingness to submit to clinical trials and accept the unknowns that we put before them when we, in our best intentions, try to help treat their children.

Thanks for your time.

(Applause.)

DR. PEIRIS: Thank you very much, Henri. I appreciate the work that you continue to do, both as a clinician and as an innovator. And I think you bring up a number of important topics that are certainly worthy of discussion. I'll just address one of the issues that you brought up in terms of expert panels. I think having expertise in any area is definitely beneficial, and you know, I completely understand the concerns regarding pulmonary vein stenosis, especially in our pediatric congenital populations, one of the areas that are very

challenging.

I will mention that in terms of developing expertise, there has been some recent collaborative work with FDA, industry, and academia, specifically with the Pediatric Electrophysiology Society. And they have also offered the option for a panel of experts, pediatric EP experts knowledgeable regarding EP issues, that will be perhaps a standing committee that industry can engage whenever they would like to. So the community certainly is stepping forward, and I appreciate those efforts.

Thank you.

Our next speaker is Dr. Janette Strasburger.

DR. STRASBURGER: Thank you, Dr. Peiris.

I'd like to thank the FDA for allowing me to speak.

(Pause.)

DR. STRASBURGER: I do research in pregnancy, and most of the diseases that we see in pediatrics now are diagnosed prenatally, and many of them, especially in cardiology, are treated prenatally. Sudden death in the fetus or stillbirth is 10 times more common than SIDS and 100 times more common than sudden death in the older child. And yet, at this point, there's not a collaboration that's clearly linking the things that we're bringing forward with this meeting to pregnancy studies, so I'd like to see that happen.

This is just a case of ventricular tachycardia diagnosed in the fetus.

I have some disclosures. My funding is from NIH, and it pays my salary. And I have worked with a number of the IDEs, and we have an active IDE, investigational device exemption, study currently. I have helped with a CPT code and also with SBIR Phase I, II, and fast-track.

So the things that I think would help would be to create a maternal fetal device consortium, or to combine those studies that ultimately benefit the pediatric patient with

this consortium, so to pull in pregnancy studies that ultimately are benefiting the neonatal patient. To establish incentives, again, has been mentioned. Streamline the research, I think there's still a lot to do there, and we have a lot of, you know, non-useful time waste in that area.

And with the NIH funding, the studies we need to look at are the SBIR grants long enough for pediatrics, because it's a much longer time to market in each phase. And then currently, the Phase II-B commercialization grants through NIH require about a third of the funding to come from venture capital or some external source. So that's been very hard, and I know of at least two examples where that's inhibited someone from applying.

The other thing we see is that the record retrieval is extremely difficult in pediatrics, and it's becoming more difficult, even though electronic medical records are present. And it's even more difficult in pregnancy because you have patients that are not even born and assigned a name yet. So that's another area to think about as we move into an area where we're looking at postmarket surveillance.

And, finally, even if we get a marketed device and the device that you saw in the area was marketed; this has a Class II-A indication on the AHA scientific statement. And, yet, as you can see on the top, the CPT code is not covered. It's considered an experimental procedure.

So those are my suggestions. And I would like to thank you for allowing me to speak.

(Applause.)

DR. PEIRIS: Thank you very much, Janette. I want to commend you on bringing up the issue of fetal medicine. As you may know, a lot of my prior clinical work was also in fetal cardiology. The advent of fetal interventions is certainly altering the natural history of pediatric disease, and this is something that certainly all pediatricians and people who work in the clinical community are very cognizant of and certainly something that has come up

for discussion around some of our PDC programs as well. So I think your point is well taken and certainly something for consideration.

With respect to your comment about the SBIR programs, we recognize that there needs to be a bit more connection between grants that are being provided by our other partner agencies like NIH. And we are working with NICHD to ensure a bit more clarity about when and how to appropriately connect with the FDA, especially for funding that is being provided through NIH, because we certainly see that there are a number of great technologies out there that certainly could get some assistance at their voluntary discretion, if they'd like to come and speak with the FDA.

So thank you once again.

Our next speaker is Dr. Victor Gura.

DR. GURA: Thank you, FDA, for letting me be here and speak.

I appreciate the work with the FDA, who's been an incredible group of people that have been extremely supportive in my research, and this is no better time to say thank you to all these incredible people.

I'm a practicing nephrologist at Cedars Sinai in Los Angeles.

Could I have a slide. One back, I think. Yeah, next.

I want to talk about the unmet need in dialyzing children. We're not doing so good. Dialysis in children, one size does not fit all. If you are an adult with 4 to 6 liters of blood in your body on 70 kilos of weight, you can afford to have an extracorporeal blood volume of 250, 300 cc in a large machine. But if you have only 20 kilos in your body, out of which maybe 1 or 2 liters of blood, then you can't afford to have that much blood out of your body into a machine.

And then dialyzing a child with a large machine like you see in the upper quadrant is not an easy task. If you're a little late, you can see in the lower panel on the left, a

Dr. Claudio Ronco in Italy doing the CARPEDIEM for a neonate, which is unheard of anywhere else. But if you have a child at least 7 or 8 years old and he needs chronic hemodialysis, we don't have too much for that. And those children are in need of something that we can dialyze them with.

And since, you know, disease in children is rare, with a prevalence of 8,500 children in the United States and only 1,500 children develop end-stage renal disease, and most of them need hemodialysis.

Well, these slides won't work, and perhaps that's the best.

So dialyzing children on dialysis with end-stage renal disease is a most challenging thing. We've been miniaturizing the dialysis machine, and we converted the 120-, 150-pound device into a bell that weighs 11 pounds. And we dialyze adults with this miniaturized device. They can walk around. The good news about this one is that the blood volume is only 25 cc as opposed to 150 cc, therefore creating an opportunity to dialyze children that otherwise couldn't do it. We made this wearable device work in adults, in Italy, in London, and in Seattle here. It's time to do it for children.

Thank you so much.

(Applause.)

DR. PEIRIS: Thank you, Victor.

As many of you know, kidney disease certainly is a very important healthcare issue across the country. This is probably one of the areas where there's a great deal of healthcare resources invested. And as you mentioned, we don't have fantastic solutions in the pediatric populations. I will once again highlight a program here at the Agency. Our Innovation Division has been working on this and working with our other sister partners in NIH to help catalyze development in renal support and renal placement.

So thank you once again.

Our final speaker is Dr. Matt Maltese, and I will hand the mic to you.

DR. MALTESE: It has been said that if we see further than others, it is because we stand on the shoulders of giants. Dr. Robert (Bob) Campbell passed away just a few weeks ago, on July 29th, 2018. Bob's innovative thought leadership and inventions changed the world's approach to caring for children with complex and life-threatening spine and chest wall deformities. His medical practice attracted children from around the world, many of whom were told that nothing could be done for them.

Bob had an engineering background, and he invented the VEPTR device, taking a customized solution for a single child in desperate need, through the device conceptualization, fabrication, testing, and regulatory path through the FDA. It took 16 years. His invention became the standard of care throughout the world for children with previously untreatable conditions. He traveled worldwide, training surgeons in the use of the VEPTR and assisting them with their most difficult cases.

Many of us in this room owe Bob a debt of gratitude. The picture at the top right is from Dr. Campbell's congressional testimony in 2007. In that testimony Dr. Campbell chronicled the creation of the VEPTR and credits specific champions within the large medical device companies, patient and provider associations, and the FDA, including especially the Orphan Products Development Grant Program, for supporting him.

Bob further testified that the pending legislation at that time that would create the Pediatric Device Consortia Program that we now enjoy, he said in his testimony that Congress should, quote, "support nonprofit consortia to provide critically needed support in helping the innovators with pediatric device ideas to navigate 'the system' successfully and bring new pediatric devices to market." That legislation passed in the House and Senate, and the PDC program we now enjoy was created.

Bob's patients and families know him for his unwavering devotion to their child's

care. Bob will be dearly missed by his friends, his patients, his family, and his colleagues, and he has left a lasting legacy through his ideas, inventions, and the many he trained. Please join me in a moment of silence as we remember Bob Campbell's legacy.

(Pause.)

DR. MALTESE: Thank you for your attention.

(Applause.)

DR. PEIRIS: Thank you very much, Matt. I think all of us can recognize the value of the work that so many before us have done. And we're fortunate to have what has been done before us, and I think the work that is ahead of us is both challenging and great opportunity. And I appreciate all the time and effort people here are putting in to clarifying an improved path forward for pediatric medical device development.

So thank you once again. Thank you once again to all of our public comment speakers. I believe we are now going to adjourn for lunch. And I do want to pose a quick question to the group. It was suggested that perhaps we could shorten our lunch period. We'll do a poll for 30 minutes versus 45 minutes for lunch versus the full hour.

So let's do full hour first. All right. Forty-five minutes? Thirty minutes?

(Laughter.)

DR. PEIRIS: I was going to try to compromise on that one, but it looks like the vast majority of people are at 30 minutes. So perhaps we'll do about 35 minutes if that's okay with everybody.

(Laughter.)

(Whereupon, at 11:31 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:11 p.m.)

DR. PEIRIS: Great. I'm glad everyone's back. Hopefully you had a short but good reprieve and lunch. I know that they're still ringing the chime maybe outside as well, to ensure that everybody knows that we're about ready to get started.

Maybe what we can do is go through our first audience poll question, because I know everybody is excited about that. Why don't we bring that audience poll question up?

So the first poll question for the session is, is there a user fee for premarket applications, PMA, or PMA panel track supplement submissions, if your application is intended solely for pediatric use? So yes, no, or don't know.

Just in case you're wondering again, the relevance here, we're going to be moving into our session that's going to talk about Developing a Supportive Marketplace and the economic and financial issues.

Great. All right. So the answer is, from the majority of people, is about 45% of people don't know. And this is a good topic that hopefully will be addressed during our next panel. And I'll hand it over to Cara to get things started off.

MS. TENENBAUM: Hi, everyone. Can I adjust the mic? Okay. Everyone can hear. All right. Guys, I'm just going to remind you to adjust the mic for your personal height because otherwise folks online can't hear.

So I'm really excited to have this panel on developing a supportive marketplace. We're going to be talking about, you know, the size of the pediatric market. And over the past day and a half, we've heard about the size, that it's small, there isn't a lot of money. We've heard about some of the ways that FDA, often at the direction of Congress, has adopted regulatory practices to help get pediatric products to market. And during this session, we'll talk about existing models for pediatric product development, if they can be

applied to the device space, the models for companies that are developing products, and of course, the reimbursement and payment, which I think folks have already touched on.

And throughout this, and I think continuing our conversation after today, I'm going to challenge a few of the things that I've heard, just the way they're addressed, because I want to focus not just on FDA, which is what we do, right, our part of it, and not just on the companies but, as so many of you have pointed out, on the children and on the value that your products can provide to them, especially as we think about over their lifetime.

And I'll just give you a quick example, to be a little bit provocative, which is I know we've talked about cardiac patients. About 1% of children have a cardiac issue at birth. The average cost and, of course, this is not knowing what the problem is, for a hospital surgery cost for a pediatric patient is about $92,000.

There's a new Fabry disease drug that just got priced today. It's $315,000 a year. The average woman with Fabry disease lives into her 70s, and the average man lives through his 50s. So just when I think about that, I know it's really different, and Gabriel's going to talk about the differences again between drugs and devices. Gabriel is one of our economists here on staff at FDA, and he's been working with us really closely on the device team.

So, Gabriel, if you want to take it away.

MR. MOVSEYSAN: I'm trying to follow your directions. Is this okay? All right.

So I'm here to talk about, you know, in order to develop a supportive marketplace, we need to be able to define it and understand some of the characteristics of it. So let's jump right into some of the numbers. In the United States, the marketplace we can understand, for devices, the number of employees that the industry has is around 356,000. For pharmaceuticals, broadly defined, it's more than double that, 810,000. We see the same number last year in United States, revenues for companies as well, approximately

$140 billion for devices, over $330 billion for drugs.

Where we start to see the stratification of numbers or the differences in the industry are in the number of firms and the types of firms. We see this in the last column, 5,800 device firms and about 1,900 pharmaceutical or drug firms. And we know from our experiences with devices that it's smaller companies that are engaged primarily with the development of these new medical technologies that we're trying to encourage.

In this slide we see, in the United States, the numbers of firms by the number of employees that they have. So these are numbers of establishments, not necessarily number of companies. So these might be one company with numerous manufacturing establishments or business establishments. But you see the difference of how the drug and device landscapes start to form here, where there are many more device establishments that are made up of smaller groupings, okay. So the blue section is fewer than 50 employees, and the purple slice are going to be more than 500 employees.

Some more numbers about the United States marketplace. And what we're going to start to see is that even in spite of those large numbers of firms with small numbers of employees at each establishment, what we're seeing in both drugs and devices are sort of increased market concentration indicators, where both industries are becoming more concentrated, fewer numbers of larger firms.

In 2016 to 2017, you had 8 of the device industry's 61 pure play leaders, by pure play, I mean not conglomerates, so firms that are devoted exclusively to devices, and not devices and drugs and other things. So eight of those top firms bolstered its top line by more than $500 million. And six of those eight firms did that by mergers and acquisitions. So there's a lot of churn happening in the landscape or in the industry, but some of it or a substantial amount of it is being driven by this merger and acquisition behavior.

On the U.S. med techs, and this is something that other speakers have talked about

and we'll be hearing about later on as well concerning the smaller firms, of the med techs that were not profitable, if we just take a snapshot of 2016, 77% of them ended the year with less than 2 years of cash reserves. So we get an understanding of how limited time some of these firms have in order to bring their products potentially to market, or to be acquired or to be merged, etc., whatever outcome they eventually face.

And we know that concentration is not just an issue in the broader industry, but also once we start to get down in the narrow product or narrow therapeutic area, that concentration becomes even more significant, where sometimes there may not be a patent or an exclusivity issue, but there's simply only one or two or three, a small number of firms supplying that drug or that device in particular.

Some more notes on concentration. This is now worldwide numbers for drugs. And we see they track pretty similarly to the U.S. numbers. The largest 25 companies account for about 73% of the 2015 drug sales. And the largest 5 companies worldwide account for about 27% of drug sales. And this is from 2015. So this is an idea about worldwide drug sales.

I'll move on to device firms, and this is a little bit different. So this is the net sales. So this is more an indication of profits for these device firms. This is from a GAO report, Government Accountability Office, from the U.S. Government, and they split up the firms into three different tiers. We see the 30 large-size companies had at least 95% of the total in each year, 95% of profits. The 35 medium-size companies had about 4% of the total net sales. And the rest of the market is left to the 37 small-size companies in that third tier, and we can only imagine what the rest of the firms are left with at that point.

So I will sort of just highlight a couple of other points about the dynamics of the business here. We know from census and from business numbers that entrepreneurial rates or startup rates are generally decreasing in the United States over time. Med tech is

part of this. This is from an AdvaMed report where census numbers back this up as well. And to talk a little bit about drugs and devices, you know, we want to again just try to find as many apples-to-apples comparisons as possible. These markets are sizable, but they're difficult to define, okay, especially once we get into pediatrics.

We know the most products are developed for adults, and so there's a lot of off-label usage. We know that it leads to issues with payer reimbursement processes, which we'll hear about from other speakers. And many drugs and devices simply are not pediatric in nature, so a lot of the data sources that we would otherwise use to try to define these markets or characterize them, we run into a lot of challenges. So that's part of, I think, the conversation here is being able to exchange these bits of information to understand more.

It's hard to even scale what the pediatric device market is. Different analyses and different studies will define the categories differently, so we have a range of analyses that say perhaps this is a $4 billion market, perhaps this is a $30 billion market, the median estimate, somewhere in the range of 8.

A couple of quick notes about pediatric drugs that are interesting to see. In 2010 we have about 264 million prescriptions dispensed to the U.S. pediatric population, which is a lower number from 2002. Over this time, this is generally due to sort of population share, prescriptions to the adult population increased. I have up there some examples of what sort of drug classes are predominant in that decrease and in that increase. Overall, just highlight the bottom number, the estimated pediatric retail pharmaceutical expenditure is estimated to be about $18 billion.

Other speakers will talk more about regulatory experience, so in the interest of time and avoiding overlap, I'm going to skip some of these.

One trend I want to highlight here are trends in pediatric labeling indications. So the

red line at the top is the pediatric labeling changes on existing drugs. So there's an existing drug in the marketplace, and a pediatric labeling change has been added to that drug. So you see the numbers of that over the last several years. Some of this is due to legislative incentives, or much of this is due to legislative incentives, trying to get more pediatric studies. So some of those pediatric clinical studies or postmarketing sort of understanding off-label usage is driving that number.

The blue line at the bottom represents newly approved drugs that have pediatric indications from their newly approved moment. And we see that number is relatively low. The green trend is a number that we talked about yesterday. Those are the PMA devices, device approvals that have pediatric indications. All right. So we know that number is relatively low, or it's not as high as we would like it to be. Missing from here, again, a data issue, are the 510(k)s or other class of approvals that we just don't have enough or reliable data on, so still a work in progress.

And so this sort of raises the question sort of to the economist's perspective of do we want more intensive or extensive growth here? Do we want existing devices to get more pediatric labeling indications? Or do we want new pediatric devices overall? You know, both I suppose, but there's going to be different ways to go about it.

So we think about, you know, how do we get these devices on the market? How do we incentivize people? It makes me think about sort of patents potentially, you know, especially in terms of smaller firms that might have patents. You know, what type of signals of quality are there in the marketplace or in the acquisition or merger behavior?

So this is a report on the number of patents that firms, U.S. firms have, or sorry, patents in the United States that different firms have. I'll highlight the top, you know, this is the top 20. This is very much like a fat-tailed distribution where there are several firms at the top that have most of the patents, or many patents. And then there are many firms

that have somewhere around 50 patents, for example. You see the 50-plus group? Of the firms that have 50-plus patents, the average firm has 200 patents. And then what we also have are 22,000 firms or organizations that have between 1 and 50 patents. So the other end of that tail explodes with just very small numbers.

I'll leave with a couple, just in the interest of time, we'll wrap up a couple of findings from economics literature about what this all means in a very uncertain regulatory environment, or even to the extent that the regulatory environment is certain or there's some understanding of it, firms are still in a constant state of uncertainty when they're trying to innovate.

In a 2017 paper, Stern found that approval times were reduced following the publication of a clear and objective regulatory guidance document. So that decrease in regulatory uncertainty had a direct and corresponding effect on decreased approval time for follow-on devices. And what she also found are significant difference in small firms' entry behavior, that small drug firms were more likely to enter or start a market than small device firms. So that means something as well, that we need to sort of understanding more the differences between drug and device firms and the landscape.

And, finally, one other significant paper talked about, you know, we talked a lot about postmarket surveillance, postmarket learning, and what that might mean. By studying the U.S. and European markets for the same types of devices, Grennan and Town found that post-approval learning, if we could make that more sophisticated, more organized, if it could be as informative and not as costly as the premarket clinical trials, we could have substantial welfare gains from that. They measure it in qualities, which is sort of econ cost-benefit talk for quality adjusted life-years, and manufacturer revenues. So sort of food for thought, like how can we improve that postmarket learning, post-approval learning process? That's DDIs, electronic health records, other speakers will talk about that.

And, fundamentally, the value of medical technology innovation depends on that two-sided aspect, the regulators' requirements for product testing, and the documentation of the products' clinical performance.

Thank you.

(Applause.)

MS. TENENBAUM: Thank you. Next we have Sam Maldonado, from Johnson & Johnson, to talk about some of the incentives that exist in the drug space and whether or not they work in the device space.

DR. MALDONADO: Thank you very much for the invitation to the FDA.

Gabriel, that was really good. When I grow up, I want to be like you.

This is really very new to me, not only the economics, because I'm not an economist, I'm a physician, a pediatrician, but also devices. I actually work and all my career has been in pediatric drug development, and I thought it was hard, until I got today and look at devices. Wow, this is really hard.

BPCA and PREA, and you already know what that is because you heard about it today. And the disclosure is that I'm conflicted. I'm from J&J, one of the largest corporations in healthcare in the United States. And I'm responsible whatever I say, just me, not the company, not my wife, not my friends, nobody else but me.

But I have a very easy task. I was asked BPCA and PREA for devices, the answer is no. I think I don't. That's it. No. Not because BPCA and PREA haven't been very good. They've been very good for pediatric drug development. Dr. Yao presented the results on how drug labels have been modified, and actually had before 1997, there were a lot of disclaimers, not to be used in children, is not approved for children, has not been studied in children. And now 700 labels for drugs have information for pediatrics. But the reason is the patents, the exclusivity in pediatrics relied on the patent. And I've been told by my friends who work

in devices that patents are not enough protection for devices.

So copying these laws for devices, it's just a waste of time. We need a new approach, a new and very different approach. I was also very, very intrigued when I saw the right incentive for the right market. That was a title that was given to me by Vasum. And I said, Vasum, you are an FDA-er; what do you care about the market? And I used to be an FDA-er too, back before BPCA and PREA were enacted as laws, and we were not supposed, as the FDA, to even talk about the market.

So thank you for talking about the market. It's just the reality. And I believe that was one of the successes about BPCA and PREA. They were possible because of an open dialogue, an open dialogue between the American Academy of Pediatrics, whose incentive was to get drugs for children, was an open dialogue that involved pharma, whose incentive was different but also was open to hear about that, and the true incentive became solutions for children. The financial incentive was just a means to that end. And incentives move people. After all, the free market economies like the United States tap into that kind of behavior. It's the incentive.

Now, let me just give you an example of two, just to illustrate the point of incentives. In my company, I witnessed two different groups, two different groups that were developing a drug for prostate cancer. Of course, they can have a waiver from the FDA, and they actually got a waiver. Yeah, prostate cancer doesn't exist in children, so you don't have to do anything in children. But they were looking for a pediatric indication. Why? Because of an incentive. And it makes sense. It was a hormonal drug. It was not a cytotoxic, so it may actually have application for children.

And they were hitting roadblocks, and they were enthusiastic to continue, going back to the drawing board, and why was that? Because of the incentive. They were really after those potential uses in children for these two different drugs. Unfortunately for them,

and for children, it didn't work, not because of the science but a lot of the practicality; the outcomes of research were not defined. But that's what I wanted to see, scientists incentivized to look hard at the science and to look hard at how the possibility to use these drugs that definitely didn't have, were not going to be for the same indication but had an opportunity for children.

And that's what I really wanted to see. And at the end they were disappointed. But I mean, that disappointment, I thought, wow, oh my goodness, clinicians and scientist disappointed because they couldn't find a pediatric indication, that didn't happen before. Now it happens because of the incentives. And the incentives have benefited children when companies are going after pediatric diseases.

Which incentives? Experts in device development and research say that should be part of the discussion, and that discussion should not be adversarial. I know, for example, and I'm a fellow of the American Academy of Pediatrics; I've been for many years. And I know that they, the American Academy of Pediatrics, has a different goal, a different mission than pharma, for example. But pharma, back in the 1990s when America was great, they talked to each other. Now they talk at each other.

I'm not saying the AAP and pharma, but the politicians who actually make the decisions. So maybe we can bring them back to that time. And James actually presented how Senator DeWine and Senator Christopher Dodd came together, from different parties, and were the champions of PREA and BPCA. So we really need to tap into the incentives.

Disagreements should not be polarizing. We should look for solutions. My predecessor in J&J and this group that I lead now, Steve Spielberg, spent most of his career in academia and then last few years went to J&J. And I asked him, why BPCA and how were you able to convince politicians that these laws make sense for children?

And you know what he said? When the American Academy of Pediatrics and pharma

and other groups that typically don't agree in many points come together with the same message, politicians listen. They say, oh, wow, the same message coming from these two disparate organizations who have different missions? And that, he attributes that the success of those laws really had to do with really the mission of both. It was to get better drugs for children.

I've been told also that tax incentives, and we have heard and I know AdvaMed has a proposal on the table that includes tax incentives. Let's talk to the experts. AdvaMed had the expertise. If they know that environment that is challenges, Gabriel just show us a picture of the different incentives. And actually it was, I believe you said that in average it's 8 billion, the profit of some of these, for year. I mean, one drug, Lipitor, and I've never worked for Pfizer, but Lipitor peak sales in 2006, only for one drug and only in the United States, $12.6 billion with a B. There is nothing in devices that comes that close. And this is only one drug.

Now, that company was asked to do a study, mandated under PREA to do study on children with hypercholesterolemia. That's a mandate; that's not an incentive. You know what? They did it. Why? Because the incentive for them was to comply because they had something bigger to protect. So when you have mandates under PREA, you should be cognizant that these mandates actually sometimes actually act like incentives. We're going to protect this baby that is producing $12 billion for us. And if the FDA wants us to do a pediatric hypercholesterolemia study, as hard as it can be, we're just going to do it to keep us in business. That's different than in devices, I understand now.

So, and for those critics, don't be afraid. Industry's not going to run amok and it'll do whatever they want. That's what many critics said back in the 1990s because they asked, after all, the FDA actually is the one that issues a written request. The written request comes from the FDA to pharma, and it tells how many studies you're going to do, how many

patients you're going to include, what are the endpoints that the FDA wants to see, and what is the time that you should have for delivery.

So it's all mandated by the FDA, and that's appropriately so. It protects children, but it also protects the companies, because when you embark in the study, you know that's exactly what the FDA wants, what is in the written request.

So my concluded remarks is the BPCA are not the right model for pediatric device development. Incentives, again incentives go further than any other instrument, including mandates. But true incentive really is to produce value for children. Tax, other financial incentives should be seriously considered, and let's work in a spirit of collaboration, all the parties.

Thank you very much.

(Applause.)

MS. TENENBAUM: Thank you.

Next we'll have Andrew Lo from MIT to talk about financial strategies for small and large companies, talking about the economics here. Thank you.

DR. LO: So I'd like to start by thanking Vasum for inviting me to participate in this gathering and to begin with a disclaimer that I am not a healthcare economist, nor do I have any great familiarity with the topic of the day, which is pediatric devices. I've gotten interested in healthcare finance over the course of the last few years, really for personal reasons, a number of friends and family dealing with various kinds of ailments, including cancer and other challenges. And it was really through that process that I began to learn a little bit more about what many of you have understood for the last several decades in terms of challenges to funding and economic development in this field.

Over the course of the last few weeks though, I've spent a lot of time reading the literature on pediatric devices and speaking with Vasum, Mary Clare, Gabriel, and others,

and I've learned a great deal. And my conclusion is, wow, this is really challenging. There's a lot of issues that need to be addressed. And what I'd like to do is just to spend my few minutes talking a bit about my perspectives on how some of these challenges might be dealt with by certain kinds of financial considerations.

So I'd like to begin with an observation that I've made as an outsider to the industry, which is that biomedicine is currently at an inflection point. And how do I know this? Well, I know this because my MIT colleagues told me this, people like Susan Hockfield, Phil Sharp, and Tyler Jacks. They published a report a couple of years ago titled *The Convergence of the Life Sciences, Physical Sciences, and Engineering*. And what they're referring to is the fact that the confluence of breakthroughs in a lot of different fields are now finally coming together to produce some really extraordinary breakthrough therapies, genomics, epigenomics, transcriptomics; all of the omics has really changed the way we think about dealing with various kinds of diseases.

But the one omics that was left out of this list, and the one that I think is severely challenging innovation in parts of this field, is economics, the ability to fund a lot of these ideas and bring them from the laboratory into the clinic. And so I'd like to spend a little bit of time talking about that and then follow up with some observations that really echo what Dr. Maldonado said about incentives.

So it turns out that devices pose unique challenges, and I want to just describe a very simple case that I read about just a few months ago. There's a device called a Codman pump, which is a device that's the size of a hockey puck that is installed in the abdomen of liver cancer patients, and it basically provides continuous infusion of chemotherapy directly to the liver. And according to doctors at Memorial Sloan Kettering, this device is, more than any other treatment, the best way to extend a liver cancer patient's life, in some cases by years and decades.

On April the 25th of this year, Cerenovus, the subsidiary of J&J, announced that they were discontinuing this Codman pump. And, of course, Memorial Sloan Kettering raised hell about this because cancer patients are dying, and they need this device. And so I didn't quite understand what was going on about this device. I thought, well, you know, maybe it's really not as useful as we thought. But the more I read about it, the more puzzled I became, because there's no doubt that this is not only safe and effective, but it's also reasonable and necessary. It satisfies all the criteria, and yet it was being discontinued. It was being taken off the market.

And so then I looked a little bit deeper, and I didn't speak to anybody at J&J. I don't know anything about what J&J's going through, but the one thing that I was actually surprised by is the price of this device. Does anybody know how much this device costs? Before you answer, by way of comparison, a 1-year supply of Gleevec, the drug that Novartis put out for dealing with chronic myelogenous leukemia, a 1-year supply of Gleevec is about $100,000. And you have to take that as long as you are alive.

This is a one-time purchase of this device. How much does this cost? Anybody want guess? 100,000? 50,000? Try $5,000. Now, the reason that was given for the discontinuation of the device is that certain components for the device are not available. And, you know, in this day and age, it's kind of hard for me to understand that. So I just did a quick back-of-the-envelope calculation, tried to understand what goes into the device. And the thought experiment was suppose this device cost 50,000 instead of 5,000. Do you think that maybe the components would become available now?

And so this gets back to this idea about incentives and, you know, what we can do to think about how to deal with these challenges. Now, again, not pointing any fingers. As an outsider to the industry, I have no idea what the various myriad factors are that go into these kind of decisions. But clearly price and viability, economic viability have something to

do with it.

So I want to just show one more slide and then wrap up, and this has to do with how I think about various different kinds of incentives. It has to do with risk and reward. And to get this point across, I'd like to stop thinking about biomedicine and focus on something that I know best, which is financial investments. I'd like to show you four different financial investments and simply ask you to comment on which one of these four you would like to have to invest your retirement wealth, your kids' college fund, your parents' savings, if you had to make a decision and pick one of these four investments.

I'm not going to tell you what they are or even over what time period they span. I'm simply going to show you what happens if you put a dollar in each of these four investments and hold it for this multi-year investment period.

So, by a show of hands, how many of you would prefer the green line, which turns a dollar into 2 dollars over this multi-year investment horizon, not particularly rewarding, but not a lot of fluctuation? It's not a lot of risk. Anybody want the green line to invest their retirement funds? Oh, okay. We got one person.

How about the red line? The red line is quite a bit more risky. It turns a dollar into about 5, but with a lot more ups and downs, more volatility, more risk. How many people would prefer the red line? A few more. I want you to remember this moment because when I tell you what the red line is later, you're going to need some rethinking here, to rebalance your portfolio.

(Laughter.)

DR. LO: How about the blue line, which is a way more risky investment? It turns a dollar into about 8 dollars, but with lots more volatility. How many people prefer that? We've got the hedge fund managers and the surgeons in the audience.

(Laughter.)

DR. LO: And finally the black line, which is somewhere in between. It turns a dollar into about 7, but with not a lot of volatility. How many people prefer the black line? Yeah. That is by far the most popular choice because it's a compromise between risk and reward.

Well, let me tell you what you all picked. First of all, the time period is between 1990 and 2008. That's where the graph goes. And the green line is U.S. Treasury bills, safest asset in the world but not a lot of return. The red line is the U.S. stock market, the S&P 500, more volatile but more rewarding. Most of you own the S&P 500 in your retirement portfolio. So if you didn't raise your hand, you may want to go back and look at your investments again.

The blue line is the single company Pfizer. Much more risky, but actually more rewarding. And I should tell you what happens afterwards. This is what happened since 2008, and you would have done quite well, especially with Pfizer.

What about the black line that is the most popular? Most of you picked that. Well, it turns out that this black line is the returns to the Bernie Madoff Ponzi scheme.

(Laughter.)

DR. LO: And that's why I had to stop it in 2008. Now, you know how the Ponzi scheme got as big as it did. It's human nature. We are all attracted to high-yielding, low-risk investments, like a moth to a flame in some cases. Financial economists have a term for it. They call it the Sharpe ratio. And the Sharpe ratio is basically the average return above and beyond the risk-free rate, divided by the standard deviation of the risk. We are drawn to high Sharpe ratio investments. The S&P 500 has a Sharpe ratio of 0.34. The S&P 500 has a Sharpe ratio of 0.33. The Bernie Madoff Ponzi scheme, which ultimately blew up, before it blew up, it had a Sharpe ratio of 3.

This is the answer to how we reinvigorate the market for pediatric devices. If you can come up with methods to increase the return, or more likely, reduce the risk, you will

be able to draw more capital into these markets. And in the slides that I'm not going to go through, the rest of the slides you can have a copy of, I go through examples of various different methods for how you go about increasing that Sharpe ratio. And there are existing business models out there right now that do that.

So, you know, instead of focusing on trying to declare war on cancer or pediatric device diseases, what we ought to do is to create incentives for being able to get more money into this industry. With the cooperation and collaboration of everybody in the audience, I believe that we can actually do that.

Thank you.

(Applause.)

MS. TENENBAUM: Thank you.

And lastly for this panel, we have Bob McDonough from Aetna to talk about what insurance companies or at least his insurance company takes into account when deciding what to cover.

DR. McDONOUGH: Thank you.

I'm Bob McDonough. I'm Senior Director for Clinical Policy Research and Development for Aetna.

Many of you are familiar with Aetna. It's a commercial insurer, has operations in all 50 states and the District of Columbia. We also have Medicare Advantage plans, Medicaid plans, and it's one of the large national insurers. So I'm bringing the perspective of a large commercial insurer.

I'd like to talk about the issues: first the goals and clinical policy within a commercial insurer, what criteria that we use to evaluate pediatric medical devices and other types of technologies, the clinical policy development process. Relevant to today's topic, what's the relationship between clinical policy at a commercial insurer and the FDA approvals? And

then the process for assessing cost impact to clinical policies, as part of that, just, you know, what is the role of costs and comparative costs when making decisions about coverage?

I'm head of the Clinical Policy Unit, which at Aetna we are responsible for those standard terms that appear in benefit plans. Services that are medically necessary are eligible for coverage. And then those services that are either experimental, investigational, or sometimes the word "unproven" is used, are an exclusion from coverage.

So we actually have what we call clinical policy bulletins. Over 750 right now are posted on our website under the medical benefit plan, and that does not include policies that deal with drugs that are covered under the pharmacy benefit.

The goal of developing policies is to have an objective basis for coverage determinations, to have them clinically supported. So each of these policies, we call them clinical policy bulletins; other payers may call them med tech documents or medical policies, is to have an objective, clinically supported, and defensible determination. So the intent is to increase the transparency. The intent is to create an objective basis for an ongoing discussion, to ensure that these policies are appropriate and accurate.

The important thing, also, to note about these clinical policy bulletins, or CPBs, is that, first off, the benefit plan provisions determine coverage. So you also have to take into account the services, the other plan provisions that describe things like copayments, deductibles, schedule of benefits, you know, what services are covered, what are not covered. Some benefit plans may exclude certain things. They may have different coverage for drugs as for devices, that are specified within the terms of the benefit plan.

Also, I had mentioned, Aetna does have business in some states that we are administering the Medicaid plans. Typically, for Medicaid plans, they apply what is called MCG guidelines. This used to be known as Milliman Care Guidelines. And that may supersede the clinical policy bulletins that Aetna creates to the extent that there is a MCG

guideline.

For Medicare Advantage plans, the rule is that we have to follow Medicare policy where it exists, so where there's an applicable national coverage determination or an applicable local coverage determination applicable to the member, that would supersede the terms of a clinical policy bulletin. And then, of course, there are state mandates, so where the state mandates apply, those would supersede the terms of any clinical policy bulletin.

These are the criteria that payers apply, and you may recognize these as the Blue Cross Blue Shield Association tech criteria. These are the standard criteria that payers will consider when evaluating any type of medical technology, be it a device or drug or other types of technologies, like procedures and other services.

So the first criterion I'm going to talk a little more in detail about this in the next slide is that the technology must have a final approval from the appropriate government bodies. And so most benefit plans have, in terms of their experimental investigational definition, some reference to regulatory approval where it applies.

The second criterion is that the scientific evidence must permit conclusions concerning the effect of the technology on health outcomes. And so what that gets to is the importance of having peer reviewed, published medical literature to demonstrate the safety, efficacy, and effectiveness of the service and its impact on health outcomes. The focus on health outcomes is outcomes that are important to patients. And so payers place more emphasis on outcomes that will matter to patients as opposed to intermediate outcomes, which may have a more indirect relationship to things that are important.

The third criterion is that the technology must improve the net health outcome. So we take into account the risks and the benefits of the service to determine whether, in fact, it is net benefit to the patient.

The fourth criterion, the technology must be as beneficial as any established alternatives. And this brings in the concept of comparative effectiveness. So it's not merely that the technology may have a physiologic impact on some type of parameter, or that it has a impact that's better than placebo, but it's really looking at the technology being as beneficial as the best standard of care.

And then the final criterion is that it must be obtainable outside of the investigational settings. And that really goes to not merely the efficacy but the effectiveness in clinical practice.

In terms of the relationship of clinical policy to FDA clearance, this I think is the important thing, is that although something has to have an approval where approval is required, we will consider other indications, sort of off-label indications for the technology. So we don't consider off-label use inherently unsafe or ineffective, that we will consider the scientific evidence for services that are available and approved.

As far as priority requests, we don't create policies on everything. It really has to do with whether there are recurrent issues, themes, whether it's something important to our members. We look at guidelines, consensus statements, and changes in regulatory status, maybe the factor in terms of creating a change to the policy.

We have a process for drafting clinical policy bulletins, and that focuses on evidence in the peer reviewed, published medical literature, as well as assessing the regulatory status, the status with CMS and FDA. We review guidelines, etc. Guidelines and consensus statements are considered according to the quality of the scientific evidence and supporting rationale.

We have a process, and the process is the same regardless of the type of technology for services that are covered under the medical benefit. We draft a clinical policy bulletin. We have a Clinical Policy Council, composed of physicians and pharmacists, that reviews

and approves these policies. It then goes through a process where it is reviewed by our chief medical officer and implemented, and then it gets posted on the internet. We review our policies annually, or more accurately each calendar year, to ensure that they are up to date.

We have a limited analysis of cost, and that is really to be able to, once the policy determination is made, we want to be able, as an insurance company, to be able to predict the impact of these technologies, so we actually do have, in some cases, we select a subset of these policies for a formal, what's called a cost analysis. Now, there's no cost effectiveness threshold, like in some other countries where something isn't covered simply because it's, you know, doesn't meet a cost effectiveness threshold, but we do look at the cost for underwriting and pricing, etc.

We reach out to specialty societies, and we have input from members, providers, manufacturers. We comply with the regulations of all 50 states' Department of Labor. And so I think that this gives you sort of an overview of pediatric medical device and how we consider them within a commercial plan.

Thank you.

(Applause.)

MS. TENENBAUM: Thank you.

And with that, we'll take questions. As always, any of the three mics, and if you're online, you can submit a question that way. And I think if you're not online, you can submit a question through the app, right, Vasum? Okay. Yes.

Okay. Fight it out.

DR. BALDWIN: All right. So I'm Tim Baldwin from NHLBI, NIH, and FDA some days.

So I'm going to speak somewhat not hypothetically. We have an investigational device for pediatric use. It's expensive. The bottom line question I have is who should pay

for it in an investigational study? And the only unacceptable answer is not me.

MS. TENENBAUM: Anybody want to take a crack? Okay.

Go ahead, Andrew. Just press the red button.

DR. LO: So just a point in clarification, when you say who should pay for it, for the clinical trials?

DR. BALDWIN: For the clinical trial, yeah. And imagine also that it's being, the device is being made by a small company that doesn't have deep pockets.

DR. LO: Yeah. So let me first ask to change the terminology. Instead of who should pay for it, because "should" is a very loaded term and it depends on who you are and where you stand to be able to figure out what that term means, let me change the question to who could pay for it. And I'll tell you who could pay for it. Investors can pay for it. The private sector can pay for it, but only if they're going to get a reasonable rate of return.

Now, how do you get a reasonable rate of return? Well, I think the answer is, based on my presentation of the Sharpe ratio, what we need to do is to figure out a way to reduce the risk and/or increase the reward for that investment. Increasing the reward is pretty simple although controversial; raise the price. Price it where the market will bear. If we care about outcomes, price it according to value added. Look at ICER or any other organizations and ask the question, how many years of quality-adjusted life are you providing, and price it according to that. That's one component.

But I think a bigger and more immediate and less controversial, less politically loaded component is let's reduce the risk. And the way to reduce the risk is instead of doing one at a time, take a large portfolio of these pediatric devices and combine them, and then get investors to invest not in one or two but in the entire portfolio.

DR. BALDWIN: Great. Thank you.

Any other? I was wondering if there was more than one opinion about this.

DR. MALDONADO: Just to remind people that actually vaccines had to do that. Remember that vaccine companies were leaving the market because of the risk of being sued because of all these other things that were being associated with vaccines. So they did it through legislation; basically, you cannot sue a vaccine company because your child had autism, because the greater good, it's so they reduced the risk.

But then Wyatt, that now no longer exists, came with Prevnar, the vaccine Prevnar. That was the first vaccine that was priced very high, at a different, much different price than the rest of the vaccines. They actually changed the price, not only for Prevnar; they changed the price for all the other vaccines that came after Prevnar because then they realized, wow, we're not charging, the vaccines, the real value. So that's exactly what you said. They changed both, the risk and the up at the same time.

DR. BALDWIN: Thank you.

MS. TENENBAUM: Sure. We need to figure out what the cost of not getting measles is, right?

Let's do this one, and then we have an online question.

DR. GURA: Okay. Dr. Lo, thank you for a wonderful presentation.

I'm a practicing nephrologist in Cedars Sinai, and I was touched by the example you gave. In my field there is another one. If you need dialysis, you need 40 gallons of fresh water. If you don't have 40 gallons of fresh water, you don't get dialysis, then you're dead.

Until the late '90s, there was a machine that did dialysis with 6 liters. It was used for years. It didn't make business sense. The company that bought that enterprise closed it down, and for the last 18, 20 years, there's no such machine. Imagine what did happen in Puerto Rico if you needed 40 gallons of water to get dialysis and what happened to the guys that didn't get it. That sort of a comment applied to what you just gave in another field.

And the question that I know who couldn't answer, from the FDA folks, is why can a

pharma, a product that will help a kid get a voucher, but a device that will help the kid with an orphan disease not get a voucher?

MS. TENENBAUM: I think the answer is the law, right. So, I mean, Vasum, you want to go into some more detail?

DR. PEIRIS: No. I think that's a very provocative question and certainly the type of questions that we're attempting to address today. And the reason that we brought into the conversation issues regarding the history on BPCA and PREA and how that has influenced the development of the pediatric drug market is to, as we very clearly put in both Dr. Lynne Yao's statements and Dr. Maldonado's statements, whether those types of incentives should be transferred to the pediatric device market, understanding very clearly that these markets are very different.

And if those incentives shouldn't be transferred, then what types of incentives will work for this market? Thus that question, you have the right incentives for the right market. So this is part of the conversation that needs to happen and that is happening, and hopefully things that we can clarify.

MS. TENENBAUM: Right. I think you need to question not why, but would they work, and then if they would work, then let's talk about doing it. Right. And we don't, that's what we're discussing here, and that's the beginning of it.

DR. PEIRIS: Yeah.

MS. TENENBAUM: The conversation.

DR. PEIRIS: Again, this is the beginning of that conversation. We need to clarify what will work for this market.

MS. TENENBAUM: So, Brittany, we had an online question?

MS. CALDWELL: Yes. The question is how does Aetna become aware of emerging technology trends, and how do device manufacturers go about advocating for coverage if

there is lacking sufficient evidence due to small *n* in pediatric trials?

DR. McDONOUGH: Well, there are a number of different ways that we become aware of products and services, pediatric medical devices and others. In some cases the manufacturer may come directly to us at the time that they have FDA clearance or approval. But with a large insurance company, often the context may be in some type of a request for coverage of the device once it becomes available. We also have a process to look at products that are in development where we have a separate unit within Aetna that looks at a horizon scanning, so that we have insight into a subset of devices that are important.

So the type of information that we would want to have is we can look at the basic data that's been developed. It may be developed in the context of the adults. Ideally, we would want to have development of data that provides information about its use in pediatrics. So it is possible that a device that is labeled for an adult, to the extent that there is scientific evidence and logic about its application in children, that we would extend coverage to children.

And so if the manufacturers develop that kind of data, they can present it to Aetna, you know, through either the Clinical Policy Unit, would be the group that would, to the extent that there's a policy that may directly apply to that technology, and then we would go through the process to evaluate that information that I've described in my presentation.

MS. TENENBAUM: And FDA is working on some efforts as well. You know, one of the things we heard, and I'm sorry that nobody from Medicaid could be here, is that with the introduction of Sovaldi, for example, that really ruined their budgets. And a lot of states have balanced budgets amendments. And so the Medicaid programs had to pay for Sovaldi, and that meant they had to move money away. And so what they wanted to know was when there are technologies coming down the pipeline, can payers get a heads up?

So that's something we've worked on, and we work with CMS on the Medicare side

for some parallel review products.

Skip, I know you've been waiting. Let's do this last question.

DR. NELSON: Yeah. I'd like to give you an opportunity to expand on the concept of final approval and just to put together a couple of thoughts. Over the last day, I've heard some comments about let's have the pre-approval process more streamlined, and then put some other more, let's say robust evaluations of safety and efficacy into the post-approval space, which sounds similar in the device space to the drug space's idea of an accelerated approval.

Well, accelerated approval has been controversial in some areas. Eteplirsen would be a good example, where it was given accelerated approval and very expensive, $300,000 I believe, and decisions around coverage were variable, to my understanding. I'm not asking what Aetna thinks about that particular drug, but I'm just pointing out that it's not clear to me that an accelerated approval on the drug side meets the final approval.

And so I'm just curious how one would respond to at least that proposal to put more of the work into the post-approval space with the hope that it would be reimbursed, as one of the earlier audience questions says that reimbursement was, in fact, one of the main drivers. So I'd just like to hear some thoughts on that, final approval versus accelerated approval or moving things into the post-approval space for more data, etc.

DR. McDONOUGH: Well, right. The FDA approval and insurance coverage are not always exactly the same. And so there is a risk with accelerated approval and that would be more applicable to drugs because most medical devices don't actually go through a full approval process, they go through a marketing clearance. So that it's very frequent that these devices get on the market with very little data. And so what payers will do is they would look at marketing clearance as a threshold, but they would have an expectation that there would be enough data, reasonable data to be able to reach conclusions about the

efficacy and its impact on outcomes.

And so to the extent that a device would actually have to go through a full PMA, I think it may be appealing to have accelerated approval, but the payers are still going to want to have at least sufficient evidence. It may not be the type of evidence that necessarily would qualify for a full FDA approval, but enough evidence that we can reach conclusions about its effect on health outcomes. And it also has to be taken into context of the particular clinical scenario, what other alternatives are available, what is the best standard of care, and what types of data do we have that this new intervention improves over best standard of care?

MS. TENENBAUM: It looks like Doug has an answer on this too.

DR. SILVERSTEIN: I have a question for Bob McDonough, but also I guess I'll open it up to the whole panel.

So here at the FDA, we do have some pediatricians who are reviewers, but we don't have an abundance of them. And I think we would all agree here that we would love to see more pediatricians as reviewers. I guess, from your perspective, if you're reviewing a coverage application for a device that has been approved or cleared or whatever the process was by the FDA, does it lend any more credibility if you have pediatric expertise at the FDA that has been involved in that review process?

DR. McDONOUGH: I think it would. Oftentimes we're not completely aware of the individuals at the FDA that might have gotten involved in the actual approval process. But to the extent that having pediatricians involved in that process to ensure that the studies are appropriately designed to answer the questions about the efficacy of a particular technology in a pediatric population, I think that would be beneficial.

DR. SILVERSTEIN: It would be beneficial. Okay, thank you.

MS. TENENBAUM: Okay, last comment?

DR. PEIRIS: So, one comment and one question. The comment is for Andrew.

So thank you, number one, for giving the talk, especially on some short notice, and for taking time away from your family's vacation. Part of the reason that I invited you here is exactly to help manage my retirement fund, so I appreciate what you said.

(Laughter.)

DR. PEIRIS: I did want to give you maybe a few minutes. I know you had to flip through some of the other additional slides that you had, and there are probably some concepts that are probably very helpful to this audience, if you would either like to maybe take that time now to go through them, address the concepts, or we can do it during the panel, whichever you feel comfortable with.

DR. LO: I'll just take maybe a couple of minutes now, very quickly, to just mention that there are some new business models that are emerging for how we can actually reduce the risk and increase the reward to these kinds of investments. And probably the one that would be most relevant for pediatric devices is similar to a paper that we had published a few months ago in *Science Translational Medicine* about, or sorry, in the *JAMA Oncology* about pediatric oncology drugs.

The idea there is to use a public-private partnership, where either philanthropic organizations or government agencies or some combination can provide resources to take ideas out of the laboratory into the clinic, so preclinical kinds of R&D funding. And then coupled with that is a for-profit fund that would actually take the ideas and commercialize them, bring them all the way to, you know, Phase III and FDA approval.

So this partnership between the public sector, meaning not just government but also philanthropic organizations, this term "venture philanthropy" has also been thrown around, that kind of combination can work very well with the private sector because the private sector views the public sector as providing some very valuable resources to be able to get

ideas to the point where they have real commercial potential, reduces the risk, increases the reward.

So there are a number of examples that are in my slides and also in some of the publications that we cite. And so I think that that could actually be a very promising avenue for pediatric devices, to be able to try to reduce that risk and increase the reward to potential investors. But the private sector is ready and able and willing to be able to make these investments, but we need to find the right structure to do that.

DR. PEIRIS: Thank you, Andrew.

And, Cara, if you don't mind, I know we're, I don't want to go too long, but I did want to address one comment to Bob, and this is an issue that seems to be bandied around quite a bit.

When we talk about an HDE device, there's a notion that many payers believe that an HDE is still an investigational device. How is that perceived at Aetna?

DR. McDONOUGH: I think, again, we would have to go, we take these devices into the context of the particular disease in question. And so if you have a device that has an HDE but that it has some data that would support its use, that would be reasonable given the size of the population and the therapeutic alternatives, that could be something that would be eligible for coverage. And so it's not unlike the FDA, you know, payers don't have sort of a clear bright line in terms of the exact evidence threshold. It may vary depending on the context of the question. And so there's no overall sort of rule that something that, quote, "merely has an HDE" is not eligible for coverage. So I think that's about the best way I could answer.

MR. CHEN: I just had one more addition to that comment is would you have any recommendations on how companies who are potentially in the pipeline of developing a device that might be currently going through clinical trials, are there recommendations on

how that company and FDA and the payers can get together so that there is sufficient data to justify it and meet the thresholds of some of the payers?

Because as you mentioned, at least for HDEs, it's safety and probable benefit. We don't reach the threshold of effectiveness, but there might be some additional data that we may not use, from a regulatory standpoint, that might be beneficial for payers. And I think, if there's some way that you can give us some options on how to obtain that data or have some discussions, I think that would be helpful.

DR. McDONOUGH: You know, I think, if a manufacturer wants to get a flavor or get an idea of how a payer is going to consider their technology, I think one of the things you may want to look at is, you know, other technologies that are covered and not covered. And we try to make all of that transparent on our own website. I mean, I know there's been discussion about parallel review with the FDA. I'm not exactly, how that would work, given that there are a lot of different payers. When you talk about a commercial payer, you're not talking about one entity; you're talking about many different entities, each of which, because of antitrust concerns and others, have to make their coverage determinations independently.

So I think there might be some opportunities for parallel review, but I'm not exactly sure logistically how that would work, so that when a device manufacturer creates a product, it not only meets the requirements for regulatory review but also takes into consideration the type of data that's necessary for an insurance coverage, which may not be identical to what the FDA would require.

DR. PEIRIS: And just to clarify the points, and so we can maybe close up as well, our parallel review process, for people that are unaware, is an opportunity for sponsors, when they come in, to have a discussion about clinical endpoints necessary for regulatory approval. They also have the opportunity, if they'd like, to invite a payer or payers to the

table and have a conversation about how, within a single perhaps clinical trial over design, that you can clarify both the clinical endpoints and the endpoints that are necessary to clarify perhaps payment and reimbursement issues.

The program currently exists, both for CMS and for some of our private payer colleagues. One of the concerns that comes up in the pediatric world is the fact that with respect to public coverage, Medicaid is the payer, from a public perspective that tends to cover many children, through the CHIP programs as well. And there is no current national coverage decision for the Medicaid system. And that is an area that we are working on and attempting to collaborate on with some of our Medicaid colleagues.

So something to be aware of, but I just wanted to clarify the parallel review pathway for all of you.

MS. TENENBAUM: So, with that, we'll take a 15-minute break. We'll be back here at 1:35.

(Off the record at 1:19 p.m.)

(On the record at 1:35 p.m.)

MS. TENENBAUM: We are going to do two last poll questions. The first one is about barriers to entering the pediatric medical device market. Which do you think is the biggest barrier?

Okay, Andy. I think you had an impact.

Where is Andy? Okay. Oh, more? Well, I for one am glad to see that FDA's role is perhaps minimally responsible. Okay.

And let's move on to Question 12, which is about reimbursement: Should the same device being used in a pediatric indication and an adult indication be reimbursed the same amount?

Do we have that up? Oh, there, thank you. There we go. Okay.

Okay, so pretty close between the exact same and totally different. I really, this going to be a really good working group, guys. I like where we're starting out.

Okay. So this is our last panel presentation. After this, we'll have a question and answer with a large group. This session is about medical device innovation models. We're going to be hearing from folks who are using or studying various models, from nonprofits to venture capital and all kinds of different ways to try to make the money work. So with that, and you have everybody's bio. With that, I'll turn it over to James Kennedy Wall.

DR. WALL: Thank you so much. Thanks, everyone, for the opportunity to share our story.

So I'm a practicing pediatric surgeon at Stanford. I also help run the Biodesign Program where we try and educate the next generation of innovators. As a disclosure, I'm unabashedly a physician-entrepreneur. Unless we change capitalism, that's how we get things to patients. I do have ownership interest, and I'm on the board of two companies that I'll talk about. Neither one of these are FDA approved yet because they're both early stage, which is the focus of this talk.

And where other people have kind of compared the drug market to the device market, what I'd like to show you is a comparison from the entrepreneur's point of view, of trying to do early stage development in adult device versus pediatric device, so within the device market, share some clear differences. I've also been asked to talk a little bit about incubators and accelerators for early stage development, and again, I'll share my experience and present a few ideas I have on improving device development for kids

Just to get some definitions out of the way, early stage development to me means going from concept to funding for commercialization. There's a couple of different ways to do this. Incubators tend to kind of be an area where you put people with expertise in a chosen vertical and then try and de-risk ideas. There's a multitude of those in the Bay Area

and elsewhere. Accelerators, I think, are a little bit more relevant, and there's no incubator for pediatric devices, let's be clear.

Accelerators are areas that or groups that kind of take an existing idea and try and put a business model for larger investment commercialization, Y Combinator, StartX, and I believe that FDA PDCs fall a little bit into this category in providing services to help commercialize.

So let me give you, I am not an economist. Professor Lo gave an unbelievable talk on economics. This is my micro-look at what I call the entrepreneur's reality check. Does your potential for sustainable and return on investment opportunity, does that equal the market opportunity you have minus your development and operational cost? It seems like a pretty simple equation, but let's put some numbers to it.

So here's two technologies that I've recently been part of. One's called Radial. It's a wearable solution for venous insufficiency, DVT prophylaxis. It's got a lot of opportunities. It's about a 12 million patient market, representing about $2 billion. And we're looking at about $40 million to develop a product here, about 5½ million in R&D, another 35 million to commercialize. Check, that makes sense, right? Going after a $2 billion market, as one of my great investor mentors said, I want a big enough bulls-eye that if I miss there's still an opportunity for return.

Novonate (ph.) is a device focused on pediatric umbilical catheters, which applies to about 200,000 patients a year. So several order of magnitude lower in terms of the number of patients. More importantly, the market size for this device is 100 times less. It's a max addressable market of $20 million. So we're trying to develop this on $188,000 in R&D and $900,000 in commercialization. And it turns out commercialization on $900,000 is pretty tough.

Just to give you a flavor of the two technologies, Radial again, going after this archaic

technology and trying to replace it with a smart compression system, early clinical data suggests it compresses better than existing systems and could lead to better outcomes. It's connected. It's smart. It kind of fits the modern life. And it drives compliance.

Most importantly, I wanted to show you the roadmap for getting this invested in as an entrepreneur. Two experienced entrepreneurs in a garage in Silicon Valley, your classic story, $300,000 in angel funding that gets you to a prototype and some early clinical evidence, $5 million in seed funding. It sounds easy. It's not. It takes a lot of trips up and down Sand Hill Road, but at least it's an investable hypothesis since it's going after such a big market. And then acceleration down at the Fogarty Institute. Will it be successful? We'll tell you that story in 5 years, but a pretty nice roadmap, pretty standard.

Here's how we do one better for pediatrics, and this is what I want to focus on. Umbilical catheters, there's about 200,000 placed a year, about half of them in premature babies, as Claudia beautifully showed us. They're necessary lifelines to deliver medications and one of the easiest way to get access in kids. Almost half of them migrate or become displaced. There's about 10,000 bloodstream infections that are associated, and there's a fair amount of money lost from lack of reimbursement for infections.

Here's two different standards of care that are shocking when you really look at them. Adult central lines are stabilized with beautiful, secure, sterile systems. These are, you know, purchased by hospitals, not an issue. Here is our most vulnerable population of immunocompromised neonates, and our standard of care is a chunk of nonsterile tape. That's what we do to secure a central line.

So we developed, within Stanford and now just recently spun out with a venture investment, yes, a venture investment in a pediatric device, a system for securing and protecting the umbilical stump. It's got some IP around ventilation and critical issues that we discovered while in the lab. So this is all done over about a 3-year period. Design

iterations, you can see. Biologic testing, mechanical testing, nurse interviews, user testing all done within the confines of Stanford using early stage funding. And I'll show you in a second.

And what that all resulted in is a device, if the movies work, that should be much simpler for users, and early biologic and mechanical testing would suggest that it can protect and secure the stump.

The roadmap for funding, which I think is really the interesting story here, instead of the 3 months we spent in early stage development at Radial, we spent 5 years here almost, $88,000 in Coulter funding, some med school development money, free R&D facilities from the university, access to the children's hospital. We then went on to PDC grants, which are very helpful. Ultimately, StartX rose and used every resource at our capabilities, an SBIR grant. And after all that de-risking to the point where the device had gone through biologic testing, mechanical testing, and really was ready to be manufactured, finally at that stage it was de-risked enough that a venture investor was willing to make a bet purely on the ability to go out and sell it.

So very different story. I think the question that comes up from this is can David beat Goliath? You know, when you look at that entrepreneur's variable, pediatric market size is a fixed variable. It's small. So there's a lot of different ways here. I won't go through them all because we're out of time. But these are available for review and comment. I think ultimately, I would challenge people to think. When you think about that entrepreneur's dilemma, my controversial question is, is it really patient population that defines an orphan population? Is it just 8,000 patients, or is it the market opportunity?

Because from an investor, an orphan device is one that fits a small market opportunity. So it could be 100,000 patients but a market opportunity of only $5 million. That's never getting invested in, and it doesn't qualify for some of the advantages that

currently exist. So I would challenge thinking around orphan populations. I think Sam recommended all pediatric devices be orphan. I'm totally cool with that, or at least thinking about market opportunity as opposed to just number of patients, because if you think just number of patients, you're going to go towards large-cost implantable devices and not spur innovation in other potential areas.

Finally is a moment of hope I'll show you from AdvaMed a few years ago. This is the Stanford-developed device up against, you know, 70 billion a year in revenue. And so I think that there is a chance for pediatric devices. I think we need to be smarter and early on have entrepreneurs thinking through, not only can I get a prototype built, but what does the commercialization look like?

I'm really looking forward to hearing from the rest of the panel, particularly Mark, who's going to talk about that next level of commercializing and putting devices together for the peds market.

So thank you very much.

(Applause.)

MS. TENENBAUM: Thank you.

And next we'll have Mark to talk about the small companies.

MR. THRODAHL: Thank you, Cara. And thank you, Vasum, for the invitation.

At the climax of *The Odyssey*, Odysseus returns to Ithaca 10 years after the Trojan War has ended, long given up for dead. He finds his palace besieged by suitors, seeking the hand of his faithful wife, Penelope. Disguising himself as a beggar, Odysseus wins back his birthright by demonstrating that he is the only one capable of stringing his great war bow and firing an arrow through 12 ax heads.

Over the last decade, OrthoPediatrics has learned that building a pediatric orthopedic company requires simultaneously satisfying 6 success factors, not 12, of which

product development is only one.

OrthoPediatrics is a company built on a powerful cause, the cause of improving, many times transforming the lives of children with orthopedic conditions. Over the last decade, we have treated between 90- and 95,000 children, like the little boy born without arms, shown in this photograph with our chief medical officer, Dr. Peter Armstrong, who is with me today.

Approximately one-third of our patients have had cerebral palsy. We sell 25 surgical systems consisting of more than 3,500 individual products in 39 countries, using the only global selling organization focused only on pediatric orthopedics. We're the only company providing extensive pediatric orthopedic clinical education programs, and last year we took the company public in an offering that was oversold eight times. As we approach $60 million in revenue this year, we recently reported second quarter sales growth accelerating to 28%.

The first of the six factors is continuous reassessing our strategy. This requires the study of the unique pediatric pathologies and surgical procedures, as well as anticipating the likely competitive responses from incumbent suppliers whose adult systems we are replacing. A pediatric company, you see, faces the strategic problem of living among giants on the Island of Cyclops, Homer might say.

These huge companies are usually disinterested in developing pediatric products because they have the strategic problem of defending much larger, mature, adult markets. And they also often do not have distribution reach into pediatric hospitals. Instead, they must be content to allow their adult surgical systems to be used by default. So we must carefully define our addressable markets, assess their attractiveness, and determine how we will reach them. And we must periodically rate our product and service quality relative to that of competitors, so we address our weaknesses, capitalize on our strengths, and

attack their vulnerabilities.

The pediatric markets we are targeting are not trivial. Using IMS procedure data, we can calculate that our current domestic addressable markets for the products we have now or have in development is $1.1 billion. And by extrapolation, the global market for those products is at least twice as large. The IMS data also suggest that 62% of these procedures are conducted in 268 pediatric hospitals. And this guides us on sizing the sales and distribution network needed to reach these addressable markets.

The second factor is developing the right kind of products. In our early days we developed minimally disruptive products that offer substantial improvements over adult systems, because they comprehend the different morphology of children's bones and the complexities of skeletal immaturity. These products have generated the revenues needed to fund the enormous investments we have had to make, building out a fully functioning orthopedic company.

Over time, however, we have increased the degree of product innovation, but never getting ahead of ourselves by developing systems that face uncertain regulatory approval, reimbursement difficulties, or a lengthy adoption by surgeons.

These are not downsized adult products. They give pediatric orthopedic surgeons greater control, greater confidence, and greater speed completing surgeries. For example, our two hip osteotomy systems are cannulated and have locking screws, allowing surgeons to position the implants over a guidewire and achieve far more accurate placement than using the freehand technique that the incumbent adult system has. We also offer no fewer than 210 different hip osteotomy plates, depending on size, length, and angle of offset.

Now that we're bigger, we can afford to work on more disruptive technologies that, for example, address osteogenesis imperfecta and early onset scoliosis. For example, the spinal tethering product now in development allows surgeons to intervene in scoliosis

patients as young as 10, with a reversible non-fusion surgery that employs the principle of a common pediatric procedure known as a hemiepiphysiodesis, which is used to treat angular deformities of the lower extremities.

The third success factor is clinical education. We see a direct correlation between clinical education and sales growth. We teach a 16-module bio-skills course that touched some 3,000 hospital personnel last year. We support multiple-day cadaver-based courses for young surgeons. These programs are managed by our chief medical officer and a panel of nine leading clinical educators, whose names appear to have been expunged here, so that those programs remain strictly non-commercial.

And, finally, we are the only pediatric company with a social media platform that allows, as of this morning's count, 759 surgeon followers to post questions and cases for comment by their colleagues around the world.

The fourth factor is focus. We believe that a focused competitor, regardless of size, will always win. There are so many unmet needs in our market that we can easily succumb to the siren song, as Homer would put it, of diversionary product development. So we remain focused on the goal of surrounding our customers with all the important surgical systems they use.

And we also insist that our distributors remain focused. Pediatric orthopedics requires sales representatives who attend every case and who are continually drilled in the unique pathologies and surgical procedures of children. And to keep our associates focused on our cause, every evening at 7 p.m., this little sales report goes out to every OP associate. Above the figures is the headline, "Number of Children Helped Today," which brings me to the fifth factor, culture.

Culture is the company's most critical asset. It is the one thing that cannot be reverse engineered or duplicated. We are building a different kind of orthopedic company,

one committed to a purpose greater than just financial performance, one focused on a neglected clinical subspecialty, and a company in tune with the very different mindset of pediatric orthopedists.

But the greatest difference is cultural. We work hard to be a loyal partner so we can attract an ecosystem of the best surgeon advisors, sales reps, and technical partners. We became a global company because the 2,000 pediatric orthopedic surgeons around the world are a global fraternity. Ours is a culture of continuous quality improvement. One of Dr. Armstrong's market surveillance roles is to personally call any surgeon who makes a complaint. They have a candid, surgeon-to-surgeon discussion of the case. And in our engaging culture, the only hierarchy is the hierarchy of good ideas, which come from everywhere. Our goal is to make OP the orthopedic industry employer of choice.

Finally, it is critical to secure the right sources of financing. There is a rule of thumb that 10 years and $100 million are required to build an orthopedic company with annual sales of 50 million, yet most sources of venture capital and private equity have a 3- to 5-year investment horizon, and PE funds typically only invest in companies that are already profitable.

We attracted 300 private investors, and ultimately, an individual investor with the personal resources of a bank. This patient capital has given us the years required to raise $142 million of patient capital, and we are just now breaking even.

To summarize, success requires more than products. It requires developing deep relationships with surgeons, surrounding them with all the important surgical systems they use, and focusing on what for a small company is a very large market. Finally, rapid growth can trigger a virtuous cycle of funding more products, more clinical education programs, and more financial support for surgical societies that advance the entire field of pediatric orthopedics.

The six factors that I have described constitute our business model, but they apply equally to large and small companies. Were I still an executive officer of Zimmer Biomet or Becton Dickinson, I would use the same factors to determine how a multi-billion-dollar company might successfully address the pediatric space.

Thank you.

(Applause.)

MS. TENENBAUM: Thank you.

Next we have Pedro del Nido from Harvard, to talk about the nonprofit and academic medical center model.

DR. del NIDO: Thank you very much. And thanks again, Vasum, for organizing. I've learned an enormous amount by listening to some impressive talks.

Well, first of all, just from my disclosure, my talk is my conflict of interest. It's going to talk about how I moved from an academic center, and my track record of doing work basically funded primarily by NIH, into a very different world, which is a world of medical device development. So I'll walk you through some of that and some of the thoughts that I've had to go through and some of the process of changing, and then what I learned in that, to give you an idea what's involved.

So, typically, what we do in academia, most of us in the surgical world, which is what I do, I do pediatric cardiac surgery full time; I'm the chief of the department at Boston Children's, we do translational research. We very rarely can do basic research. We don't have the knowledge, and if we'd have the knowledge, we don't have the time. So instead what we try to do is we try to come up with solutions to relevant clinical problems.

And in that process, we go through a development scheme, which I hope you can read, but I'll walk you through it, which is we identify a clinical problem or a need. We think about the problem, and often this comes from our own clinical practice and what we know

about what can be done in the laboratory. We then look at the applicable technology to address that question in the laboratory. And if we don't have it ourselves, we go and acquire it or we collaborate with someone to get it. And then we start coming up with a solution; we start iterating.

And in this collaborative process, we disseminate some of our information, whether it's through publications or through presentations at national or international meetings. We try to get our ideas out to get feedback as quickly as we can because that's how we're iterating. And then, in the process, hopefully we come up with a final solution.

If you think about the product development process, it's quite different. It often is based on a novel technology which you think has applications to your particular problem. Then you want to characterize the impact of that technology in the area that you're specifically working in. And you look at a variety of different applications. And then you identify the key application. And then you pursue that. Now, this is often what happens in an engineering department, where you come up with a cool technology and you think you've got a solution to some problem, and you spend your time looking for it. And once you do, then you pursue it, you come up with a prototype, and then you collaborate and disseminate.

What's the problem with that is how do you fund this kind of work? Well, I think in academia we've gotten all really good at funding our projects. We've got a standard model. We usually start off with internal seed funding. This is when we start out as a junior faculty member; we talk to our department chairman, we say, I want some seed capital so I can get my projects off the ground. They usually will give you some money. You get off the ground. If you're successful, then you start to get regional grants, federal grants. Sometimes non-federal money comes in, and you're funding your work.

You rarely worry about the commercial value of this, but you're thinking in terms of

the academic value. And the academic coin of the realm is publication and known as dissemination because that's what gives you your promotion, which is obviously very different than product development process.

If you think about the product development process, there's still ways that academia can be involved, and this is typically through the Small Business Administration in funds that are available to combination or to the collaboration between a small company and academia. And I'm thinking specifically here of the SBIR or more specifically the STTR process, where the academia is very much involved in that process of early development.

You're still driving. As an academic, you're still driving the concept because you know what the unmet need is. Perhaps the engineering colleague or perhaps the small company can help you with the innovation component of it and can help you develop what the commercial value is to their business plan, but you're still very much involved.

And then you start looking at, okay, you have an idea, you've done some prototyping; how do you get it into the market? How do you actually get it into your patients so you can actually use it? Well, now you begin to see that the product development critical pathway is actually pretty complicated. You go through very much similar work that we go through when we're actually doing a research project, but the difference is that now you're developing a product, and therefore there is other components that come into play.

You have to protect your knowledge. You have to also understand that at some point this is going to be put into humans. And so it has to really work, and the methodology that you use to make it, to develop it has to be trackable. People have to know how you got there. And, again, that's a concept that's quite different than what we're accustomed to. This is where, I think, a small company can help you in order to do that because you're going to need to partner with individuals that know how to do this. So that's when the

transition starts between academia and the commercial world. And it's that early partnership which is critical, and finding the right individual that can help you walk through that.

For some reason, I think this is not working. Maybe you can advance to the next slide for me.

Something you need to think about is who owns the technology. Well, if you're in academia, the answer is pretty simple. It's whoever you work for. Whether it's a university or in my case a hospital, they own it. They have the rights of first refusal. And then they generally split licensing fees and royalty fees with you, but that's way down the road. They don't really share anything with you early on.

So what do you have to do? Well, you have to protect the technology regardless, and so we file a provisional patent, which after a year most institutions will make a hard decision. Do you have a chance of bringing this to the commercial world or not? And if so, then they will invest the money that's necessary to convert it into a full application. Prior to that, most institutions will let you file a provisional because that's relatively inexpensive. But the full patent has to have much more promise. You do need to remember, though, that without that protection, nothing that you develop really is going to have that value, and so that's the challenge.

Once you get past that hurdle, then you really begin to understand what product development is all about. And now the list becomes a whole lot longer. And we're talking about scaling a company, this is scaling of work, which there's many, many factors which we have talked about over the last couple of days that go into a product development. And you in academia really can't do this. So at some point in time, you have to figure out, okay, how much time can I devote to this?

Well, academic medical centers usually have a very straightforward answer. The

most you can devote is 20% of your time. What does that mean? Well, they define it pretty clearly. It's 20% of your total professional effort. It's not 8 hours a week. Most surgeons work 60, 80 hours a week. That would be great. But, no, it's 20% of your total effort.

You can't serve as an officer in a company. That's pretty clear. You can have a board seat early on as long as it's a very small company, but once it becomes anything more than a small company, you cannot participate any longer on the board. And this is true, I think, pretty much across the board of any academic institution. So what ends up happening is that most founders end up playing an advisory role as a consultant. And so you come up with some sort of consultant agreement to stay involved and maybe have an observer seat on the board where you can actually make comments, but you really don't have a vote anymore.

Well, so if you can't do it, who can? What are the options? Well, there's two options here, and one is a startup company, and the other is, in my view, a strategic partner. What is the advantage of a startup company? Well, you'll have control. You have much more control just because it's a much smaller entity. The problem is you have very limited resources, and you really have to focus in order to succeed. And you have a great number of hurdles. What does a strategic partner bring into this? Well, they obviously have extensive resources. But the downside is this may not be, what you're developing may not be in part of their strategic plan.

So I'll tell you what I've done in my world. This is the introduction of the CardioPort, which is a very simple technology. If you think about cardiac surgery in general, there's two ways to do it. One is by the standard way, which is you put a child on cardiopulmonary bypass, open their chest, stop the heart, fix the problem, close their chest, and you're done. Pretty invasive.

The other way is through a catheter. You go through a vessel, and you deploy a

device, and that device does its work. Pretty limited. So the CardioPort actually is something that works in that in between space, a direct access to the heart, and provides you an ability to actually work directly inside the heart.

How did this start for me? It was a 10-year process. It started with an NIH bioengineering research partnership grant, which got us going. Eventually we decided that the only way this is ever going to come into clinical practice was if we started a company, so we founded it in 2015. We obtained an STTR fast-track grant, which was a huge, huge help. That really made the whole difference. But, finally, we found what I think had been termed before as venture philanthropy. This is Broadview Ventures. Broadview Ventures is a family office that actually funds companies, and they were the ones who actually got us over the hurdle.

How do we fund it? Well, in academic medical centers, we can get off the ground with a company effort with money from the tech transfer office or through angels. But eventually you're going to need real money. And that's where the hurdle that we've been talking about comes in. For something like a Series A, I think for pediatric devices, family offices do offer an opportunity. They have a very different mission in the sense that they're not like most venture capitals, which is, you know, they want a 10X return. Most family offices have a mission, and so they don't need necessarily that 10X return.

Thank you very much.

(Applause.)

MS. TENENBAUM: Thank you.

Next is Tiffany Wilson, to talk about federal-state public-private partnerships.

(Off microphone discussion.)

DR. PEIRIS: Don't say the FDA never bought you anything, Tiffany.

MS. WILSON: Thank you. I feel truly special now. I have fresh batteries.

So good afternoon, and thanks again, Vasum and Mary Clare. for the invitation to share with you today.

So I'm introducing GCMI. GCMI is a nonprofit organization. We're an affiliate of Georgia Tech. But we have really been able to scale and grow to help innovators, entrepreneurs, new product development teams, including those in the pediatric space, to get to market using capital efficiency and the use of partnerships.

So I'm excited listening to the program yesterday and today. I'm hearing these recurring themes of collaboration and being creative, process efficiencies and standardizing some of those things, which I think really drives what we're trying to address here in increasing the speed of these devices to market.

So GCMI is very focused on becoming the world leader in efficient product development. My colleagues and I come from the industry side, from the dark side, and are now working in this nonprofit scenario where we've seen a lot of waste along the way, both on the devices and the drug side. There's a lot of activities and processes not being followed that just adds cost to the system. So we're really focused on doing that, because at the end of the day, we've got these activities in place to really benefit patients. And that's why we come to work every day, including pediatrics.

So just to give you a brief overview and kind of touching on the federal side, so GCMI opened about 6 years ago predominantly funded by the U.S. Department of Commerce, the i6 Challenge grants, some EDA funding, along with a grant from the Georgia Research Alliance to address a gap that exists not only in Atlanta but across the Southeast and I see in many parts of the country. There's a tremendous amount of innovation coming out of our hospital systems and academic centers, but where's the startup activity?

So, really, from an economic development standpoint, I find my surgeon at Emory, and I come up with an idea for a new technology, it gets to a certain point, and then I end

up going to Boston or the West Coast really to take advantage of those ecosystems. So the thought was if you had a physical center that just focused on med tech that had the right product development expertise versus academic engineering, quality systems, clean room space, machine tools, that you could build an ecosystem around that and really help move those innovations into the market.

Pediatrics has always been at the core of what we've done at GCMI, given the great collaboration between Georgia Tech and Children's Healthcare of Atlanta. And so we came online around that time to really help translate some of those technologies forward.

About 2 years ago we acquired T3 Labs from Emory Healthcare. T3 is a preclinical testing and training facility. So now, within about a 4 or 5 mile radius in midtown Atlanta, we've got all of the expertise, infrastructure, and know-how to go from back of the napkin through large animal preclinical studies and clinical trials without leaving the city, and a broad network of ecosystem resources really across the country that we draw on for various expertise. And we continue to receive EDA and grants like that as federal partnerships for supporting this innovation activity.

So this is how we're structured now. What was initially what we called our GCMI is now our design and development team. We've got a team of biomedical engineers from industry as well as a surgeon on our team a couple of days a week to provide those clinical assessments. We've got then T3 Labs where we've got four operating rooms, everything from small to large animal studies. And so by integrating those two teams, we're able to go very much faster through the design-build iterative process in drawing expertise from all of their experiences to help that move.

We found, after a few years, that if we could work with the right team at the right time, we could go really quickly from kind of concept through say a 510(k). We've done it in as little as 10 months, supporting a team, that they were the first one there, a pediatric

company, first one there in the morning, last one to leave at night, very coachable, knew how to connect with experienced business leaders and investors in the community, and just go. So it is achievable by following that process.

So that led us to launch our med tech accelerator program, which is really the first example of a partnership model that we used. In addition, we're working with several hospitals, working with their clinicians who have unmet clinical needs or ideas that they want to brainstorm. And longer term, we're looking at expanding this accelerator, adding funding mechanisms, really drawing from that capital continuum from the early stage, whether it be SBIR, NIH, or FDA grants all the way through private investment and commercialization.

So the first model that I'm going to highlight is this partnership with Becton Dickinson. So at a time we found we could really help with the capital efficacy of product development and getting to market, we were hearing from big industry partners that there's a lack of early stage venture investment. They're not making acquisitions or strategic investments until much later in the process. And so there's a risk in this innovation gap. Where is the next generation of their products going to come from?

At the same time, they are at engaging at an early stage, working with these startup companies, and it may not even be a startup yet, and sharing guidance on the types of de-risking milestones that they would want to see to position the startup for maybe an earlier stage investment. But it was really ineffective because they don't have a lot of time and they're seeing you know, 8- to 900 deals a year.

And so we partnered up to use this accelerator methodology to come together with a large strategic partner, our team, outside investors, to say, you know what, over the next 6 to 12 months, these are the milestones that we need to knock down. And then if you're successful, then we're well positioned for the next round of investment. And so that

process worked really well. We were able to work with our initial company to de-risk the things that needed to be de-risked and get them on the right pathway.

And so I think this is something to think about, as we think about pediatrics and some of the discussions about how to engage strategics, is if there's a closer partnership and alignment, and then the acceleration model holds that startup team or that investigator accountable on a weekly basis, and makes sure that that team has the resources, the expertise, and the right contacts in the right context along the way.

The second model is one we announced earlier this year on the nonprofit side. So we partnered with American Cancer Society. American Cancer Society, they have a research portfolio of about $450 million, $500 million across the country. They like to fund PIs very early in their career, but then what? Right. And this addresses the whole problem, how do you get the research out into the market, into products that can benefit patients?

And so they put a new strategy in place where they wanted to increase their research dollars but also start investing more in this development cycle, where, you know, is this a project that can spin out into a product, into a company? And how does that de-risking process work? At the same time, ACS is launching an early stage venture fund, venture philanthropy this fall. And so we're thinking about this capital continuum, and pediatric cancers devices, diagnostics will be part of this process as well, from bridging the research dollars to private investment.

And then, finally, I've got something that I can't really disclose yet, but I imagine an announcement will come this fall. We've been working with an innovative pediatric team, compassionate use type cases, growing opportunities in the market, but really, how do you get that out and get it developed in a way that's compliant with FDA, with all of the design controls and everything that needs to be done? And then how do you get it paid for?

So we're working closely, bringing together state funders, the academics, and the

healthcare system as a team, really collaborative partners to figure this out, and using this as a test case to make a more sustainable process to get early stage pediatric innovations, high risk, to the market.

So, finally, just kind of key takeaways that, you know, kind of thinking back as we've built these partnerships, the big one is just to encourage everyone to get creative. I don't think there's any right or wrong at this point. But I think when we're talking about large healthcare systems, large universities, and the standard way that we've always done it isn't the way that we're going to really move the needle on this, the pediatric innovation stuff.

The other aspect of it is to really embrace the collaboration. I would encourage all of us to get out of our silos and work together. It's not a competition. We're talking about kids' lives and getting these technologies to market. So the only way we're going to do that is by working together.

This came up in the last talk, thinking about is it a product or is it a project, right? At some point, it's got to move out of the academic system into a product that can get through FDA that somebody's going to pay for because that's going to benefit the life.

Engage FDA early, I think that's kind of a given, and just stepping outside your comfort zone and remaining flexible. I think we've got a tremendous opportunity with all the people in the room and online to come together as a community to do something a different way to benefit kids.

Thank you.

(Applause.)

MS. TENENBAUM: Thank you.

Next is Grace Zhang, to talk about your work at GW and also your funding, which is from a nonprofit. So I think this will be interesting.

DR. ZHANG: Thank you very much for the invitation.

My name is Lijie Grace Zhang. I'm an associate professor from the George Washington University. Back to the spring, I received a message from the March of Dimes Foundation about that excellent meeting information. So after talking with Cara, I think is a great meeting and also will have significant effect on future pediatric medical device development.

So in the following, I'm going to give a kind of case study, one March of Dimes sponsored research project at the GW. I prepared a outline here. So at the beginning I will introduction the March of Dimes Foundation. And then I'm going to briefly overview my lab's research. We have many ongoing research over there, so including for the pediatric-related and also for the adults, medical device development. And also specifically, I'm going to talk about the project sponsored by March of Dimes Foundation. So the last part, I want to share my own experience, either from the reviewer's and also from the applicant's point of view, about the challenge of the federal grants and also the advantage of March of Dime funds.

So for the March of Dimes Foundation, the mission of the foundation is to improve the health of the babies by preventing the birth defects, premature birth, and also infant mortality. So they provide a very diverse funding portfolio. They can fund the different research area, including the fundamental, like the biological process, and also clinical study and also the bioengineering-related research like mine.

So in the following, I'm going back to the research part. Currently, I am directing the bioengineering laboratory for nanomedicine and tissue engineering. So the key technique in my lab is the 3D/4D bioprinting and also nanobiomaterial. We combine them together for complex tissue organ regeneration. So, for example, we use 3D/4D bioprinting to fabricate the nano-neural constructs, can repair the neural defect. We also design different vascularized tissue, like vascularized bone and also, vascularized cardiac patch.

In addition, we work on the 3D bioprinting for the cartilage and osteochondral regeneration, by collaborating with professor from GW Medical School and also the Georgetown Medical School, the two professors. We also work on design, like in vitro 3D bone model, which can be used for future breast cancer bone metastasis study and also therapeutic discovery.

So for the specific project sponsored by March of Dimes Foundation, the program sponsored my project, it's called a gene discovery, and the translational research grant. So it provide around $250,000 for 3 years. The project is related to use the 3D bioprinting to fabricate a smart nano soft tissue graft, which can repair like the neural defects.

So here is just a brief introduction. We use the nanomaterial. For example, we create different nanoparticles. We call them the Coshell nanoparticle, biocompatible one. We are loading different therapeutic into that nanoparticle and using the bioprinting system in my lab to fabricate a nano soft tissue graft. So you can see many film on the picture I show here. So we also evaluated the printed, the therapeutic loaded constructs, observed the axilant (ph.), the neural cells. One is the perturbation, another is the axon extension when compared to the control, without any nanomaterial inside.

So, in addition, besides the 3-dimensional bioprinting, we also have some ongoing exciting 4-dimensional bioprinting. I think it's ideal for the pediatric medical device development. So the 4-dimensional printing means including the time to the printed constructs, which means the printed constructs can change their shape based on different mechanism. So I think, for the adult medical device, they normally they're static. But for the children, they grow up, like a tissue, organ, they grow up. So if we can use the 4-dimensional printing to fabricate that expanding feature, it will be perfect.

So we use the laser-based printing system. We also create some smart material. So that material can change their shape based on the temperature and based on the saline

system. So you can see the picture I show here. So if we put that printed structure into a isononyl solution, they going to like a flower to open. We put the opened structure into a water system, they going to, like a flower, to close.

Using that smart material, we designed it in our lab, but we also 4-dimensional print a neural guidance construct, so they can automatically load into a tubular structure, which can be used for, for example, like a peripheral nerve repair. So, more importantly, the biomaterial very biocompatible. We also observed that the axilant of the neural stem cells, perturbation, and the axon extension.

So that's the research related to the 3D/4-dimensional bioprinting for like pediatric-related medical device development. So in the following, I'm going to talk about the challenge for the federal grants, majorly regards to the application. So in my field, the typical, the federal funding sources, including like the NIH and also the NSF. So from my point of view as a applicant, I feel the competition is definitely very intense. Like I submitted 10 proposals, cannot get one funded.

And also I serve as mainly, like on each study session, to review the proposal, I have the same feeling. For example, like we review like over 100 proposals in the study session. Half of the proposals cannot be discussed. Probably eventually like 10 proposal, even less, can be possibly funded eventually.

So I also search online the data a little bit. I found out, for example, the National Institute of Child Health and Human Development, in 2016, the pay line is 10%. So I think many institutes even have a little bit lower pay line. So that as a result, many excellent proposals is really hard can be funded because the federal funding budget constrained.

I think that that's the benefit part about the March of Dimes fund. So the March of Dimes Foundation, they provide a bridge fund, especially for the early career researcher. So I think that's very critical for either early career or middle career researcher, because when

compared to like NIH, NSF funding, so we compete with a senior researcher over there. So normally we like has a very disadvantaged position when compete with them. So I think the March of Dimes Foundation provide a very nice kind of bridge or seed fund for the early career and also very highly innovative early stage of ideas.

In addition, I think the areas target by the March of Dime funds, so I already know the covered by the general funding sources. For example, like NSF, they funding the mainly fundamental research. The NIH, they funding a lot of clinical study. The March of Dimes fund, they target the baby, the infant. I think that's pretty unique. I think that can serve as a very important future, like a private, nonprofit sector for some related research in the future.

So I think the last part is the acknowledgement. I would like to thank the March of Dimes Foundation for this part, and also the FDA Pediatric Medical Device Development Workshop invitation.

Thank you very much for your attention.

(Applause.)

MS. TENENBAUM: Thank you so much.

And to present our last model to discuss today is John Parker from Springhood Ventures, to talk about venture capital.

MR. PARKER: Thank you. Thank you, Vasum. Thank you, everyone at the FDA.

It has been an amazing session. It's just fantastic to see all these people in this room. And for those who are still here, thank you for staying.

So I'm here to talk about the venture perspective. But I'm not a true venture capitalist. We heard yesterday that mainstream VCs aren't interested in pediatric devices, and that's largely true. I, on the other hand, do invest in pediatric devices and other things in children's health. I created and run an investment program on behalf of the Charles H.

Hood Foundation, a Boston-based private foundation focused on children's health.

We currently have a portfolio of five companies that are tackling important pediatric issues. We expect to double this portfolio over the course of the next couple of years, speaking to Andrew Lo's point about trying to get a portfolio approach to our investing, but this takes some time. We will get there. We have time.

What we're doing, though, is a drop in the proverbial ocean. So I'm working to bring more mission-aligned or at least mission-tolerant investors into this space.

I invest not for returns but for outcomes. I'm lucky to have a risk-tolerant mission-focused backer who allows me to do this investing and does not require me to have a certain IRR or return bogey. It does not mean that I don't require commercial success, though. A successful investment achieves improved outcomes, and it does it at scale, and it does it sustainably. This doesn't happen if the economics don't work. Nevertheless, there are easier ways to make money. So I invest in children's health largely because no one else will do it.

So why is it so hard? Let me paint a simple picture here, overly simplified picture. In theory, investors expect this, a natural course of attrition of good ideas that some fail, some succeed, and you work through them over time, and the good ones survive and reach patients. What we have is this, though, a bottleneck. There are actually multiple bottlenecks. I'll come back to that. And this is true across all of life sciences. This happens because what we see in life science is a funding picture that looks like this. There's lots of grant money, not much seed funding, and institutional return-driven investment funding that comes largely as a result of what's happening at the seed stage, some at the grant stage.

I don't have the hard data, but if you were to look at this from a pediatric perspective, I know the numbers are going to be lower, and my guess is that the right side

of this chart will have a lower ratio relative to the left side. When you look at pediatric devices, it's going to be even a smaller fraction of this.

One interesting thing that I see in this chart is that there is a lot of innovation. There's a lot of money supporting good ideas and good innovations. I see it in practice, too. I see about 60 new companies proposing investments in pediatric devices every single year. Many of them won't and shouldn't make it, but a lot of them deserve to be, to have a good shot at making it through at least those early stages. Most of them don't. What we're not seeing is devices actually getting through the whole process and getting to market. As we've heard, they're barely getting to the point where they're applying for FDA approval.

One of the things that I like to talk about when I think about this space, think about when I look at this space, is comparing this to getting to the moon. So we did this. We managed to get to the moon 50 years ago. What we're doing in pediatric devices is similar. We've got a lot of great rockets right now; that's all the innovations. And we've got to figure out how to get to the moon. The trick is, and I think we can do this, I spend a lot of time doing this, and if we get them through to the FDA, we've gotten them to the moon. You still have to get back. And this is one of the big problems that I'm trying to work on right now.

We have to get home. We have to get these innovations to market. So there are two bottlenecks, as I mentioned earlier: First, how do we get these innovations through the early stages of commercialization? And then how do we get them to the patient? These are both very different problems.

I'm not going to spend a lot of time talking about the risks in the system because this has been covered by so many folks. It's supposed to say here, all healthcare investment has risks. Child health technologies have more risk. We've seen this throughout the 2 days here. There are a ton of different risks in the system. I'm going to touch on one that I don't

think has been covered too much here, which is the lack of investor interest.

Children's health is generally associated with philanthropy. The people that are deeply engaged are folks who have sick kids, and most investors have healthy kids, just like the general population. It's hard, hard, hard to engage the investors here. Investors will look at things that are interesting to them. That can be often things that touch them. They might not think about it that way, but they do sort of the fear factor. Folks will invest in cancer. They'll invest in Alzheimer's. Children, not so much.

With pediatric devices, it gets even harder. Again, I'm just going to touch on a couple of these. The scaling issue is very real. I was thinking about the slide that was up yesterday of the picture of a NICU. Not only can you not sell easily into NICUs, but where's it going to go? Where's your device going to go? They're overloaded. This is a tough, tough system to sell into. The other point I'd raise here is, ultimately, investors are very interested in things that are hot. They want to invest in what their peers are investing in. I'm sorry to say, pediatric devices aren't hot.

I won't spend too much time on this. Quick and early, this is what the funding landscape looks like right now. Friends and family, accelerators, and incubators are actually investing in this space. I see a lot of pediatric companies that are raising money from these sources. Where we run into trouble is when you get to angel investors, VCs, industry players. This is where you start to get some real money, and most of this money is return-driven. It's very hard for folks to engage, especially when they need early exits, like angels do, when they need big investments, like VCs do, when they have to justify the bottom line for the whole company, as industry players do.

There is an emerging set, not in a side where I think the opportunity lies when you heard a little bit about it earlier from this panel, which is some of the things that foundations, other nonprofits and family offices can do. They can do what they want, to a

certain extent, or at least invest in a mission. So put all these things together, no wonder it's hard to attract investigators. There are just easier, more profitable, less risky, and more exciting ways to make money than investing in pediatric devices.

The things that I like to raise as an investor in the space, some of the things that might help, I think it would help if the process were a little easier. I think the FDA has done an amazing job in becoming a friendlier, easier organization to deal with, but there's always room for improvement. I talk to companies all the time that don't understand the process. They learn, but it takes time, and there are often mistakes made. It's the kiss of death for a startup company.

There are also great opportunities to make it easier to deploy capital in creative ways that are better aligned with the stage the company is at. I would love to see some efforts on legislation that makes it easier for nonprofits to invest in, to make non-fiduciary investments in startup companies. The mechanisms are there, but they're not always well defined. Nonprofits have a hard time figuring out what the rules are.

We've heard a lot about how to make it more profitable. Tax incentives, speeding up the process, these are all important things, and I don't need to dive in too much further. I do believe that a tax credit upon approval of a pediatric device would go a long ways to attracting investors.

Make it less risky. I would like to see more development efforts as a PDC, and for them to think about how do you direct people to the best expertise, get best practice into these companies? I would also like to see some efforts to help companies post-approval, help with the return trip from the moon. There are a lot of things that companies could use some help with. It's still hard to get to the patient. Something equivalent to a Phase II SBIR to mirror the PDC program could be really an interesting approach. I also think there's an opportunity to engage more people who aren't necessarily going to end up in this room,

whether it's politicians, industry players, investors, KOLs in their respective fields. Engage them.

I'll close this, and there's no silver bullet. There are a lot of factors that need to be considered in trying to improve the landscape to attract capital to pediatric devices, but if we can attack a number of those things, we'll be able to make a little dent, get a few more of these projects through, and have a little more impact on kids that need these solutions.

Thank you.

(Applause.)

MS. TENENBAUM: Thank you.

And next we'll have Mark Schlesinger to talk about what the CEOs are saying they need to get into this field.

DR. SCHLESINGER: Or something kind of like that. All right. As Monty Python used to say, and now for something completely different.

Imagine the last panel is over. A new panel is beginning, a very small panel, a short panel, a panel with only me on it. This panel is entitled How Does the FDA More Creatively Learn From All of You?

Now, the FDA has mechanisms it's traditionally used, public meetings like this one, public commentary on postings in the *Federal Register*. These are good, effective means of getting feedback, as we've heard over the last couple of days. But sometimes they're not enough. And let me argue why we think they're not enough in these particular circumstances, particular circumstances which involve, in this case, basically shooting arrows at a moving target. Because as we have heard over the course of the past 2 days, the FDA is in the process of transforming itself, of becoming the new FDA.

And in that process, what it can learn from and how it can learn from the industry becomes a more complicated and challenging task. So let's start by asking ourselves, first,

how are those aspirations changing?

Step back. Up until about 25 years ago, the U.S. was exceptional compared to most other countries in the world, and not necessarily in a good way but in how it defined the role of regulation over healthcare and the role of the FDA in particular. We saw healthcare regulatory agencies as being the equivalent of police agencies, of protecting the public from bad actors, bad ideas, and bad practices.

But as we've heard, over the past 25 years, partly in conjunction with prodding or at least acquiescence from Congress, the FDA has been shifting away from a policing model towards more what we would call a partnership model, and be a partnership model that was, in fact, the primary standard that was used by comparable health regulatory agencies around the world. So we are becoming more like comparable FDA-like agencies around the world in thinking about partnership with industry in a variety of creative ways. And we've seen that exemplified over the past 2 days.

Lots of good comes from that, but along with that good comes some complications, in particular, the challenges of carefully sorting out the right balance of public and private motivations. That's particularly complicated in the pediatric space, where we've heard so effectively demonstrated in this last panel when the public and private motives are, in fact, deeply embedded in all the different actors. It's not just government versus industry here. It's that everyone involved has this complex mix of altruistic and financial motivations. And sorting out what that balance could and should be becomes complicated.

So that's the first part of what makes learning hard. The second part is that I would argue the FDA is only partway through its transformational process. The move from policing to partnership is a clear and important one. But I would argue it's a way station on a move to something bigger, which I will call leadership. That is the capacity of the FDA to shift the priorities and strategic thinking in the field, all while maintaining its carefully

maintained value neutrality over the submissions of any individual actor that are made to it.

That poses yet a different kind of learning that has to go on. And so it's this challenge of trying to learn effectively in this complicated space where the FDA is remaking itself systematically over time that led Vasum to commission me, my able graduate student, Emily Boudreau, and with the very good advice and assistance of Andy Lo and Greg Licholai, to think about other ways of learning from industry, in particular of designing a survey that could systematically sample a set of different perspectives from industry and help us gain a more nuanced understanding, a variety of the issues that we've been discussing for the past 2 days.

Emily and I have spent much of the summer designing this survey. We are currently pilot-testing that survey, including with a number of you who are in this room, so thank you for your participation in that regard. The survey is predicated, well think of it as being like the survey equivalent of a Kurosawa (ph.) film. Right. It's basically predicated on the notion that for any complex area, and we've seen pediatric medical devices are complex in their implementation, in any complex area, you have to get a set of multiple perspectives.

So the survey is designed to triangulate both the perspectives of the device developers, the industry, with the investors, with the clinical academic partnerships that are involved in clinical trials, and to get all of those perspectives on the role that the FDA is playing and could be playing over time, but also to triangulate within the industry to collect information from multiple actors within given companies, to understand the difference between how a regulatory affairs person views the FDA compared to a science person within each of these companies.

We're going to administer the survey in a variety of ways. We don't have to go into those details. Just understand there will be a mixed mode of administration designed to make maximum participation as easy and flexible as possible, maximize our responses.

Mysteriously, there we go.

The scope of the survey will be familiar to all of you who've been here for the past 2 days, but we're going to try to put a distinct twist on different elements of it. We, in the survey, explore different barriers and impediments to device development. Those will be very similar to the themes that came out particularly in today's conversation. But what we are going to do in the survey is to distinctly differentiate the responses among industry segments, between some types of devices and other types of cardiac versus orthopedic devices, for example, and to distinguish between large and small players within the industry.

Similarly, we're going to look at incentives and mandates, in a way very similar to those discussed today, but thinking creatively about how to package those together. And then finally we're going to look at a scope of different factors ranging from things the FDA can do to things that go beyond the FDA but involve congressional legislation, that is public sector action, to things that involve collaboration with the private sector.

Let me offer you, in the few minutes I have remaining, four little previews of coming attractions, with the understanding these are based on the pilot results. They may not be replicated when we do the whole survey in the fall, but I think they will be. Finding number one, everyone loves Vasum.

(Laughter.)

DR. SCHLESINGER: If the state of pediatric medical device development was a place, Vasum could run for governor and easily be elected. Key point number two, the FDA is not seen as the problem here. Its transformation has largely successfully recast it in this partnership model. Now, there are a small number of respondents who longingly look at the drug side of the FDA and say, oh gee, we'd like to have some of those incentives, we'd like to have some of those same timeline markers that they have.

So there may be ways in which things can be borrowed from one part of the FDA to the other, but it's not the primary barrier. However, many respondents still view the FDA as a key actor, not to remedy its failings but to compensate for other market failures and other kinds of shortcomings in the development of the industry.

Third, there are some areas of call them key ambivalence. And you hear ambivalence in the kinds of survey that we're doing in the following way. A respondent says, I think about it this way, but everyone else in the industry thinks about it this other way. Chief among these are related to the role of off-label utilization and how we translate the current highly prevalent off-label use of pediatric devices into either more on-label or more transparency in off-label use.

That's a complicated process. There's a lot of ambivalence out there about how best to do that. That's going to pose a challenge. That complexity will only get greater when some of the workings on the drug side related to the advertising of off-label use come down through court cases over the next few years. That's going to be a big complex area.

Finally, the fourth key finding. As I mentioned earlier, there's a difference between being a good partner and being a good leader. And we hear our respondents struggling to kind of define a leadership model for the FDA. Arguably, one thing we may be able to do, and one challenge I'd like to pose to this group, is to think about what the FDA might learn from the NIH, which has, while maintaining its kind of value neutrality over external submissions, has nonetheless established a clear and effective way of shifting the priorities, not just for medical research but for the translation of medical research knowledge into clinical practice. To what extent can we look to NIH practices, NIH governance, NIH approaches to these issues and think about how they could be imported back into the FDA context? More once we have the survey done later this fall.

Thank you.

(Applause.)

MS. TENENBAUM: Thank you.

And with that, we have 10 minutes for questions and answers to this panel.

(No response.)

MS. TENENBAUM: So we have solved everything? I love it.

Do you have a question? Great.

UNIDENTIFIED SPEAKER: Thank you very much for the very interesting models and the presentations. My question is that 3 years ago we developed a biocompatible coating. It was applicable to polymers, especially the extracorporeal membrane system section. It was a black biocompatible coating.

At that time I was a post-doc fellow at the University of Maryland, and I applied for Maryland Innovation Initiative, that's called MII, is short. And we could conduct some pre-clinical experiments using both in vitro and in vivo systems. And it was about to be funded, but at that time I got opportunity to work in FDA here, so I came here actually, so I could not further work on that.

But I'm very confident that that business can be definitely successful because it was proven successfully by means of both in vitro and in vivo experiments for the durations up to 30 days actually.

So at this point, suppose if I have to launch that kind of a small project, especially because the duration of coating, as we evaluated, was up to 30 days actually maximum, like we can keep the blood stable and without any great amount of systemic anticoagulation. We can keep the blood and the blood cells, everything properly for the maximum duration of 30 days actually.

So from the points of where to discuss it today, the models and what you presented today, so what kind of initiative is good for this actually? Can you please consider this as a

case study and give some idea about taking this kind of project?

DR. del NIDO: I guess I'll start. I mean, this is a classic academic dilemma, right. You have an innovation, which you've tested in your own models, and you've shown that it works. The question is that what you haven't shown is can you make it a product, right. So that's a very different question. And to do that, you have to, A) show that you can make it in large quantities in a way that's safe and also that it is just like it works in the large animals or small animals, it also works in humans. So that's what product development is all about.

In order to cross that chasm, then you have to get some additional data to say that this is feasible. And that's where money makes the difference, okay, money and someone to give you advice as to which is the best way to navigate. And I mean, what you're telling me as an example is exactly what I went through and what a lot of folks around here went through. Great idea, you got preliminary data that looks very promising. Do you have the other you said six factors? I think it's closer to 10.

It's literally a checklist. You just have to have somebody write down the checklist, and then you objectively look at those. And if you don't have the checklist there, it doesn't mean you stop. It just means that you got to fix that problem. And when you fix that problem, then you go to the next one. That's really, that's what it is all about.

MS. TENENBAUM: Does anyone, go ahead. The panel. Anyone else?

DR. WALL: I would also just comment, you know, you sort of made your decision in some ways, right? I think, for this to be pursued, you really need to think through the cost, the development cycle, and what's at the end of it, and what will it get paid for. It sounds like you've de-risked the science. I don't doubt the regulatory, in the new environment it would get passed, but what's the value? And did you think about that when you put all the time into it?

That's what we argue in the Biodesign Program is think that value up front. Is it worth your time and effort? Or is someone going to put their time and effort into it? So in addition to the whole checklist, you're also going to have to find someone who gets up every day and is willing to work on this and take a risk with you.

UNIDENTIFIED SPEAKER: Thank you.

MS. TENENBAUM: Great. We'll move to the next one

DR. ESPINOZA: Hi. Juan Espinoza, Children's Hospital, Los Angeles.

Thank you all for your time today. As a clinician, researcher, and academic center, these are not often the issues that I'm thinking about. Usually when we're working, we're thinking a lot more about the science and the technology behind it. So it's good to think about these, the return trip back from the moon, as John Parker put it.

Everybody called him Andy, but I don't know him and it makes me uncomfortable to say that, so I'm going to say Andrew Lo mentioned earlier about de-risking the process. And I think a lot of the things we've talked about, especially what Tiffany Wilson mentioned about GCMI, about de-risking the science up front, and I wonder if there's a role for de-risking the actual business venture from the perspective of providing support.

There are all of these sort of, there's this corporate stack, right. There's HR and payroll and insurance and filings and taxes that takes money and FTEs to do. And I wonder if that would, some sort of shared cost structure that pediatric device companies could use to do that, to de-risk that. And the model that comes to mind is in Norway they have something like that for software development.

So the Norwegian government wanted to invest in creating a software sector. And so they created a public corporation that handles all of those corporate aspects so that companies can come to them with an idea with an IP. They get to keep their IP, but they have the government basically supplies has that entire side of sort of the corporate chain

that allows for companies to move forward. And I'd love to hear from the various perspective on here, if they think that there is something, there's a role for something, there's a role for something like that in the U.S.

Thank you.

MS. WILSON: Yeah. So I think, I hadn't thought about it that way, but what I will say is that really, over the last 8 years or so, there's been a tremendous amount of investment across the country in various communities, in programs like the EDAs, i6, and the Seed Fund Support grant to build these entrepreneurial ecosystems. And so I would encourage people to look within their cities, that there are nonprofit entities kind of adjacent to academic research centers that can work really closely with you and startup teams, spinning things out.

That enables you to focus on the technology and getting that product developed to market, and then connecting with the broader ecosystem of experienced entrepreneurs and folks who, those activities in terms of, you know, HR and taxes and setting up your business may be daunting to someone on the technology side but not necessarily to a businessperson. And so I think there are resources out there. It's just a matter of connecting with them early enough to start building that out.

MS. TENENBAUM: Do any incubators do that kind of

MS. WILSON: A lot do.

MS. TENENBAUM: A lot?

MS. WILSON: Yeah. Incubators, accelerators, there's lots of different models. Yeah.

MS. TENENBAUM: Okay. Well, we have time for one last question, so let's do that.

UNIDENTIFIED SPEAKER: Hi. More of a comment, maybe a suggestion. Thanks for the excellent discussion on different ways of funding these companies. You know, we've talked about, obviously, nondiluted family offices, venture, but I do want to go back to two

other areas, one strategic partnership.

Even though the bigs haven't done much in pediatric devices, there are plenty of recent examples of strategic partnership based on milestones and hitting objectives on the adult side, that if you do the heavy lifting and present this to the right contact within a larger company, you might get some traction.

Number two, foreign investment. Our company was successful with a Chinese syndicate. And, you know, there are certainly, you know, pluses and minuses with taking that route, but for example, to show the lead investor in what we were in our syndicate is the former executive director of Cambi for 15 years. So, you know, people that are very experienced and highly cached in a space, and Chinese investment money has different incentives and agendas than U.S. investment money.

So there are other things out there. And, you know, for what it's worth, leave no stone unturned. Flex your network muscle. Talk to different people in your network who have a lot of experiences and may have ideas. It only takes one.

Thank you.

DR. del NIDO: If I could just echo what you said about the strategics, I think that that's a huge untapped opportunity. Clearly, they have their priorities. But there are large enough strategics that also, they do have a mission. And often, if they find the right fit, they'll support it. The challenge for them is they can't waste a lot of time on things that will take a very long time because, you know, they could be investing that money in something that will give them 10X as opposed to your 1X. But if you get to the right person and you get the right connection, you can make it work.

MR. THRODAHL: There's also the challenge, I think, with the strategies, and it sounds paradoxical, capital is extremely scarce in big companies. And there is great impatience with regard to seeing returns on any initial investment in a technology. And

that's because most of the big companies have the strategic problem of defending enormous mature markets that soak up huge amounts of capital. And they're working on the 32nd generation hip or the 22nd generation knee, but they have to do that to continue to maintain a market share that may be worth billions of dollars to them.

So from that standpoint, one of the key learnings I'm taking away from this conference is the importance of finding a source of financing that may be a family office. I thought this was a stroke of good fortune by our company, that we ultimately found a single investor with the personal resources of a bank. But I learned from others that there may be other family offices or angel investor groups that are far more patient with regard to seeing returns, and I think that's just very interesting.

MS. TENENBAUM: So I want to say two things. One, thank you to both panels from this session. Thank you to all of you who are participating in this. I know it's been a long 2 days, and that leads me to my second point, which is we're going to take a 10-minute break. And then we'll come back and have a very lively discussion. So please do come back in 10 minutes.

(Off the record at 3:05 p.m.)

(On the record at 3:32 p.m.)

DR. PEIRIS: I think we are about ready. I'm assuming we have run the chime outside to ensure that people know that we're started again. Thank you to all of you for making it this far and for staying for this very important panel. The intent of this panel is really to integrate the concepts and ideas that we've been talking about for the last 2 days and begin to focus our initiatives again on the topics that Congress asked us to focus on, which are the five areas that will be highlighted in the slide shortly.

I want to thank all the panelists as well, for taking the time out of their schedules for being here. I know a few people also have to leave to catch flights, but most importantly, I

want to thank some of the panelists that have actually taken time out of their family vacations and personal vacations to come here and specifically be part of this.

We're going to try something a little new with this panel, the concept of by the public and for the public. So the panel will be run by the panelists. The audience certainly is intended to be engaged. Each of the specific topics that we'll be addressing will be championed, posed, and the discussion will be led by one of the panelists.

So, Chester, I'm going to hand it off to you and let you get started.

DR. KOH: Sure. So, actually, myself and Bob are responsible for the first topic, and really the topic is really about the PDC program and the HDE activity. So we'd like to open up to the community and one of the first questions, does the community feel that these programs are sufficiently fulfilling the pediatric medical device ecosystem?

I think you heard a lot about the PDC programs and what it's currently doing. Are there any comments from the community about the PDC program, specifically for this time? Any suggestions, any ways that we can improve the program? I think it's open to the panel members as well.

MS. WILSON: Okay. So prior to coming here, I kind of took this question and I posed it to some people in my ecosystem who haven't necessarily been part of the PDC program. And some of the feedback that I got that it hasn't quite been as effective as we've wanted it to be, although it's off to a great start. I think there's been tremendous lessons learned. Some of the feedback that I received was that there seemed to be, unless you're in the club, they seem very difficult to access, some of these resources.

And so, in terms of looking forward, you know, how do you start to market those, market the PDCs in a different way so there's broader reach and so you've got more inclusion and diversity in the innovators who are addressing some of these unmet pediatric needs? In addition, I think there's an opportunity to take best practices and put them all in

one spot that somebody is updating regularly. So, do you need separate PDC websites with all the kind of same but not the same information? If the processes, you know, to your point, is a check, we've got your checklist, right, there's certain things that just fundamentally have to be done. Can you standardize that in one place that everybody can access and then use the PDCs to access as specific key opinion leaders and technical expertise and things that are unique to each PDC? So that's some of the feedback that I got from our community.

DR. KOH: Right. And those are all great suggestions. I think some of those actually have come up in the PI calls for the PDC program. So I think those will all be addressed. I think, as the next cycle comes around, I think we'll probably will see more of the closer collaboration between the PDCs so there is lack of the siloing, you could say. There's supposed to be a smaller number of sites, only five in the next one, with increased funding for those five.

But I think, you know, in general, I mean, I think the fact is that we would not be able to have tracked it without the PDC program. We talked about having 1,000 projects being assisted over the life of the program. But there definitely is areas that need to be improved. And I think we agree. I think best practices, for sure, and I think all of us are aware, including the PDC program, about what information we can share and what we're trying to keep confidential on behalf of the portfolio device projects. So just keeping those in mind, that yes, we definitely want to share those best practices but do it in a HIPAA-like compliant manner.

MR. KROSLOWITZ: I think that each of the PDCs may be actually to run a little bit differently than interact with their people that are, you know, petitioning them differently. I've worked with or had interaction with two of the PDCs, and I've had really tremendous experiences with them. I think that the PDCs have been a great step in the right direction,

at least at the very ground level of, you know, trying to move forward the early development of pediatric devices.

However, I think that part of the problem is the programs are underfunded. I think that if we funded them a little better, that they could really play a much larger role in the ecosystem and I think, with that, also take on larger responsibilities and potentially, you know, we talked about this, you know, developing these communities, that they could help aid in that and to bring people together. I think they could serve as potentially, you know, clinical study consortia or some sort, that there's many other things they could do. But I think that, I think they needed to be funded better than they are.

DR. KOH: And if I could add to that, actually some of the things that Bob mentioned, you know, we've heard from IACC and the Duke Trial Institute, determined to try and improve the pediatric clinical trials network and help to get these studies off the ground, mostly for drugs but are meant to include devices as well. So I think everyone agrees that we need more money for the PDC program. You know, that is an appropriations question, as well as maintaining renewal of the program every 5 years.

Perhaps we need to look for other potential funding sources as well. But for sure, their early goal is continue to have the full appropriation for the PDC program.

DR. WALL: One comment to sort of build on that, Chester. I think that, to Mark's point earlier, learning from other organizations such as the NSF and NIH, the way they run SBIRs, I like the idea of Phase II money. It's more focused on commercialization and holds people to commercialization milestones. I think the early PDC grants really hold you to prototype early proof, and that's great, but to get to the market we have to be real.

And then I think also thinking about what metrics we hold ourself to in that program, I mean, I think some of the initial talk was how many PMAs would come out of the PDCs, with a total grant funding over 10 years of $30 million. I mean, that's what Medtronic

spends on one PMA. So I think really being real about what that amount of money can really lead to. I think what's been done has been great, you know, Class I approvals and 510(k)s, but that's what you'd expect at that level of funding. So if we really want to take it to the next level, significant up in Phase II, hold people really accountable for what Phase II means and coach them on it, and then, you know, have a realistic metric around it.

MR. KROSLOWITZ: I think that was Pedro's approach, and the guys in Boston, that they really tried more with the Class II or Class III devices. Pedro, maybe you could just comment on that.

DR. del NIDO: Yeah. I think, you know, you really have to separate the two. I think, just to answer your early comment, you know, I've been in the PDC from the beginning, from 2009 when we first got funded, and it's been a very evolutionary process. People really didn't know what to do, and we spent most of our time actually educating our own community as to how to get their ideas even to the point where they can think about a market.

So that process, I think the PDCs have been hugely successful. You raise an awareness amongst the scientists that, in fact, what they do has value in a commercial way. And the way to do it is a very prescribed way. So that is clear. But what hasn't happened is that we haven't really tackled well the hard to get through devices, the Class IIs and the Class IIIs. And that's where, I think, ideas about how to do that, those probably need to be concentrated into a separate group because it's a very different type of effort.

And I would suggest somewhere keeping that effort alive, because at the end of the day, that's probably going to have the biggest impact on lives as opposed to other classes.

MS. WILSON: And I think, you know, I'll add, you know, again just kind of to that point on Class II and Class III, really thinking holistically about the capital continuum and what it's going to need to get there and making sure we've got the right people at the table

at the right time to set those de-risking milestones, right, so that the funding, no matter how small, whether it's a $50,000 grant, $100,000 grant, that you're spending that money on the activities which may or may not be a prototype, right, but answering critical questions that are going to position you for that conversation with John. Right.

DR. KOH: And just before we go to Juan, just, we know the level of funding is $50,000, which kind of leans us towards the early stage funding. I think I mentioned in the presentation earlier today that we probably need to get to the $250,000 funding for the Class II or higher. And that's going to require a different program. And I think one of the ideas is do we need, you know, we have SBIR Phase II; do we need a PDC Phase II where you get those higher amounts? And, really, graduates of the peds are going to go to that, but that's just an idea now.

Juan, do you have a comment?

DR. ESPINOZA: Yeah, just around, there were PDCs, I think, you know, in our experience over the last 5 years, the number one request from supported companies that we can fulfill are regulatory support and clinical and scientific partnerships and support. The number one request we can't is business development, networking, and moving the business side of that pediatric device forward.

Some of that is because of our limitations on how we can spend funding. We can't do programming; we can't do certain things. The other part is that we don't necessarily have that expertise in-house. And if we're prioritizing the development of the device and that's how we want to spend our dollars, then we can't spend dollars on these other sides. So those are some of the things that we also think about, and how can we either use existing resources at the university or the hospital or philanthropy or partner with other organizations to fill in those voids where we simply can't.

MR. KROSLOWITZ: I thought though that, Eric, that was part of the funding initiative,

that they would be able to provide all levels of support, development, regulatory, quality, and even some business advice.

MR. CHEN: Right. So the requirements for the PDC is to provide assistance to pediatric device innovators. A few of the limitations that we have is surrounding funding that a consortium can provide to an innovator to actually, for example, move from a prototype stage of their device to animal testing. So the consortiums have the ability of providing funds to advance the device development. But that is a limited amount at this point in time, so that the consortiums can focus on some of the other questions that may come up from an innovator.

MR. KROSLOWITZ: One last comment I'd like to make on that is that I had the opportunity, and it was really impressive, to look at some of these applications in the review process for one of the PDCs. And, I mean, there were really some great ideas coming forward. It was difficult, you know, to decide what you would and what you would not fund. But it was, I tell you, it really, that's why I think it's really serving a purpose, because there's just some really impressive ideas that people are coming forward with.

DR. MALTESE: Yeah, Matt Maltese from Philly PDC. And following up what this gentleman said earlier, that we rarely provide help for prototype development, it's much of what you talked about; it's how do you integrate with the clinical environment and get clinical expertise involved with the project and even facilitate some sort of trial or some sort of a focus group with the clinicians.

And we work really hard to try to make sure that the funding we provide, although small, gets groups to that next point where they can make a really compelling value proposition for the next level of funding. We don't look to just push them further down the road. We try to move them to a place where they can really be compelling for a next level of funding.

Thanks.

DR. KOH: Vasum?

DR. PEIRIS: Chester, maybe provide a more, little bit more of a provocative question. The point about the context of how much funding is available came up, and the context of that funding, as James mentioned, at $6 million, certainly as many people may think, that's very small amount considering what we're trying to accomplish. Maybe another way to pose this issue is could the $6 million be spent in another way? Or are the PDCs truly making the difference in this ecosystem that it needs to be?

DR. del NIDO: Can I just respond to that? I think the PDCs in the current form serve a critical purpose. I don't know if you can hear me. But, you know, they serve a critical purpose, and that is that there's a lot of good ideas that just never make it out of the, you know, out of the idea box. And the PDCs, I think, have gotten very, very good at getting them to the next level. But there's been an engineering focus rather than a commercialization focus.

The problem with the commercialization focus is that, A, you need a lot of dollars, okay, but you also need expertise that isn't often a level of expertise, such as managing, you know, how to deal with a venture investor or how to identify a family office or how to finance your, you know, your commercialization plan, that's not readily available in an academic institution or in where most of these PDCs are coming from.

So I think you're going to have to bring that in. And maybe some of those funds can be set aside to do that, if you look around the table, there's no shortage of interest in doing that from individuals who have decades of experience. Maybe harnessing that would be a hugely useful thing.

MR. CHEN: Well, I think I would ask the question of, you know, so we have the funding that has come from the agencies, and since the program has been funded since

2009, the Agency has given out $31 million across these groups. But that funding has allowed the innovators and the consortiums to bring in over $120 million in research. And the question is if the funding of that much is available, what else do you guys think needs to be done? Because is that funding enough? Or does there need to be more from the groups that need to provide that, or is there something else that we need to be focusing on as well?

DR. KOH: Right. I mean, I can give an example of where it could be like, and that's really the NIH, CTSA funding. And we are acting I would say like CTSAs, and those are actually $40 million grants over 5 years. And so if you want some type of benchmark to try to get to, I would say that these need to be $40 million grants for 5 years at each PDC. And that's because we are saying it be consortia. Some of these CTs, they do have preclinical, clinical, different components. Some even have actually a device module. But they have much higher funding amounts.

So the current funding is great, great for early development. But when we start getting into larger direct device funding for the Class IIs and higher, we're going to need much higher amounts.

MR. KROSLOWITZ: I think also, you know, I had an idea that perhaps we could somehow have additional funding to support some sort of an organization or group around the PDC, right, that after they had their initial investments to, you know, like Pedro said, get the idea out of the box, right, that really then took the next, took the most promising devices to the next level, right, with some business or business advice or whatever needed to happen to the next level. I think that that might be something we should perhaps think about.

DR. WALL: Just to give an analogy, maybe on the adult side to again compare adult to peds, the Biodesign Program at Stanford, which is about 15 years old now, spends about

$2 million a year of which a small chunk of that is early stage grants. Those companies have gone on to raise over a billion, so that's a, you know, 10 times the ratio of what the PDCs have raised, and it's because they're going after adult markets, generally speaking, as opposed to peds. And that's resulted in, you know, 40 startups, of which 15 have gotten to the market.

So, you know, that's the kind of success I think we're looking for. We have the fixed issue of a small market. But I think to put the 120 million is admirable, and it's a good start, but in comparison to what groups do when they're going after adult markets, it's tenfold less, just to give it a context.

DR. KOH: I think one more comment from Susan, and then we're going to move on to HDE.

MS. ALPERT: Yeah. So I'm Susan Alpert.

I wanted to comment on two aspects of this conversation. One was about bringing other expertise to the table. So I have the experience of working with a program at the business school at the University of Minnesota, and it's a Medical Industry Leadership Institute; it's part of the M.B.A. program. But what we've developed there is a group; we're now up to, I believe we're 15 executives-in-residence. We don't get paid. We don't cost anything. And we have various expertise from in the industry.

You have to realize, there are a lot of us now who are reaching a certain age where a lot of these people are not working full-time. They have a lot to offer. We have not been highly visible with the PDCs beyond the group that knows. And one of the things that we might think about is expanding our visibility and bringing those people, the business skills, the IP skills from people in our communities to this effort. I think if you reach out, you'll find that there's a lot of interest.

And so that's one of the things. And the second is the visibility, and I don't know

how visible the PDCs are, for example, in each of the communities beyond just the hospital and the in-group. I think we need to think about how do we make more visibility? This meeting is one good way to get visibility to the program, but I think we need to work on what are some good ways to get more visibility so that we can bring all that expertise to the table, and money, because many of those people also have money, might be interested in investing in some of these startups, and also thinking about ways of identifying other people to bring in.

Thanks.

MR. BILLIG: Let's see if I can say something here. Susan, I fit into that same category as you. And it was only probably back in May that I became aware of the PDC and got very involved. I've been doing regulatory work for 45 years. In fact, Susan, we worked together when she was at FDA. She signed my wife's PMA, in fact, back then, a long time ago.

MS. ALPERT: Many of them in the room.

MR. BILLIG: But I think the thing that is important here is that there isn't enough awareness. And I think that's the thing. This has been an excellent meeting, and I really have appreciated being part of it. Shuvo Roy invited me up to be on a panel up at UCSF, and that's where I met Vasum and shared in some of the experiences that I've had. But one of the things that I think is very important is that there really isn't enough public awareness of pediatrics.

I've done hundreds of submissions, been doing it, this hair used to be red back a number of years ago, but I can tell you that the number of submissions that I've had with pediatric indications I can probably count on one hand. Now, I've worked for big companies, I've been bought by big companies, and now I'm doing a consulting. And I have 40 people in my company. And we work with probably maybe a half dozen that are in the pediatric sector, and some of them that are early stage funding. And it is really, really

difficult to get money.

And I think Mark did an excellent job to be able to take a company public. It just doesn't happen. Being in the Bay Area, you know, I see a lot of venture groups, and I work with a lot of early startup companies, and there just is not a opportunity to get funding, because of that return of investment, it's not there. The other part is there's no corporate entity, from a strategic partnership, that is interested in pediatric.

So, you know, my experience may be different than all of you, because of when I came and saw the first question on the board yesterday, and it said 70% had been involved in bringing products to market. And I'm looking at it, and I'm going, but how many of those 70%, the products that you had, what percentage of that was the overall product? And I'd say that that's probably less than 5, at least from my standpoint.

So I think that there's a tremendous importance. I think this is going to do it. But we need different models. We need a lot of things that we're talking about here, to be able to make a change.

DR. KOH: And just one last comment before I hand it over to Bob for the HDE is, you know, in terms of what has currently been used, probably by most of the PDCs to have the pediatric pitch competitions and the handing out the money, but I think, of course, as with all suggestions, is something that probably in the next cycle probably have to be looked at by the consortium.

So, Bob.

MR. BILLIG: Thank you.

MR. KROSLOWITZ: So the next question was then related to the HDE program: Is the HDE program designed to help the development of pediatric programs at the Agency? Does the community feel each program is sufficiently filling the pediatric medical device ecosystem?

DR. PEIRIS: And I just want to remind everybody, the time that we have allotted is until 4:50. I know a couple of panelists will need to leave at around 4:30. I want to give enough time to get through these topics, so let's try to keep focused on priority areas and key things that we can consider in putting into the report to Congress about these topics.

MR. KROSLOWITZ: Does anybody have a comment about the HDE program?

DR. PEIRIS: James, do you have any thoughts?

DR. WALL: Yeah. I think I mentioned my one provocative question, but I do think that when you talk about the HDE designation that leads to HDE eligibility, I think that there has been progress. I think the for-profit motive is a bonus. It has been, in my experience, and it's something that is a driver. I think, however, thinking of it as a population in terms of number of patients does a disservice because it disproportionately motivates companies with high-value devices or high-cost implants.

So it makes sense for 4,000 patients, for a $50,000 implant to develop. There's going to be a potential return on investment. That sort of fits the entrepreneur's dilemma that I laid out. For a company doing 50,000 patients but it's $100 device, that math no longer works out because there's a fixed cost of developing things. So, again, maybe I'm just beating it to death, but I think that instead of a population number, it should be thought of as an orphan market and that the value of that market should be brought into play, or at least considered as opposed to just the population.

DR. PEIRIS: Thank you, James. And I just want to chime in here, I know Andrew, you posed the issue also about evaluation of a market. If we were to switch between a population number versus what your potential value of the market is, is there a concept that you think could be incorporated into this program, to help facilitate devices specifically for kids?

DR. LO: Well, I think that that would certainly help. But it seems to me that there's

a bigger issue. And the bigger issue is changing the narrative of exactly what it is that investors are getting for the funding. I mean, a good case in point is that, you know, so far we've mentioned funding on a number of occasions and the challenges. By a show of hands, can anybody tell me, how many people here in the audience are investors?

Now, by investors, I mean not just people that are looking to try to make a difference for philanthropic reasons, but greedy capitalist pigs.

(Laughter.)

DR. LO: Like me. How many investors, purely private sector investors are there in the audience? So someone once said that, you know, when they asked a bank robber why they rob banks, the bank robber said, that's where the money is. If you're looking for funding, shouldn't you have some investors here? Shouldn't they be part of the audience?

So I think that the way to change the narrative is first to bring in the people that actually have the money to deploy and ask them what they're looking for. And, you know, I've described the Sharpe ratio as one very great coarse characterization, but if you get the right investors, they can tell you in a much more detailed way what hoops you need to jump through in order to access much, much larger pools of capital. And I don't think they're very complicated hoops.

And I think this group, you've brought together an amazing group here. So this group is capable of creating the structures that are necessary to deal with these challenges. But I would urge you to bring in the investors sooner rather than later, to have them join the discussion.

MR. KROSLOWITZ: I just had one more comment on the HDE program, I think, and then we should probably move on in the interest of time. But if you look at, again, the FDA reports that were required by FDAAA, we discussed that yesterday, there were 380 applications approved, medical device applications approved over the last decade. Only 24

of those applications were HDE applications that were approved over the last decade, and zero of them were approved solely for the pediatric population. So if we answer the question, is it really serving the needs of the pediatric ecosystem, I think probably the answer is no.

MR. BILLIG: If I can make one comment there too: We've done a number of, maybe a half dozen of those submissions, and they're arduous. I mean, they really aren't easy. But, yet, it's worthwhile, and it's a better way to get there and get to market. You know, we've got it where it's up to 8,000 patients now that you treat, so it's up from 4. I think that's good. I think that's an improvement. But at the same time, it's not going to be the answer. It needs to be better than that.

DR. PEIRIS: Now, thank you. I'm going to help move us along here as well. I just want to clarify something. There are a few devices that are pediatric-specific. So I just want to clarify that point. And the data that we've demonstrated that Mary Clare presented reflects that there hasn't been much of a change over this past decade with respect to applications, both coming our way and approvals in pediatric specifically. So, again, we have to be thinking a little different. But I just want to clarify that topic.

Mark, I'll have you take the next one.

DR. SCHLESINGER: Okay, guys. I know it's late, but I really need you to be with us on this one. We got panelists who are signed on. We now have two of the best questions you're going to get for this final session.

For the optimists, Question Number 1, what's the most effective kind of incentive you think could be brought to motivate greater development of pediatric devices? For the pessimists, what are the kinds of interventions that could go wrong? Sorry, for the pessimists, what are the kinds of interventions that could go wrong? In other words, if you have a policy, what kinds of policies might actually produce counterproductive results?

I'll give you an example. As you saw on the congressional mandated discussion topics, use of postmarket registries is one of the things Congress wants this group to talk about. The feedback we got from the pilot study on the survey was that a lot of people are really nervous about postmarket registries because they're afraid it will actually discourage off-label innovation and otherwise actually impede the development of new device utilization. That's just one example.

So what are the key incentives that we should really be pushing? What are the things we should be watching out for? The flourishers.

Greg, come on up.

DR. LICHOLAI: So I'll dive into that snake pit. Greg Licholai from Yale.

So thank you for a wonderful discussion, and thank you for wonderful presentations, and I guess, trying to put together what Professor Schlesinger and Professor Lo were commenting on, and thinking back on the earlier discussion today about the history of orphan devices and, you know, cautioning here that I don't know if this is a third rail conversation or not, but the orphan legislation has been described as the most successful legislation ever.

You know, since I think it was written in 1983, many hundreds of millions of dollars have been a value creation as well as many dozens of drugs have been approved on the basis of that. And I think it has more to do with Professor Lo's direction of providing financial incentives, pure financial incentives that, you know, possibly have gone further than expected in such things as pediatric vouchers and other sort of permissive attitudes towards very high prices for certain drugs.

It seems that, you know, there's a bit of an elephant in the room in terms of looking at what incentive is possible, if that's, you know, at least kind of taking a view of history, of what's happened previously with orphan drugs, you know, which was facing similar sorts of

issues in terms of small markets. We're not going to suddenly create much more patients to have more statistical populations, which really would probably solve everything. So I guess I wanted to put that out there as a possible discussion point and question.

DR. LO: Yeah. So I'd be happy to respond to that, but I suspect other panelists will have a lot more to say.

So the Orphan Drug Act of 1983, from an economist's perspective, was a brilliant piece of legislation, because prior to 1983, over the course of a 10-year period, there were maybe eight orphan drugs approved by the FDA. And since then, I don't know exactly what the number is, but I think we're at about 300 orphan drugs since 1983. And it's an amazing thing because you're talking about a patient population that is by definition small. That's what we mean by orphan or rare disease. But in many cases, the therapies that are being developed were absolutely transformational for these neglected patients.

And so that's actually a very interesting idea that we ought to think about for pediatric devices. If you can get legislation such as that, I think that would actually do a lot of good. It would change the dynamic. But there's a lot of things that could be done even without that kind of legislation that takes a page out of the playbook of the orphan disease space.

We actually have here in the audience somebody from the National Center for Advancing Translational Sciences, Nora Yang. Is Nora still here? She may have had to leave. But NCATS is a part of NIH that actually helps scientists take their ideas from the laboratory into the clinic. And I think it was Juan Espinoza who asked the question about are there resources available to centralize the development of commercializable strategies? Well, NCATS actually helps scientists do that.

There's no reason why you can't have an NCATS for devices and specifically for pediatric devices. So I think that's another example of things that can be done. But,

certainly, I think the Orphan Drug Act and the way that the FDA has really focused and has done some tremendous things for patients in that space, I think, is a great way to think about what we can be doing here.

DR. KOH: Just to add, I believe NCATS is the CTSA grants, with the range in the $40 million grants.

DR. WALL: Could I just point out one glaring difference between orphan drugs and potentially orphan devices, though, is that orphan drugs tend to get priced at lifetime value, or at least companies are trying to go there. So a recent drug for, you know, congenital blindness was priced at $800,000, or something in that range. That payment mechanism doesn't really exist on the device side.

So I think, in conjunction with development, we also really have to talk about payment, which I think we'll get to, but there is a glaring difference on the payment and potential profitability side that has to be, I think, dealt with.

DR. LO: So I couldn't agree with you more. That is an important difference that I noticed, and again as an outsider that's new to this area, I have to tell you that I don't understand why that is. You know, the example that I gave of the Codman pump, that pump being priced at $5,000 to $7,000, it should be priced, you know, I think on the order, an order of magnitude higher.

And I don't understand why that's the case. I understand that the healthcare system has all sorts of burdens and pressures. But I think it is possible for drugs to be priced too low. And a case in point is sterile injectable cancer drugs that have tremendous shortages because they're priced too low. And the same is true for devices.

DR. SCHLESINGER: Other ideas, suggestions?

MS. TENENBAUM: So I think that, you know, when you talk about these kind of things, we've seen a little bit of the value base, right. And I think the $800,000, you know,

genetic cure for congenital blindness is an interesting model because it is a lifetime of benefit realized. But there's also, if it doesn't work, then I think the payer gets some part, I don't know how much, of that back. So there is something there I, from putting my patient hat on, I'd like to know if the family gets any of their copay back. But that's neither here nor there.

You know, but I think that looking at the value and looking at the lifetime benefit realized, we've talked about this a little bit, me and some of the panel members, and I'm sure a lot of other folks. But, you know, if you have especially a health insurance that is tied to your job, then when you're under 22, 26 now, right, you have one insurance, maybe more, but whatever your parents have, and then another one and then another one and then another one, and then you're finally in Medicare.

And so the benefit of you not being sick, being able to be a productive member of society or what have you, is not realized by any single payer, right. And how do we capture that value, and how do we get that back into the system appropriately?

UNIDENTIFIED SPEAKER: Yes. This is a fascinating discussion, but I'm afraid there are a couple of elephants that we have not noticed in this room. In this society today, there are those that write checks for healthcare, whose best patient is a death patient because he's the cheapest. They're busy in getting as low a payment as they possibly can get away, and profit is no object.

You have now people proposing a law in California and in Ohio whereby they want to regulate how much money can you make delivering a dialysis service. There are people that say, we don't care what your cost is, we're going to pay X. Managed care is a glaring example of this thing. And the people from managed care that are running a lot of what happens today in healthcare are not here. And they're not here for a reason. They don't care. They want it cheap. That's all there is to it.

And if we, this forum does not deal with whatever society is willing to pay for whatever we want, nothing else is going to happen.

MR. BAUMBERGER: I just want to address your point about, you know, what potential pitfalls there are in incentives. And I think, from American Academy of Pediatrics' perspective, we very much hope that we can come out of this with some good ideas for some new incentives that will drive additional development. We've talked a little bit about the pediatric rare disease voucher, and Dr. Yao said how the jury is still a little bit out on that. GAO has looked at it.

I think there are a couple of pitfalls in how that program was developed that make it difficult to really see what we've gotten out of it, at least so far. Some of the drugs that have been approved under that system were going through the pipeline and were about to be approved anyhow. There's also the potential pitfall that a company seeks approval, if the bar is just approval and not some sort of additional metric; if a company could just seek approval to get a big reward, that doesn't necessarily mean that patients are benefitting from it.

So I think incentives are good. I think we just need to be sure that any incentives that we're putting forward are well targeted and are going to end up, you know, improving kids' lives.

DR. SCHLESINGER: Okay. You're on.

UNIDENTIFIED SPEAKER: As an academic person, I would like to see some credit to the younger people who are involved in device development research and perhaps a pathway to promotion, and defining what aspects of device development could be used as a means for their academic advancement. Oftentimes, working with the companies is sort of viewed as not something you should do when you're young, and not something you should do sometimes at all. And so I think that that would be one academic advance that I would

suggest.

DR. PEIRIS: And, Mark, if you don't mind, I think the PDC programs certainly are doing that, and I think that cadre of generational individuals in training, I'll put that out there, are learning to advance their careers through device development as well. So I think that's part of the process, with the ecosystems developing around the PDCs.

Tiffany, if you want to take on the next question. I know we've addressed it, but perhaps there's other nuances you'd like to bring up.

MS. WILSON: Excuse me. The question was, really, how can FDA increase assistance to medical device manufacturers in developing devices for pediatric populations, and what resources would be required.

So what I heard earlier, I think, were some great ideas around kind of looking at NIH models and NSF models and the Phase II kind of SBIR and some other funding mechanisms, but really curious to hear other ideas.

DR. PEIRIS: I'd just encourage everyone to speak into the mic, because of everybody who can't hear, either in person, online.

DR. KAPPETEIN: So maybe if I can address that question. So we're talking about the incentives in techs, you know, in monetary incentives, but I think what is also very important, that the regulatory process is clear, that there's a uniform process. And I think, also to attract capital investors, you want to make clear how long the process will take and what the burdens are and so I think harmonization is extremely important, that people know exactly what the rules are so experts at the FDA that are experts in pediatric devices is necessary, that the harmonization of the regulatory process, I think, is key here.

MR. THRODAHL: I would like to second that. I think we can talk about financial incentives for promoting research, but I think what really is expensive is the regulatory approval process. I remember vividly, when I was group president of Zimmer, there were

no PMAs underway. It was viewed as simply too expensive. And so anything that could be done to second the comment the gentleman just made, to make the process simpler and clearer, and I think we would argue a process in dialogue with clinicians, clinical experts who really understand how these devices might be used, that's what FDA should focus on. That is within their power to do tomorrow.

MS. WILSON: And this is (interrupted)

DR. KAPPETEIN: So maybe if I can give a good example of this is in heart valve device. So for children, there's a heart valve sometimes needed. You try to repair a mitral valve, but sometimes if you cannot do this, you have to replace a valve. A 50 mm heart valve is exceptional. So St. Jude got the approval, but they had to do a study with 15 patients to get it approved. There are already 17 and 19 and 21 mm valves on the market. They just have to prove that it also works in children. So, of course, you need some data to see how it works in children.

But what you can do is also in the lab, you can mimic the hemodynamic circumstances in the heart, and you know what the gradient will be of this new heart valve. You know what the sufficiency will be. You know exactly what the valve thrombosis rate will be. And that were exactly the endpoints that the FDA asked for the study.

And so to recruit patients, it's very hard. They sold, up until today, only 15 of those valves. They will never make a profit out of it. But it's the regulatory process is also very difficult. It's a real burden for industry to put something on the market for such a small patient population.

MR. KROSLOWITZ: And I don't know that anybody really understands the cost, right, associated with these studies. So I was advising another company that had a valve product that they are in an early study, and centers were asking up to $60,000 per patient, to draw some labs, do some echoes and enter the data. We heard yesterday that, right, the average

cost of a surgical procedure in the pediatric population is around about $90,000. That's the cost. Hospitals are reimbursed about a third of that, so say they get $30,000 for the procedure.

And then the industry comes, and not for the whole procedure. The device was included. We gave the device. We didn't charge for the device. We had a clinical study protocol to collect data, included some laboratory evaluations and some echoes at certain time points. And the institutions were asking for up to $60,000 a patient. How do startup companies afford that? How do you do it?

DR. PEIRIS: So I'm going to translate that. The question is (interrupted)

MR. BILLIG: Yeah. I think this is the crux of the situation. Oh, go ahead.

DR. PEIRIS: The question is how can the FDA improve assistance to medical device manufacturers?

DR. WALL: CanI add one thing to it, which is, I think it's if you (interrupted)

MR. BILLIG: Yeah. I think it's almost a catch-22. We don't want to lower the bar on these products, but we want to get regulatory approval without having to go through something that it's going to take years and years and years and a lot of dollars to bring that product to market.

So I think that there is a way that we could learn from some of what Bakul's been doing and what he talked about yesterday with the lower risk products, at least, where we take those and we do a precert program, where you don't have to go through all that for some of the Class I, maybe some of the Class II products. You can bring them to market quicker and easier, without having to go through that burden and that cost, and then focus your attention on the Class III, which is where you really want that technology and the studies.

But you've got to be very careful, because studies, it's hard enough to do a study,

and you do a study in pediatrics, you're talking about very, very difficult. You have less patients to deal with. You have a situation where you've got the parent, you've got the child, and you're having an ethical decision as to whether or not you want to subject your child to that. And I think that us, as parents, we can say that we probably, unless there was a last resort, I'd have a hard time putting my child through that.

So it really has so many outside factors on it that really make it very difficult to get that patient population and study it, to a degree that you really have that high safety and efficacy confidence.

DR. PEIRIS: Thank you, James.

MR. KROSLOWITZ: And to you your point, I mean, this is not something necessarily that the FDA could control or address, right. I mean, we're looking, we're making a report to Congress, and this is an issue. Is this somehow something that Congress could influence with some legislation, perhaps tied to reimbursement and to Medicare funding of pediatric institutions, that there's some mandate that they are, you know, there's some requirement that they could, you know, participate in clinical studies for pediatric devices at a reasonable cost or at a cost of, you know, whatever they would normally be reimbursed for the procedures?

But these clinical trial offices and the hospitals have now turned, like the IRBs, they've turned into profit centers. And it's amazing, amazing the amount of money that they're looking for, for clinical studies.

DR. PEIRIS: Okay. I don't know if my microphone's working, so hopefully all of you can hear me. So, I'm going to have James speak and then Andrew, I want you to take the next question.

DR. WALL: I don't think, yeah, I don't think this is working at all, is it?

DR. PEIRIS: Yeah. There, well, speak up there.

DR. WALL: Thank you. That's actually working.

I just want to make the point that there is a down side of potentially decreasing regulatory burden. I think generally it lowers cost, but if you don't solve the amount of clinical data and clarity into payment, then you may have just kicked the can down the road. And the thing that keeps me up at night as an entrepreneur is how I'm going to get paid for it, no longer the regulatory burden for the most part. There's a few exceptions to that.

And I I applaud the FDA for trying to work with CMS. It's a glaring deficiency that they're not here at this meeting. But national coverage decisions, clarity into what it will take and how long it will take to get payment, is something that's absolutely critical. And if you don't combine that with your regulatory burden, then I think, you know, you can end up just kicking the can down the road without developing the clinical evidence you're ultimately going to need to get paid.

MR. KROSLOWITZ: Related to the topic, you have to convince CMS to be involved. I mean, they have no purview over the pediatric population, and that's their stance. They won't make a decision or recommendation because, right, pediatric patients are (inaudible).

DR. WALL: Fair enough.

MR. KROSLOWITZ: (inaudible) covered by Medicare and not by Medicaid.

DR. WALL: I guess you're right.

MR. KROSLOWITZ: No purview.

MS. WILSON: That's where FDA could be influential, I think, in thinking about interagency and this isn't working. But how do you facilitate interagency collaboration and getting everyone together around the same table and working together to get some of the stuff done?

DR. PEIRIS: Thank you very much.

Andrew, do you want to take on the next topic?

DR. LO: Sure. Yeah.

So the next topic has to do with business models. You've seen a number of business models discussed in the last few sessions. Are any of these models scalable? Anybody have any comments on various different business models that may or may not be appropriate to deal with this challenge?

(No response.)

DR. PEIRIS: I'll talk and open up the questions here. So OrthoPediatrics presented a case example where a company that went straight in, focuses specifically on pediatric devices, has been relatively successful. One of the key factors that they mentioned was almost good support, economically from, as you mentioned, at least one individual or a number individuals, but at least one that had a significant amount of, as you mentioned, almost a bankroll. Is that model something that could work for other areas of pediatrics, like congenital heart disease?

MR. THRODAHL: Just to clarify, I think though the real model was beginning with in the company's infancy by developing products that were not orphan products by any means. They were identifying where adult surgical systems were being inappropriately used, plates being sawed off with a hacksaw in the operating room and bent by the surgeon to conform to the different curvature of children's bones, surgeons who weren't utilizing the adult instruments because they didn't work. They had cobbled together a series of instruments from other places and they carried them around like a chef with his knives. And they would use these instruments and MacGyver their way through procedures.

And the development of many of our surgical systems capitalized on much larger adults and markets, shall we say, that were used with children. But then that has enabled the company to begin funding, on its own, more orphan-like disease states, like osteogenesis imperfecta or early onset scoliosis, which themselves will be substantial

markets.

Where we were fortunate was the ability to find a family office that was able to then help carry the company, because we still are not even at break even, even at $60 million in revenue. And I was intrigued that there were others who observed that there were family offices that might be motivated by a longer-term kind of investment horizon than the guys with suits from New York who show up on your board because they own 40% of your company and they got a 3-year time frame.

MS. TENENBAUM: So I don't, this is not working (interrupted).

DR. del NIDO: I'm sorry. Can I just add one comment, or just a follow-up comment to that?

When I got traction on our device was when we can actually put it inside the ventricle and show a heart valve. And so the heart valve company said, well, then you can see our device being deployed in an adult. Suddenly, it become something that they were very interested, something very real, because they were having a hard time implanting a mitral valve device transcatheter that was not quite stable.

So that model, I think, works quite well. And I do have to say that not all family offices are the same. Some do still have the same motivation as a venture group. But you can definitely find ones that have a real mission and are willing to bridge you to that next level.

MS. TENENBAUM: So what I want to just bring up is that the different models may work better in different phases of development, right. And we saw that kind of, we used to call it the valley of death. I don't know if you guys call it that. We called it that in oncology. You know, and there might be a specific need for a different model, right, in that phase of development than the last phase. Or, you know, maybe the government funding is best for the preclinical phase. And so I don't know that there's going to be necessarily one model

that fits all, but even one model that fits all across the spectrum. And so I just want to take that into account as we have this discussion.

DR. WALL: I just want to, you know, I think we're sort of talking about maybe two things here. So one is funding business model, and then the other is commercialization business model. Just to comment on the later part, what we have seen recently, a fair amount of success with some startups, more on the adult side, frankly, out of our program, is an at-risk selling model, meaning that they will go at-risk with hospitals, who frankly, hospitals run on razor-thin margins. So they're not the bad guy.

But if you're making a hospital base sale, you tend to be much more successful these days if you will go at-risk in some way with the hospital and say, look, our value proposition is to get you this outcome. If you don't get it, then we're both going to take a hit for that. And I think that that's been quite successful. That can be operationalized in a lot of different ways, but that at-risk model has resounded really well with hospitals who are dealing with thin margins.

DR. LO: So maybe we can just go back to the example of OrthoPediatrics, because I think there's some really interesting things that we can learn from that experience, and it would get back to this issue about different funding models for different stages.

So I know very little about the company, although I did watch its IPO. That is my domain. And it was very curious that the IPO did as well as it did, given that this is a medical device company and not only a medical device company but a specifically pediatric-focused medical device company. So the question is why. Why did they succeed?

And I'm going to argue that there are actually a few characteristics that make OrthoPediatrics unique. One is that they actually have already de-risked their portfolio to investors. And the way that they did that was with 3,000 different products. Now, of course, not all of these products are unique and different from each other, in the sense that

if one product fails, presumably that's going to affect the other products. There's going to be some bad news. If one catheter fails, other catheter products that are in the pipeline may also be hurt. But over the course of 3,000 different products, they have enormous diversification, enormous risk reduction, so that's point number one.

Point number two, if you take a look at their earnings, year-on-year, prior to IPO, it looks very predictable. I don't want to say that it's a Ponzi scheme, because I'm sure it's not, but it sort of looked like that straight line going up, right. And investors respond to that.

The third thing is that the company has a very clear narrative. They don't do all things pediatric. They don't do all things devices. Their focus is on orthopedic pediatric surgical devices. And there's a very clear narrative that can be explained in about 10 seconds to any investor.

So having those three characteristics, being able to diversify across a large number of projects, being able to show consistency of performance, even though they're not break even yet, it's pretty clear where they're headed. And, finally, a clear narrative of exactly what it is that you as an investor are getting when you put your money in that company, that to me explains why OrthoPediatrics has been such a success. And I think all of those things can be transported to other aspects of pediatric devices.

DR. KAPPETEIN: But that we as adults also do this. It's a quite easier device to get approval for. So it's not a very complex device. But if you get to more complex or something that you put in the bloodstream, you know, or in the heart, then the approval process might be more cumbersome and not predictable

DR. LO: So I think we can maybe turn to Mark and ask whether or not there are any complex devices. I don't know what the 3,000 devices are, but I imagine that some of them can be more complicated than the other. But remember that, yes, complicated devices may

be a regulatory, more risky from a regulatory perspective, but complexity also means you can charge more for it.

DR. KAPPETEIN: Sure.

DR. LO: At least I think you can.

DR. KAPPETEIN: But to come up with 3,000 very complex devices within one company is hard.

DR. LO: Right. And I'm not suggesting that you need to.

MR. THRODAHL: Just to clarify, Professor Lo, your analysis was spot on. But there are 25 surgical systems, but within those systems are all of these things. So in our scoliosis implant system, there are 500 different components. Half of them are instruments, half of them are all of the little implants. These, though as a system, wind up being pretty complex, but from a regulatory standpoint, they don't require PMAs. So from that standpoint, we are not dealing with the problem that you were referring to, Pieter, with regard to a very complex regulatory pathway.

I seem to think of it in terms of it, in terms of every company has a business strategy problem they have to figure out. How do they finance this thing? How do they work on what kind of products at what point in time? And it's just a tough row to hoe when you start out with basically a very small target population you're going after, with a very complex product, with enormously unclear reimbursement and regulatory approval. That is a real strategic problem.

I'd much rather do the simple things, of going after products that are easier to develop, building out the company on that basis, and moving up a curve of innovation so that then you can afford ultimately to do many of these more difficult kinds of things.

DR. LO: Yes.

MR. THRODAHL: But every company has to find its own way through that strategic

puzzle, I think.

DR. PEIRIS: Thank you. I don't want to interrupt the conversation, but there is a question online.

Brittany?

DR. GOLDBERG: Yes. Is it feasible for Congress to establish a global health initiative to pull orphan disease through the world from idea through commercialization of pediatric devices to help incentivize the entire process?

DR. LO: I'll be happy to take that, since nobody else wants to. So I think that it is definitely possible. Whether or not it's currently feasible, given our current Congress, I think is a different question. There's definitely a global challenge. And I was in Hong Kong a few months ago, and I have to tell you that the biomedical ecosystem in Hong Kong and China is just extraordinary. I mean, they are pouring tens of billions of dollars, the government is pouring tens of billions of dollars into their biomedical infrastructure.

And so from a global perspective, I think that there are tremendous opportunities. Somebody mentioned that you might think about pursuing various kinds of fundraising activities in China and in Asia more broadly. So I think that that's definitely a possibility. Whether or not we can get our government to focus on this issue is a different question. I think that's a bit of a challenge, although if there's any issue that can actually bring together the reds and the blues, I think it would be pediatric challenges, illnesses. So I think if we formulate it the right way, there's definitely progress that can be made.

DR. PEIRIS: Thank you, Andrew.

James, do you want to take on the next topic?

DR. WALL: Yeah. Is this still not working? I'll talk, oh, perfect.

I actually just want to add one more point to the last discussion for business models. From Silicon Valley Bank analysis and Wilson's in Simi, over the last 5 years, return on

investment has actually been higher on PMAs than 510(k)s, and there's a lot of different reasons potentially for that, but again, developing the evidence for PMA ends up probably with quicker payment, so there is data to suggest that that really matters.

So let's move on to the next (interrupted)

DR. LO: Sorry. Actually, can I add just one thing to that? Data is a critical issue that's been mentioned a few times. One of the things that the FDA can do to actually help accelerate innovation in this space is to provide data, or perhaps to collect data on probability of success for various different approvals and other thresholds. The more data that we can bring to bear, the lower the risk we can, you know, get from the investor's point of view.

DR. PEIRIS: I love that idea. Just the data that we presented today was a enormous undertaking with respect to our data systems and our workforce capabilities to clean and clarify that information. So I think the data certainly is important. But the resource necessary to engage that data is important as well.

MR. CHEN: I'm going to make one very quick comment because I know we got to move on, but in the nephrology world, about several years ago, it was recognized by everybody, all the stakeholders, FDA, industry, academia, that we weren't developing enough devices to help adult and children who have kidney disease. They established something called the Kidney Health Initiative. And the reason I mention this, it is a consortium which was started as a link between the American Society of Nephrology and the FDA. And then we brought in industry, patient groups, etc. And it's resulted in many publications, including *Endpoints*, and various ways that we can get medical devices to the market quicker. It includes drugs, but it's also devices.

The point I wanted to make is do we have anything like that in pediatrics where we have established consortia which can attract industry to say I can invest in certain projects

that may be proposed to the Kidney Health Initiative, that includes academia, includes industry partners? There are dozens of industry partners that have been, have given funding to the Kidney Health Initiative. That includes the American Academy of Pediatrics. It maybe includes some other specialty organizations.

I'm not aware of anything like that. And the reason I bring it up, last point, is that the funding for kidney disease and the difficulty in getting funding parallels that we're seeing in pediatrics. There just doesn't seem to be a lot of venture capital that's going toward it. There hasn't been, and we're struggling to result in, to get improvements in outcomes.

So that sounds like a pie in the sky, but we did it here with the Kidney Health Initiative. Are we actually marshaling all the resources and the stakeholders together that would then be an attractive entity for industry to say, I'm going to try and maybe invest? Because people can propose things to that initiative, and then they can maybe get funding. This would more be start funds, but is there anything like that in the pediatric world?

MR. PARKER: Susie.

DR. McCUNE: Hi, Susie McCune, Office of Pediatric Therapeutics here at the FDA.

Not in the device arena, but to give you an example of another very successful consortium is the International Neonatal Consortium, where we now have over 200 stakeholder institutions, including industry, academia, patient-parent advocacy groups, and a number of regulators, global regulators as well. Started with about five working groups, white papers, looking at endpoints, providing a guidance document to the Agency. And now I think we have, we've proposed I think closer to 15 to 20 working groups right now.

So there are, not in the device space exactly, but certainly the potential to have that group of stakeholders, which is all of the neonatal stakeholders to have potentially a device working group of that consortium as well. So another opportunity there.

DR. KAPPETEIN: Maybe, can that be an example? In the adult cardiac space, there's the Valve Academic Research Consortium. So when transcatheter heart valves were put on the market, nobody knew exactly what, how to study them, you know, what the endpoints should be, whether you should do echo exams, what is a mean mortality, should you measure it at 10 days, at 30 days, at 1 year? So this Valve Academic Research Consortium wrote two documents, a Part 1 and Part 2, and that is absolutely always used by every industry to come up with study designs, what is the appropriate design and what are the definitions and variables.

And I think something similar, we could do here. I have groups and, of course, it'd have to be very different for orthopedics, for valvular disease, or etc., but that would help very much to define what studies should you do, what are the endpoints that you should measure, and what are the variables, how to define them. It would also enable registries to adopt those variables and those definitions. So I think that's, next time is, the next point on the questionnaire is the next steps, and that could be one of the next steps, maybe.

DR. WALL: Well, we touch on payment, really quickly. This is going to be easy. First question, yes or no, I want an audience poll: Should there be special reimbursement considerations for pediatrics? Who says yes? Anyone who says no has to leave. Okay.

(Laughter.)

DR. WALL: But, of course, the devil's in the details, so let's talk details of special considerations. I'll give an example of how complicated it is. In pediatric surgery, there's specific 3 mm surgical devices that are being made. Currently they're about twice the cost of 5 mm adult devices. Because we get a single payment through DRG for the episode of care, the hospital basically just has to eat that cost. It doesn't seem fair to me, but there doesn't really seem to be a structure around it.

That changes a little bit when you get into fully reimbursed devices. But does

anyone have a suggestion, functionally, how we could consider reimbursement for pediatrics? And I might point to my partner in this discussion, Bob, who's from the payer side.

How could we consider that in the framework of how we pay for care?

DR. McDONOUGH: It sounds like, just to take from your example, that maybe the DRGs are wrong, that there should be a separate DRG for pediatrics if in fact the costs of the management are higher. But part of the question here was, you know, also fee-for-service, value-based reimbursement models. I think it's a good idea that reimbursement be commensurate with the value. I mean, there are people that have been working on this in the area of drugs, like the Institute for Clinical and Economic Review, that could also extrapolate that to devices.

But what I see of the issues with respect to pediatric devices also have to do with issues around patent protection, market exclusivity, and market clearance. I mean, if we can get adequate market exclusivity and patent protection, that would affect the ability to be able to gain reimbursement. And what I see right now with respect to many devices in pediatrics is that there's very poor market exclusivity, and sort of an adverse consequence of sort of the easy market clearance through the 510(k) process is that there's no manufacturer that's willing to invest the money because there could be another me-too company that makes exactly the same product for a lower cost.

I think another thing that we need to focus on is an example within pediatric oncology where almost all children are entered into clinical trials. I think we need to have the same laws with respect to pediatric medical devices where it's common for children to enter into clinical trials rather than an exception.

DR. WALL: Any other thoughts? Or we're getting pretty close up to it, so I think I win the award for the quickest question discussion. Let's move on.

DR. PEIRIS: Thank you, James.

Pieter, I'll hand it over to you.

DR. KAPPETEIN: Thank you very much. And, of course, the last question is where everybody has been waiting for, for 2 days, what are the next steps? What are we going to do with what we have learned during the last 2 days?

And as I just mentioned, you know, one of the suggestions for me was this kind of definition and point group. There's a VARC. There's an NVARC module. There's a BARC, a bleeding. There's NARC for neurological endpoints. And maybe we could also have a PARC for pediatric endpoint definitions.

So having said that, what would be the next steps that we need to take? Has anybody suggestions? Besides a working group on definitions and study designs.

MR. BILLIG: One thing that I think it's been brought up is the stakeholders. And I think it's really, really important to get the VC community involved, to find out what it will take for them to change their acceptance. Some of it may have to do with incentives. Some of it may have to do with things that they can forego that they normally don't in looking at that profitability, because right now we just don't have a system that allows investment to be a good return on investment for pediatric use.

DR. KAPPETEIN: So you would suggest one group that comes together to work on this specific topic?

MR. BILLIG: I don't know if you'd put them all together, but I think you need to at some point. But I think we need to feed and start working with the VC community, to be able to see what they would require and how they would change their program, because there's got to be a paradigm shift.

DR. KAPPETEIN: Right.

DR. PEIRIS: So just to add on to that, so the survey that Mark Schlesinger had

mentioned is intended to get some more nuanced perspectives from a number of different stakeholder groups in the ecosystem, including VCs. So I think that certainly will add to the conversation.

Andrew, I know that we have some things in play, so I'll open that to you as well.

DR. LO: Yeah. So, actually, I just wanted to add to that and suggest a slight adjustment. I'm not so sure that the VC community is the community you want to target, because I think that venture capitalists, while they have a lot of expertise, they themselves are challenged in being able to make investments in a market like pediatric devices where the economics just don't work for the venture capital model. The venture capital model is the wrong model for this particular market.

I would urge you to think about getting other investors. So we've already talked about family offices. That's certainly a very important stakeholder group. But I would also talk about philanthropic organizations. I would talk about patient advocacy groups. In fact, one of the narratives that you might think about, and we talked about this earlier, when medical devices are considered, the adult population is typically first.

Well, what if it's the case that you focus on changing the narrative and approaching all of the various different adult device manufacturers and asking whether you can sublicense pediatric devices from their adult indications and then create a portfolio of those pediatric device indications and then now use the power of that portfolio to be able to attract a different set of investors, not venture capitalists, but investors that are willing to be more patient, longer horizon, and are willing to look for that long term, while at the same time, you know, being able to step up and invest in the short term.

I think that that's a different business model that really comes out of thinking creatively, of bringing together these various different stakeholders. Because as was mentioned earlier, different investors are appropriate for different stages of clinical

development and different kinds of risks. So bringing them all together, I think, would be very advantageous.

DR. KOH: And I think there is some history that we can look back at, regarding pediatric clinical trials, is that the AAP actually helped to bring together stakeholders to a stakeholders' meeting. Now, we'd have to work out what some of those details are, but I think that is something that could be proposed. And they did a good job, it's really more pediatric therapeutics, pharma, to talk about pediatric clinical trials and how to improve that.

DR. KAPPETEIN: So how often would a group need to come together? So that was also one of the sub-questions here. So if we would form different groups that look deeper into those issues of regulatory approval, IAP processes, reimbursement, incentives, etc., so how often should those working groups come together?

DR. KOH: I mean just, if you look back at the history, there was one big stakeholders meeting. Then there was some kind of organizational entity of that experience to bring everyone else together afterwards. So one big meeting, several meetings after that. There's a history of that for PF clinical trials. I think that it's something that may apply in this situation.

DR. KAPPETEIN: Do we agree who should be around the table? Is it societies? Is it physicians? It's industry, FDA?

DR. KOH: Yes. And then those were all at the table at that time. So (pause)

MR. CHEN: And investors.

DR. KOH: And investors as well.

DR. LO: And payers.

MR. KROSLOWITZ: I think one area that we've overlooked with this whole discussion is, and Dr. Zhang had mentioned this before, she gets funding from the March of Dimes.

And I met, at an investment meeting, a gentleman who represents nonprofits like I know the American Cancer Society or the Catholic Charities or big groups like this who have large amounts of money that they look to invest in something that is good, they're doing good with their money and not looking for huge returns. You see an opportunity there?

DR. LO: I do, but let me actually again change the narrative slightly and go back to an example that many of you may have heard of, which is the Cystic Fibrosis Foundation. The CF Foundation, for decades, was really focused on dealing with symptoms. But when Bob Beall took over in the 1990s, he said, I'm tired of dealing with symptoms. I want a drug. I want a drug for our patients. And so for a period of about 10 or 15 years, the CF Foundation invested in developing drugs, and by investment, I mean they actually gave money to commercial entities, and in exchange for the money, they got royalty interests in those various different companies and in the drugs.

And they were perfectly aligned with those companies in the sense that they did not want to get paid a dollar until and unless a drug for CF was approved. And they provided hundreds of millions of dollars over the course of several years to be able to fund these projects. In 2012 a drug was approved. In 2014 the Cystic Fibrosis Foundation sold their royalty interests. They sold it for $3.3 billion. They had put in 150 million, over years. And that's an example of how focusing on philanthropy does not have to sacrifice return.

The reason that they were successful was very much along the lines of what Mark said about OrthoPediatrics. They were successful because the people that were investing, namely the CF Foundation, they wanted a drug. They didn't care how long it took. They didn't care how much money it took. They wanted a drug. And that's an instance where that goal actually is perfectly coincident with a goal of making tons of money for your investors.

So it's not to say that you have to sacrifice one to get the other. But that's where

bringing those kinds of investigators to this group could be transformational.

DR. KAPPETEIN: Thanks very much. I think we have to, the time is over, isn't it? Oh, one more question.

DR. ESPINOZA: Oh, so one thing that I think that we, the PDCs, could do is earlier it was mentioned the idea of having this shared portfolio of companies, and I think we, as PDCs, receive dozens if not hundreds of applications, whether it's for grants or to be a portfolio-supported company. And so we could start sharing those applications, those profiles of those companies, and putting together basically a national, nationwide dataset that nonprofits, that venture funds could start looking at and scan, because maybe they might be impact motivated and say, well, I'm looking for a company that does this thing, and maybe we don't have it at CTIP, but maybe Philadelphia does or maybe Georgia does.

And so I think that there's ways that we can start using the insight and knowledge and connections that we have as centers, to start building that portfolio that could eventually become something much larger.

DR. LO: So another idea along those lines is putting together that database is a great, great thought. In addition, you might think about stratifying that data according to different indications, because pediatric devices, as a kind of a category, is kind of amorphous. But if you focus on, you know, orthopedic pediatric devices, that's clear what that is. If you focus on cardiac pediatric devices, it's clear what that is. And there are investors out there, families, that want to do something about a particular disease that has affected their family. They don't want to give money to pediatric devices, but if it's pediatric devices focused on neurological disorders that afflicted their child at some point, they're willing to invest in that.

So giving a better narrative of these different diseases while at the same time allowing investors to invest in a larger portfolio could be a really significant change.

MR. BAUMBERGER: Yeah. I know we're almost out of time, and just to get your question, Vasum, about next steps, I think one of the things that I think would be helpful, and you're probably going to do this next, is to hear from FDA about what your plan is going forward, on sort of taking what you've heard and putting together something for Congress. But certainly it will be helpful for us to know, at this point, what we can do most to help FDA as you go through this process.

I think, from the perspective of the Academy of Pediatrics, we're happy to help in any way we can. I think this has been a really truly wonderful meeting. Thank you all for being here. And thank you, Vasum, and your whole team for putting this on. I think this has been great. There's totally a lot of energy and a lot of new ideas, and we hope we can help you capitalize on those.

DR. PEIRIS: No, I definitely appreciate the transition, James. Thank you.

I also want to take a moment just to say thank you to everyone, all of you for staying this long, and to all the panelists. The zeal that I see for this is something that we seem to always think about when we think about pediatrics. We think about passion, people that want to make a difference. What we need now is some clarity in terms of utilizing that energy towards some clear path and direction.

The notion of the PDCs, and I'll try to go through these in a kind of sequential manner, but the potential of the PDCs, and we've always thought about what's the maturation model for the PDCs. Chester Koh had brought up some concepts. I think others have talked about this as well. But certainly the PDCs being charged with assisting device development as a partner of the FDA across the country have a great potential in clarifying what the path forward is. And you have, I think, a person that you can certainly work with here, Eric Chen, who directs the program. So I'll point that out.

A lot of other conversations have taken place prior to this meeting as well, and I'll

point out some of these so that we can clarify what paths we're moving forward on. Chester Koh has been putting together an ad hoc committee both of clinicians, AAP membership, that includes representatives from industry and academia and payers as well. And that group has also been considering some ideas and topics that hopefully will create some alignment across a number of different stakeholders in the community.

As I mentioned to you, Mark Schlesinger and my team, we've been working on the CEO survey, as we've called it, but it's really something a little bit more expanded so we can get some more nuanced perspectives of what truly will help people, companies specifically, invest, sustain, and innovate in the pediatric market. And hopefully the information we'll get as we move forward with that will be very helpful and insightful.

Andrew, we've had a number of conversations about how do we move forward, about clarifying financial models that could work in this market as well, both for the small players and the big players. And perhaps being able to clarify that in a document is something that we'll be working on as we move forward.

And then I don't want to say finally, but more as a very global approach, the concept that we brought together at the very beginning of these 2 days about a collaborative community, a pediatric medical device collaborative community perhaps convened by pediatric academic medical centers, and then creating the right framework to incorporate a number of other members across the ecosystem, including industry, patient advocates, payers, and others, to begin to work on, in a long-term fashion, some of these issues as well, both in terms of constructing clinical trial design, improvements in efficiency, in evidence generation, and more clarity about how regulatory science and the economy of the entire pediatric academic medical center hospital service market could make a difference in developing devices for pediatrics. So those are all areas that I think the momentum is building on and that we'll continue to work out after this meeting.

Any other points that anybody would like to make, in terms of key areas that we should be working, moving forward on?

Andrew?

DR. LO: Well, I just want to say one thing. You know, as somebody that comes from the financial industry, this gathering to me is just really extraordinary. To have a regulator inviting people from industry, from academic medical centers, from academia to come together to think creatively about how to change this market and make it healthier and more robust, that's just extraordinary, from my perspective. And if you want to understand just how special this is, can you imagine Goldman Sachs getting together with the SEC to figure out how to come up with better retirement products for everybody?

(Laughter.)

DR. LO: They should, but they won't. And that suggests that there's incredible convening power that the FDA has and that it's using and that it continues to use. So bringing together the larger stakeholder community now of investors and business experts to figure out how to crack the appropriate business structures can actually be transformational. And I think the reason that all of the parts are moving together is I think we all have a unified goal here. Everybody understands that we want to be able to deal with the challenges that afflict our children.

So this is a wonderful community and effort. Thank you for including me.

DR. PEIRIS: I think you said it so well, Andrew. Thank you very much.

And I think, I want to thank all of you, and I do want one more second just to say thank you to all of the volunteers, the people that have really put this, helped keep this moving smoothly.

(Applause.)

DR. PEIRIS: I think, despite some technological issues with the mics at the end, a

very successful conference overall, and we'll keep you posted about how progress was made on these other topics.

Thank you once again. Safe travels.

(Whereupon, at 5:00 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

PEDIATRIC MEDICAL DEVICE DEVELOPMENT

August 14, 2018

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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SHAYLAH LYNN BURRILL

Official Reporter