

Food and Drug Administration (FDA)

Center for Devices and Radiological Health  
(CDRH)

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Complex Issues in Developing Medical Devices  
For Pediatric Patients Affected  
By Rare Diseases

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Workshop

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Wednesday

January 8, 2014

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The Workshop met at the Food and Drug Administration, Building 31, Room 1503,  
10903 New Hampshire Avenue, Silver Spring, Maryland, at 8:00 a.m.

Present

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## Proceedings

(8:19 a.m.)

### Introductions

Dr. Francis: Good morning, everyone. Our workshop is entitled the Complex Issues in Developing Medical Devices for Pediatric Patients Affected with Rare Diseases. So, I really appreciate you coming out so early on this very cold morning.

I have been asked to remind you all to please turn off your cell phones, vibrating loud machinery that you may have so that we may proceed with the meeting uninterrupted.

So, if you haven't already, there is a kiosk outside. During our next break, you can take the opportunity to do this if you need to. There is a kiosk outside where you can purchase your snack or your lunch ticket. So, once you purchase your ticket, your lunch, they will give you a ticket. And it is very important that you do this now or during the break because we have about 15 minutes run overtime between our last session for the morning and our lunchtime breakout sessions where we are going to ask you to get together and talk in a lunchtime group. So, please make sure that you purchase your lunch ticket before the lunch break and that way, we can proceed moving and not take too much time between.

And at that time, we will go off into separate our specialty groups. Presumably, you have also signed up for those as well and you will, at that time, discuss more specific issues that are specific to your areas of interest.

So this is our FDA disclaimer. It is quite long but it essentially says that and you have probably all seen this before- that we are here to facilitate dialogue and exchange of ideas

but we are not here to promote commercial devices or any commercial interests. And I think that will suffice but if anyone needs any more information on that, how about if you just talk to me afterwards.

So, at the moment, we will welcome you and again our viewers who are online. Thank you for attending, even if you couldn't be here in person. If you have any comments about anything that we discuss today, particularly things that you think will be helpful in moving this process of promoting the development of rare device issues for pediatric patients forward, then please make sure you make comments through our docket. The website is here and our comment period will close on February 5th of this year.

So for today's workshop, we have a series of presentations with topics that are relevant to pediatric medical devices for rare diseases. And each presentation will be followed by an opportunity for everyone here, stakeholders and participants, to voice their opinions, provide insight, comments, and questions. And that is actually going to be critical for us because we actually want this information from you and this is the impetus for this gathering.

And again, at noon we will have a facilitated roundtable discussion where we will have moderators who are from here in FDA who can help to spark conversation and take ideas from you that hopefully will help us to move this forward.

And at the end, once we are done with this great day, we hope to take all of this information and put it towards a strategic plan for this initiative. So again, your input is extremely critical and important to us and so we value it and hope you will be freely giving of

your ideas and thoughts on this.

So again, once you have your lunch ticket, please quickly proceed to your designated table. There will be signs that will indicate where you should go. And we encourage you to sit next to someone new for a couple of reasons. One, we would like to make sure we foster a conversation of different perspectives and get you to meet other people and network. So, please take that opportunity again to sit next to someone new and talk your hearts away.

So, we are going to now have some introductions. Well, we have two people who are going to be welcoming you more who are very important to FDA, Michelle McMurry-Heath and Gayatri Rao.

So, first we will have some introductory remarks by Michelle McMurry-Heath and actually, I am going to offer her full introductory biography when she does her main presentation.

So, please welcome Michelle McMurry-Heath.

(Applause.)

Welcome

Dr. McMurry-Heath: Good morning. And you don't even have to worry about that Jackie. I am sure that it is in the bios. And we are going to be hearing a lot of information as the day progresses. So, my name is Michelle McMurry-Heath. I am the Associate Director for Science in the Center for Devices and Radiological Health. And I want to commend you for

not just coming to a workshop on rare disorders but for your even more rarified interest in how medical devices can impact the pediatric population with rare disorders.

Many American patients don't realize the huge role that devices play in not just the treatment of their diseases and disorders but the detection of their diseases and disorders. I believe that NORD estimates that a patient with a rare disease spends, on average, two to three years before they are accurately diagnosed. And many of the diagnostic approaches, everything from in vitro diagnostics to imaging, to many of our monitoring equipment, everything that clinicians use to try to diagnose a disease is pretty much monitored and regulated by the Center for Devices and Radiological Health.

So this device space is critically important to patients with rare disorders. And I am sure many of you in the audience are parents and you know that two years in the life of a child is just an incredible amount of time. So much changes in that time, and so much can be done to help with more accurate and more rapid diagnosis and detection of rare disorders and diseases. So, thank you for realizing the impact of this space on that pediatric population. And we know it is a tough nut to crack. It has perhaps been particularly difficult in the Center for Devices because we are trying to look over a space that has a huge range in terms of complexity and potential risk to patients.

So, we applaud your interest. We thank you for coming to this workshop. We thank you for those of you who have been here for the last several days looking at the drug issues, for staying on to discuss this important space of medical devices. And I bring you greetings from our Center Director, Jeff Shuren, who looks forward to hearing about the



outcome of your work today so that we can further our work in the Center for Devices.

And with that, Gayatri.

Dr. Rao: Thanks, Michelle. My name is Gayatri Rao and I am Director for the Office of Orphan Products Development here at FDA. We are not part of one of the centers. We are sort of located separately and that is really done by design, which I will talk about in just one quick minute.

But today really rounds out basically a three-day marathon on rare diseases. For those of you who have been here for all three days, I applaud you for your tenacity. It has been a long couple of days but very, very fruitful. And for those of you who weren't here, the first two days really focused on drug and biologic issues related to rare diseases and generated a lot of very interesting discussion on just some very tough subjects. We talked a lot about natural history studies, biomarker development and validation, risk tolerance, and a whole host of other issues.

But today as Michelle mentioned, we are going to switch gears and we are going to focus on devices. And I have to admit, you know I am particularly excited about today's discussion. My office, as I mentioned, is the Office of Orphan Products Development and for the last 30 years, our mission has really been to focus on promoting the development of all products, and that includes drugs, biologics, medical foods and medical devices for the use, treatment, diagnosis in rare diseases.

But for a long time the focus has really, really been on promoting the

development of drugs and, to some extent, biologics, for rare diseases for sort of the obvious reasons. A lot of this was patient-driven because they are looking for therapies for their diseases. That is not to say that big strides haven't been made in the device space. Big strides have been made.

Since 1990, we have had legislation to really promote the development of devices for rare diseases. We have the humanitarian use designation program and the humanitarian device exemption program. There is the Pediatric Device Consortia Grants Program to really promote the development of devices in the pediatric space, even though that is not limited to rare diseases. And there are a number of other innovation-related initiatives within the Center to really promote the development of devices. But while these good strides have been made, there is a lot more that needs to be done in the device space and we are really committed to sort of focusing on that issue.

And Michelle touched on this very issue, which is, you know when you talk about rare diseases, one of the biggest things you hear is how long it takes for diagnosis for rare diseases. And not to belabor that point, but that is one of the key areas that requires more focus and more focused energy.

Similarly with respect to therapeutics, the HUD and HDE programs have been good programs but, thus far, since 1990, we have had 58 products come to market that are predominately therapeutically based, which is great but there is clearly a lot more that can be done.

So what is really the goal of today's meeting? That is something that we have been hearing about and some of the feedback that we have gotten. The impetus for today's meeting was Section 510 of FDASIA, which really mandated that the agency conduct a public meeting to really talk about ways to encourage and accelerate therapies for developing devices for pediatric rare diseases. But what Section 510 also requires is for the agency to issue a strategic plan for how it intends to help encourage and accelerate the development of therapies for pediatric rare diseases within six months of this meeting. That is a pretty tall order.

So, we are thrilled that you are all here. If you came here thinking you were just going to be a passive listener at a conference, let me just disabuse you of that notion. We are really looking for you to actively participate in these discussions. The sessions were really built around providing a lot of time for discussion. Because truly, the idea and the goal is to hear what your ideas are in an effort to see what we can incorporate as part of our strategic plan going forward.

Obviously, we are not going to be able to include everything. Some of it is going to be outside of our purview and some of it is just not going to be things that are attainable but we want to hear those ideas. And to the extent that there are suggestions that we could incorporate into our plan we would really like to be able to do so.

So with that, I welcome all of you. I look forward to a very robust discussion and I thank all of you in advance for your participation. Thanks very much.

## What's Happening Clinically

Capt Ulrich: Okay, Jim, if you would come up.

Good morning everyone. I am Linda Ulrich and I am a medical officer in Office of Orphan Products Development. And it is my pleasure and honor to be starting to introduce Jim Geiger for our first session here this morning.

This first session is going to focus on what is happening in actual practice of pediatrics, pediatrics for rare diseases, in terms of medical device use, and what people who are actually using the equipment and the people who are receiving them, our patients, are experiencing.

We wanted to start with this today as a way of grounding things and really keeping the clinical perspective right up front and center.

So, our first speaker is going to be Dr. Jim Geiger. I have had the pleasure of working with Jim as the Director of one of our Pediatric Device Consortia Grants. And maybe the worst or the best thing I can say about Jim is that he is really hard to get in touch with because he is always in the OR seeing patients. And so that is kind of frustrating for me but I also think that really who else is better to be able to start telling us about what is happening in the clinical realm.

Dr. Geiger is Director of the University of Michigan Pediatric Device Consortium. He earned his medical degree from Case Western and completed his general surgery residency and a fellowship in surgical critical care at the University of Michigan Hospitals.

He also completed a fellowship in pediatric surgery at Mott Children's Hospital in Ann Arbor and now continues to serve there as an associate professor of surgery.

Dr. Geiger is board certified in pediatric surgery, general surgery, and surgery critical care. He is the director of pediatric trauma and associate director for surgical services at the pediatric intensive care unit at Saint Vincent Medical Center. He is also the Executive Director of the University of Michigan Medical Innovation Center.

And so with that, Jim.

#### Clinician's View

Dr. Geiger: Thank you very much, Linda. Good morning everybody.

So, I have ten minutes. I will try to do it efficiently to talk about all these thousands of rare diseases, I guess. But I am not going to really try to do that. What I really just want to do is to set the stage for us to sort of understand that there is still a big issue about having devices available to help children.

In our practices as a pediatric surgeon, every day we deal with rare diseases. And the difficulty of that is that you think about it as a surgeon is that you might see a certain rare disease, you might see five of them in a year. And not only do you want to take care of them at a high level, but you need the equipment available to do that. So, It is a tremendous challenge. But I wanted to talk about it a little bit.

First of all, we all know the challenges, any of you that are pediatric care givers,

we have this huge range of size and I put one chart here and then listed below is the FDA's normal standard for age differentiation.

And the graphic is just to show you the tremendous range we have in size. But to show it in more visual form, there is the size of a small preemie baby to the human hand. And unfortunately, today, I also do bariatric surgery, and I see patients that weigh over 500 pounds. Now these are not the same also as adult bariatric patients. They are smaller inside and their tissue properties are also different.

So and it isn't just the size. Their tissue is handled differently. If you have a premature baby's tissues, they are much more delicate than an older child's tissues. The liver, for example, in a neonate is just like a little thing of Jell-O that can easily fracture and then bleed and lead to the death of the baby. So, there is tremendous challenges.

And then of course, the significant differences in physiology that children have. And again, this occurs over the whole range of patients. So, it is a real challenge for us.

We might solve a problem for an adolescent population but it still would be unsolved for the neonatal population.

So, what I want to do, I thought instead of trying to do all of them, I am going to tell you about one rare disease that I deal with and that many pediatric surgeons deal with on a relatively regular basis and this is something that is a congenital lung lesion called the CPAM. This is a developmental abnormality of the lung. It has an incidence of 1 to 25,000 out of 35,000 births. What has happened over the last 15 years is that prenatal diagnosis, primarily

with fetal ultrasound, has become quite common and this has been recognized earlier. And because it is being recognized, there has been an increase in the surgeries for this condition.

The reason to remove these lung lesions are that they can lead to infection and there is sort of an unknown rate of malignancy. So this is also just sort of demonstrates some of the challenges. As we get better technologies, we start to learn about diseases in a different way. We don't necessarily know all the answers yet about this disease but there has been a significant increase in the surgery for this disease.

Now, there is two potential treatments. You could observe these but we don't really know what the outcome is and some groups have recommended this. There is a concern about malignancy. So, like I mentioned, there has been a big increase in surgeries for this. And surgery could be done open. That is called a thoracotomy. Or it could be done closed with small little incisions or a minimally invasive approach, which is called thoracoscopy.

It is early in the morning, but graphically, when you do an open operation, we have instruments that are sort of what I would call traditional instruments. And in pediatric surgery, if you go back 50 years, maybe 60 years when pediatric surgeons, the field first started to develop, we actually didn't have all the instruments we needed, even for open surgery. But those instruments are a lot easier to make. And in general today, for open surgery, we have most of the instrumentation we need or we can more easily get it. The approval process is either nonexistent or it is very easy. The devices are cheap to manufacture. So, it is really not as much a problem for open surgery.

But when we made this shift to try to do these operations with a minimally invasive approach, which we think brings benefits to these patients, we now found that we didn't have the equipment we needed.

And so you see in this picture that these are three millimeter ports, one five millimeter port. So the instrumentation available to go through these was quite limited. And this has really pushed the challenge. And I think this is a fundamental thing that is really important for the audience and for everybody to understand is that this isn't going to stop. Technology continues to evolve and, primarily, it is being evolved for the larger populations and that is only going to put more challenges that when we want to apply -- we as clinicians are going to want to apply a great technology to our patients but it is not being developed for our patients, in general.

So, let me just take you through an operation that we do for this. First off, there is the anesthesia considerations. In most cases in adult surgery, you would want to have what we call single-lung ventilation. You would like to isolate the lung so that the lung could collapse that you are working on. The instrumentation for this exists but it is really poor for children, especially for small children. You don't have the technologies available and it is a challenge but they haven't really been developed to allow us to have effective single-lung ventilation. So, that is the first thing, we have to compromise how we sort of do the operation from an anesthesia standpoint.

When we do this operation, there is three things you have to do, really. You have to dissect out and expose the area and you have to then divide the blood vessels and



divide the bronchus. And to do that, we primarily have used a number of different devices, but I will show you here, first of all we use electro-surgical devices. So, if you look at this, this is a six-month-old baby, who is getting ready to have this surgery done. And there is next to it is the electro-surgical device that we are going to use to do this operation. So, I don't know if you are out in your garden or you do bonsai or the little tree things, you would not use a big hedge trimmer to trim a little bush. Right? This is what we are faced with. That device, maybe three inches of that device are going to actually be in the patient's chest. The rest are going to be outside. Clearly, not designed for use in this child. Yet, we want to use an electro-surgical device to divide the blood vessels. And to show that graphically, here is an example. This is an intraoperative photograph, showing the tip of that instrument. And you can see the blood vessel in the center there. And then just look at the size of the instrument, compared to the blood vessel.

So, these are the types of things that, again, we have to use. And in this particular case, there was a device on the market that pediatric surgeons were using but it was used at such a low rate that the company eventually dropped it from manufacturing it because they couldn't justify it from a financial standpoint.

Now, staplers would be another device that would be used in adult surgery in these lung operations. While staplers require a 12 millimeter port, which is a big incision in these babies, the cartridges are 10 millimeters wide and the staples are often too large for these small neonatal vessels. In addition, we have to do what is called articulation. We have to move the stapling device inside this small working space. So again, it is not just the small size

on the outside. Inside creates very small working spaces in which these instruments have to work and it is really not possible. And you can see here the size of an adult type stapler, which we are faced to use.

So these are, again, some of the challenges that were faced.

Now, there is hope. There is, for instance, on the electrosurgical device situation, there is a company that is marketing now a three millimeter, a ceiling device. There is a, I know of at least one stapling company that is coming out with a five millimeter stapler. They are pending FDA approval. But this is years later that we should have these devices. We could have had these devices easily ten years ago. There is not any huge technological barriers. There is really just barriers of approval, maybe, and not even so much that for some of these companies, but really just the manufacturing and marketing of the device.

And I have learned through working with some of the larger companies, and I know some that are here have a focus on pediatrics, which I am very appreciative, but I know some of the major, one of the major medical companies that I have worked for, they had developed a five millimeter stapler more than ten years ago and they never brought it to market because of purely the market, the market issues for them and the financial issues.

So what a shame that is that here is the technology that has been developed, that works, that they tested but we don't have it available for us to use for children. And I think that that is really, it is very sad and every day, literally, in my practice, there are times when or almost every case or every day when I say gee, if we just had this this size. Or if I just had this in

a different length or whatever. So, it is really very frustrating.

Now, I am going to talk about another -- this is a more common procedure maybe but done for many rare diseases for we have so many children that have different issues. And it has become very common to do approaches again with a percutaneous approach where we go through the abdominal wall to place a feeding tube. And in this case, I am showing where we have a feeding tube that actually bypasses the stomach. It is called a gastrojejunal feeding tube. So, the tube ends up here into the small bowel and these are done in cases where the stomach doesn't empty well.

So the good news is here there are pediatric tubes available. This is probably a success story that we should look at in more detail but there are a number of companies that make specific pediatric tubes. And in fact what is also another benefit of this is those pediatric tubes, especially a small little tube called a button, has now been applied to adults and improve the quality of life of adults. So, it is always an argument I use to big device companies is that there are collateral benefits if you participate in these markets.

But anyway, the problem is that even when we have devices that are made specifically for pediatrics, there are extremes of size. So, smaller babies, smaller and smaller neonates, premature babies that we work on and it still creates challenges.

So, here is an endoscope. This is the smallest endoscope that I am aware of that is available, at least a traditional endoscope. And you can still see that this is 100 centimeters or so in length.

And the other issue we have is that these feeding tubes come with a length. Here is the balloon here and this is the tip of the tube. And so there is two challenges that we face and, again, we can't solve all these here today but the companies have decided on certain lengths that they need to make. And so the smallest one that this comes in is 22 centimeters from the tip of the balloon to here. But that distance is too long for some premature babies, where the distance from where that balloon sits in the stomach to the point where it ends in the small bowel is longer than that. And then the tube ends up being too stiff.

The other problem is that hospitals can only have so much stock. So one of the other challenges we have for pediatric devices is that with the expiration dates of products and needing it that moment at that time, that is another challenge. It actually might be available sometimes but we don't have it at the moment we need it. So, that is another big challenge for us.

So, this is a case where one of those gastrojejunal tubes was probably a little bit too long for the baby and it eventually perforated through the intestine. You can see it coming through the intestine here and you can see the debris and stuff that stay in the intestine.

And so that that same type tube that I showed you here. And there has been a lot of reports of this in the literature but another big challenge I think we all face and that we need to improve on, despite the efforts of the FDA and others to put out their reporting mechanisms is that we don't capture these. They happen in our hospital every day and I know that we don't capture them all.

And I also know that for myself, I have gone through some of the reporting mechanisms and I haven't always been very thrilled with the response or sort of how that process goes. So, this is something I think that is a big challenge to us.

So let me talk about, I guess some opportunities, I would say. These are sort of some unsolved problems. So, esophageal atresia, this is a condition, there are a number of variants of this condition but there is the most common one is where you have this one here where you have the esophagus is not connected to the lower part and there is a connection between the esophagus and the trachea. That certainly can be challenging, especially this gap between these two. The longer that gap is, the bigger the challenge can be.

And then you can have cases where there is a pure atresia, meaning that there is no connection to the trachea and the gap can be quite long. This is an area where pediatric surgeons around the country are innovating trying to solve the problem, especially these difficult cases and they are trying to apply the minimally invasive surgery techniques to this particular condition. But the equipment and the devices are not there. We know, I think, how to solve this problem and I know of at least four or five groups around the country that are actually working to develop devices for this.

Again, though, this is a situation with the right funding, collaborative approach, partnerships with major medical device companies- in a very short period of time we could bring a device to market that could meet this need.

So, I think that these are some of the opportunities that are out there.

Another one is congenital diaphragmatic hernia. So, another rare disease you have, in this case, the diaphragm doesn't form correctly. The intestine is up in the chest and that leads to -- and sometimes the liver also up in the chest, it leads to the lungs to not develop correctly or lung hypoplasia. Often also the heart will not form correctly and you can have heart issues related to this. These babies, this is a condition that has a high morbidity and mortality. It sometimes requires something called extracorporeal membrane oxygenation, or ECMO, heart/lung support for these babies.

And again, we are trying to apply minimally invasive surgery approaches to some of these babies, the techniques and the instrumentation is not really there to always do that efficiently.

And, in addition, we have some new technologies. This is a device called or a procedure called the FETO. It is a fetally-placed or endoscopically placed balloon. If you occlude the trachea, it turns out if you clear the trachea in babies with diaphragmatic hernia, the lungs will actually grow and can reduce the -- give better lung growth and may help to reduce some of the morbidity and mortality of this disease.

Now, it is not a completely proven procedure. There has been one study done over in Europe. And there are now efforts hoping to maybe bring this technology to the United States and to study it and to show can we make a difference with this technology or others.

But again, the challenges that are faced in this case is finding a manufacturer, the approval process. So, these are just some of the barriers. But again, something that if we

applied our resources in a different way, that we could really solve some of these problems.

And the other thing to recognize about these rare diseases, so if you take many of these rare diseases, although they are rare, and although the markets are small from a standpoint of looking at it from the device manufacture, for society, the costs are huge.

You know one of the joys of being a pediatric care giver is that when you save a life or impact a life, as a team of caregivers, it is a lifetime sometimes. Of course, on the opposite side of that, when you can't impact a life, then you have lost the potential of what that person can contribute to our society.

And not to mention the cost; the cost of some of these conditions, take a condition like short bowel syndrome that one of my partners is working on a device to treat. Those patients require IV supplementation for years, sometimes; in and out of the hospital with line infections. So, quality of life and cost. There is tremendous savings if we were to impact some of these rare diseases with new devices.

So, what are some of the things that we can do? And then we will open it up for some discussion. I think we need better data. Again, I know there has been efforts made. I don't mean to criticize it, but we have to figure out a way with the smart phones that we all and carry with us everywhere, we should be capturing every time there is an event that happens, so that we can learn from these events.

We need sustained programs and pediatric device development. And the program that Linda leads in the orphan drug program, I can't say enough about how important

that is. And I think it needs to continue.

Funding for these projects, it is out there but it is difficult and we certainly need it. I think we still have to look at the regulatory process and ways to accelerate it and incentivize it, especially for the major medical device companies.

Partnerships with clinicians and other innovators with the major medical device companies, we could really solve many of these problems much faster. I had the pleasure to do a project with one of the major medical device companies with one of their lead engineers. He had won an award as their innovator of the year and he wanted to work, he decided. He got a \$100,000 award. Not bad. He said I want to solve the pediatric problem. So, he approached us because of the pediatric device consortium. We brought him into our hospital. We let him meet with our doctors, come to our operating rooms.

We had multiple iterative processes through his design process. We then looked at his prototypes, gave him feedback. But what he leveraged was this huge machine of his major company. Within that year, he solved the problem, made an unbelievably clever device that looked beautiful. And but the problem is that when it came time to take it to the market, the company is not going to market it because of the size of the market.

So, we can do better. We just have to figure out a way to incentivize companies to do that, or at least figure out a way to leverage their resources to help smaller companies or nonprofits, for example, bring some of these things to market.

I do think it takes unique collaborations. It takes a lot of us working together to



solve these problems and that is, hopefully, what will come out of some of this today.

There, I think, to commercialized pediatric devices, you do need, I think, some novel business development concepts. L3C is a type of sort of a mix between a nonprofit and a for-profit company, where you can take in donor dollars but also have a different structure.

The electrosurgical device company that I was referring to, it is a very unique group of people. They have raised over ten million dollars but they are there because of a passion for wanting to solve a problem in children. And so right now, it takes, unfortunately, sort of this really magical mix of things to come together for a company to be successful. And we need to figure out how that happens but also we need to figure out ways to make that easier and to increase that.

Clinical trials, I think the pediatric device clinical trials network is something that is a barrier that we really need to reduce or improve, is that how can you get the data in a quicker way and with participating institutions, reduce the barrier sort of of getting through multiple IRBs and the difficulties in that.

We have it in children's cancer, and probably you guys talked about it in therapeutic sessions. We have done that pretty well in some of these other areas and it really helps. It is not really there for devices.

There certainly are, obviously, reimbursement and value issues but, again, as I talked about the cost for society, if a device, maybe the device right now you are not going to get a device to market, unless it is going to make money. And the margins still have to be

pretty good. And all of you know, with the Affordable Care Act and other pressures in healthcare, the cost of a device to the value it provides, that ratio is only going to become more important.

So, that is going to even make the challenge greater for us, not to say that our device doesn't bring value, but it has to bring value within that economic equation today.

I think we should look to global markets. We have a small pediatric population, relative to other countries in the United States and our pediatric population is certainly not growing as fast as it is in other countries. So, I think that is something that if we use the wealth of this nation to look to solve some of those problems and the larger markets for children in other places, that could really be of benefit.

And I think we do have to celebrate some success stories and learn from them. How have some people and how have some companies been able to take an interest in this and be successful? Both small startup companies and also some of the major medical companies that have taken an interest, unfortunately, it is only a handful that actually have a pediatric focus or a pediatric division, I would think that and some of them might be here, they could tell us that my guess and my feeling is that they have been rewarded for that effort and I hope that we can encourage others to do that.

#### Participant Comments

So, that is pretty much the comments I wanted to make. And I think now we will open it up to the floor for questions or more comments, so that we can sort of set the clinical

background for the meeting.

Capt Ulrich: Any comments from the audience?

(Off mic question)

Dr. Geiger: Yes, it is a great question. So, two things. One is that the reasons are multi-factorial. And I didn't understand them all to begin with. The one about market size, that one is sort of obvious. You know you get that, and I think that kills a lot of things right up front because even they always look at the market size and then they make that decision.

But if you were to sort of convince them or get over that hurdle, then sales and distribution and manufacturing are all issues, because you can't just put a product out there and not monitor it or not see. And then you have to manufacture it. And the shorter the run on manufacturing, the increased the cost to manufacturer, the margin goes down. So, that is a big problem. So, I think it is multi-factorial.

The second part of your question I think is a really important one. If you look at the case with repurposing of drugs, for example, I mean I think we could do more, but it is happening and I wasn't here for the first two sessions but I am sure it was talked about. We should be doing the same with these device companies. One, they sometimes have technology that they have buried because it didn't work for whatever markets they were but it might work for us. And two, I think they could partner with organizations. Maybe it is a device company that is more of a different model, more of a nonprofit model or something where they are going to bring the device to market. But some of the risk has been taken out of it or some of

the development has been done by the larger company.

And I think these sort of partnerships should and could happen but the trick is finding ways to make it happen.

I have tried a little bit. I have failed, I guess, so far, but I do think it is a great question and it is something that definitely could happen.

Participant: I have a question. From my perception of the presentation many of these equipment being done for the pediatrics actually is almost like a child of a bigger adult-like thing. And the question is, what mechanism do we have for really for stimulating, protecting et cetera, this product? Because obviously, the money is not going to be as much there but if are you going to link with the adult, it could be useful.

Dr. Geiger: Yes, so I think if I understand the question, I think that if anytime if you can -- I think if you can link solving a problem in pediatrics to an adult market, then the chance of getting it to market is definitely there.

I think it is ironic. You know we approached, probably 15 years ago, we wanted to create a micro-set of laparoscopic instruments, two millimeter instruments. And we couldn't really get a company to do all the work that we want to do. It really wasn't even a hard technical challenge.

But now today, there is a trend in adult surgery to exactly do that and some of the companies have now spent lots of money on it. So, I think there is advantages for the big companies to solve some of the problems. If you look at the space program, you know, if you

solve things in an extreme environment, often it has application to the rest of the world down here on earth. So, I don't think it is that much different and it is not going to be for everything but I think for many things, it is going to be true.

Yes?

Participant: So on these rare diseases, cutting edge areas, have you already developed registries, research type platforms so that at least the experience can be reported and perhaps it could be more available. If you let the companies know, they might be interested in helping.

Dr. Geiger: Yes, it is a great question. There are -- the question was have there been registries created for some of these rare diseases to help collect data.

I am not up on all the registries. One that I am somewhat familiar with is for -- there is the condition I talked about diaphragmatic hernia. There is something called the ECMO registry, which is for patients that actually go on this heart/lung machine and that has been very important in recognizing issues, for instance, the cannulation procedure that is done there when there has been complications or problems, the data is very quickly, I think, or more quickly recognized than it is in other areas. But we definitely could benefit from creating or having registries for some of these other conditions.

And the other issue that goes with that is that we don't learn necessarily from each other's experience. So, when we do have a problem with a device or maybe there is a better way to even use an established device to do a procedure, that information gets

disseminated in a very slow process and that is an area where even with the currently established technologies, we could improve. Even within our own group, in our hospital, for instance, in pediatric surgery, we have started to work towards standardizing some of our operations. There is a lot of resistance to that but there are best practices and it shouldn't be just always like off the shelf or try to make it up as you go.

So, I do think that is a great opportunity. There was another question. Yes?

Participant: I wanted to comment. I work for pediatric --

Court Reporter: Sir, can you come to one of the microphones?

Participant: And regarding the scaling down of devices, the biggest hurdle that we have had is because it is smaller, it is going to be more difficult because they won't recognize that we have a device that is equivalent.

So, then, it becomes much more possible to develop, then we usually drop the product. I don't know if that is something that you have experienced.

Dr. Geiger: Yes. No, absolutely. I mean I think when you scale down, of course there is multiple challenges in that. I mean the materials, you will only have so much you can do with thinning of the material so that the material properties can change. So, there is definitely challenges to solve these problems. And I do agree, though, that if you can come up with something, then we have to look at ways to somehow if it is safe, make ways to get it out there to patients.

Other comments or questions? Yes.

Participant: I was wondering if you would share your great success with mPED.

Dr. Geiger: Sure. So, the commercialization of medical devices, even for the adult market, it takes a good seven years at least to get things onto the market. But what I definitely think that we have done with that is some of these stories that I have sort of told you, some of the interactions I have had, those have occurred because of mPED. We have managed quite a large portfolio of projects and we are moving through the product life cycle.

We have had a few products that have actually made it to the point of being used to impact children's lives. So, it is coming.

It takes time. I think it will be a logarithmic scale. And it is an effort that I think to start to develop a level of expertise and help people with a place where they can go. And that is a lot what trips people up early on. But then I think what is going to happen, we are going to have a pile up of a bunch of things that are developed to some degree that we then need to get over the valley, which is true for all medical devices. And I think that is where we are going to have to come up with some novel business models, partnerships with big companies and stuff to get stuff actually out where it is going to impact children's lives.

There was another question or comment back here? Yes, go ahead.

Participant: (Speaking off mic)

So, I would think that there is an opportunity, perhaps, for successful companies

to meet together and begin to try to map out if you were to have a new pathway in which you would be developing different type products, how would that done? And perhaps as a consortium of all these companies working together, something new could be brought to bear.

But I think the paradigm of profit is not going to work here.

Dr. Geiger: I think that is true. And I would love to get the major medical device manufacturers in the United States together and have this discussion. I think there is at least one representative of one of them here, maybe they can give us some insight on how we might make that happen, maybe at their CEO level or something we could pull that off. I think that would be great.

I think though, there are good people in these companies. They care about kids but, as a company there, the pressures they are under for stockholders and there is now an added level of pressures with some of the changes in the accountable care act and the financial pressures on these companies and the margins are less all the time, I don't know that they are going to do it out of their good will.

What I think needs to happen is fundamental change in the incentives, truthfully. And I don't think it would cost a lot. I mean in other words, I think patent extensions, some of the other barriers, regulatory patent barriers, the legislation, the way it is now with you have to mention if there is a pediatric indication, it doesn't do anything, truthfully. I mean, it really doesn't. Someone else may have a different opinion but I don't think that is changing anything.

We need to really put true incentives for these companies to participate in this



process. And I think if those incentives are there, I think then they are going to do it.

Capt Ulrich: And with that, I would like to refocus the discussion. We are going to be having a session, actually, later this afternoon, specifically on the issues of what can be done and what potential incentives are.

So, at this point, is there any more last parting thoughts on what is happening clinically right now in practice of general pediatrics in regards to medical device use?

Participant: So as far as clinical trials go for pediatrics, I know that is a big concern. And as a physician, you certainly want to try out new devices as well clinically and kind of getting that sample size to get over that regulatory hurdle.

Have you faced any of those challenges and do have any advice or assistance for innovators that are working and seeing that hurdle forthcoming?

Dr. Geiger: I don't have an easy answer for you. There is a Pediatric Clinical Trials Network but it has primarily been based around pharmaceuticals and repurposing of drugs.

So, I don't think really anything has been established. I think there is models that are, like I mentioned, the children's oncology group model is something like that that could work. I think it is not an area that the pediatric device consortium has dug into but maybe one we could, where we could organize a network of hospitals. I don't know if Michael Harrison is here but he is probably listening. But you know I know Michael Harrison, who has developed some pediatric products and was looking to do his trials had some frustration. How do you get

a number of groups of centers to then get it through. And then right now, each of them have to go through their each individual IRBs and these things can bog down pretty quickly.

So, something we still, I think, have to work on.

Capt Ulrich: Thanks.

Dr. Geiger: I think there is one more.

Capt Ulrich: Barbara and then this will be the last question for this session and we will move on.

We will be talking about clinical trials issues again later this afternoon. So, if we could just keep things here for what is happening clinically.

Participant: Actually, it was just a comment in response to your comment.

Virginia Commonwealth University has a universal pediatric IRB possible. So for those of you who are wondering whether you can do it, yes, you can.

Capt Ulrich: Okay, great. So now we can move on to our next session. It is going to be an overview of what FDA is doing and the different programs that we have in place.

Thanks, Jim. And we will move on to our next session.

Jackie Francis is going to be our first presenter. Jackie is a pediatrician and medical officer here at FDA. She began her career at FDA in the Office of In Vitro Diagnostic Devices, where she worked in the Microbiology Branch as a clinical consultant. In her current

home office, the Office of Device Evaluation in the Division of Surgical Devices, she specializes in policy regulation and clinical protocol design of plastic and reconstructive surgery devices as well as pediatric surgical devices.

Jackie graduated from Cornell and continued on to Temple University of Medicine, where she earned her medical degree and went to Georgetown University for her internship and residency and fellowship, which she completed in clinical pharmacology and completed her training at Johns Hopkins in a preventative medicine residency, where she also earned an MPH. Jackie.

#### What We're Doing

Dr. Francis: I'm back. Okay. So, I'm going to talk today about our programs and initiatives within the Center for Devices and Radiological Health, generally speaking, that are aimed towards pediatric issues. Not necessarily all of them are aimed towards rare diseases but they are aimed towards pediatric issues.

So, this is the outline of my presentation. I will be talking about FDAISA implementation. I will be talking about our guidance development, OSEL activities, other activities, and looking forward, which really just means looking forward to the next few minutes or today, as we continue to talk.

With regard to FDAISA implementation, FDAISA, well that is pretty much old news at this point. But the main pediatric issues with regard to the new regulations and FDAISA really changed or addressed this workshop, which was one of the main -- well not main but one

of the decisions that we are working on or that we have worked on with this implementation.

This workshop is, as you know, designed to accelerate and discuss ways to develop new therapies for rare diseases. And that was, again, one of the factors of the FDAISA regulations.

The next would be HDE implementation and changes. HDEs are human device exemptions and they are pretty critical to pediatric devices because so many of our pediatric devices are approved under HDEs because they are such small populations. But the changes to HDE regulations, particularly with regard to FDAISA included expanding the ability to distribute profit to devices that are intended to treat or diagnose diseases or conditions that don't occur in pediatrics or that occur in such small numbers that the development of the device is impossible, or highly impractical, or unsafe.

And this regulation also changed the annual distribution number, which is a number that is determined by the regulators here at FDA. And that number is a number that takes into consideration the incidence or prevalence of a disease and the likelihood of the use of the device. So, that regulation also changed the ADN.

And with regard to HDE, it also allowed devices that were already approved under HDE to seek the determination for an exemption from profit prohibition.

#### Pediatric Device Issues Update

FDAISA also addressed the pediatric device consortia, which actually Linda will talk about more later, but really it just addressed the amount of the allocation for those grants

that will be distributed -- well, that have already been distributed for this year.

And also, with regard to the custom devices guidance, the custom devices guidance was modified in some ways that are pretty specific to custom devices. And I won't go into that in detail but those were the major changes in FDAISA implementation that impacted pediatric device regulation and development.

Specifically with regard to guidances, we have a few guidances that are either in the process of development or almost on the way to actual implementation. Specifically, the Pediatric Tracking Rule and Guidance, which is a rule and guidance designed to assist the FDA in tracking actual development of pediatric devices with applications as they come in and out of the center. The law was passed, actually, in FDAAA in 2007 and it was 515(a), which required that the FDA submitters of PMAs, PMA supplements -- I'm sorry -- Pre-Market Approval Applications or PMAs, PMA supplements, Humanitarian Device Exemptions or HDEs, Product Development Protocols or PDPs, for all of those applications, for any new device, they would include readily information about pediatric subpopulations that suffer from a disease or a condition that the device is intended to treat, diagnose, or cure. And hopefully this guidance and the following rule will help sponsors to better understand how to report this information to us.

And we are also internally working to make sure that we are able to collect all the information within the center, so that we can accurately report how well we are doing and our growth in the area of approving devices for pediatric indications.

The extrapolation of adult data guidance is one that I have been working on. It was actually proposed in the Pediatric Medical Device Safety and Improvement of 2007 and it allowed extrapolation of adult efficacy data for approved devices in order to extend claims to pediatric patients. And this guidance is designed to help both the industry and FDA to establish some more consistency in their approaches to determining whether or not it is appropriate to extrapolate adult data to pediatric indications. We are in the final phases of this guidance approval as well. And hopefully, that will be something that you will see soon but that is about all I can say about that today.

And last year, there was actually a guidance that was already cleared, and this was the Pediatric Information for X-ray Pre-market Notification. And briefly, this guidance really just worked to reduce the amount of unnecessary radiation to pediatric patients who were receiving any kind of medical imaging. And we actually had a workshop on that last year that went very well.

With regard to OSEL, there are two major initiatives with OSEL. And OSEL typically works on more human factors, issues, and practical use of devices or medications. And in particular, they are working on dosing devices. There has been an issue with different devices with liquid formulations that seemed to have inaccuracies in the amount of medication that actually gets delivered. Sometimes the medication has varying levels of viscosity and the medication may stick to the sides of the device. And so maybe you think you are getting X amount but you are really getting less. So, OSEL has been working to -- well, a workgroup has been established. Actually CDRH, CBER, CDER, and CDC are all working together to address this

issue. And actually, they intend to hold a conference sometime this year or next year which will address these issues and how, hopefully, there will be a more uniform approach to dosing devices.

In addition, thermometers have been proven to be a little less accurate in their fast modes. And so this is another initiative that is being explored by OSEL and hopefully there will be some more guidance in the months to come.

So, other activities, the Federal SIDS Initiative is a large network of federal agencies that have been working to address Sudden Infant Death issues, particularly with crib safety. So, we have been working in collaboration with that organization, as well as the Pediatric Advisory Committee, which you all may be familiar with but it is a committee within the Center that works on a number of issues, but specific to pediatric devices. We review applications each year that have been approved through HDE for adverse events and appropriateness of continued profit prohibition.

And the decorative lens initiative which was just started last year with Michelle Tarver was designed to address issues with decorative contact lenses that were not prescribed by medical practitioners. There have been high incidences of corneal abrasions and infections and different issues with non-regulated decorative lenses. And so there is a collaborative effort now with AAP, our ophthalmology division, as well as other stakeholders, in order to promote awareness and education about these issues with these contact lenses to users, consumers, particularly adolescents with different public health service announcements, et cetera, et cetera.

So looking ahead, I am very hopeful that -- you know Dr. Geiger raised a lot of issues that are concerning with regard to pediatric device development in general. And so it becomes a lot more concerning for rare diseases and, hopefully, we can make a better effort to collaborate on ways to move forward and attack the challenges ahead with proper strategies and approaches that can yield some more positive results in this arena.

So, I am now tasked to also introduce the speakers of our panel and they will talk more about what we are doing. First is Linda Ulrich. Linda is a pediatrician who works in FDA's Orphan -- in the Office of Orphan Product Development. She has been the director of the FDA's Pediatric Device Consortia Grant Program since its inception in March of 2009. She holds the rank of Captain in the United States Public Health Service.

Prior to coming to OOPD, Linda served as medical officer to FDA's Office of Generic Drugs. Before that, she served seven years as a full-time general pediatrician in the U.S. Navy and she completed her internship and residency at Portsmouth Naval Medical Center, received her medical degree from Uniformed Services University in Bethesda and she completed her undergraduate training in biology and English at Duke University.

So, are you ready, Linda?

Pediatric Device Consortia Grant Program

Capt Ulrich: I'm as ready as I am going to be.

All right, so we have already done the introductions. I work in the Office of Orphan Products Development which, as you all have heard, is the office that encourages the



development of products for rare diseases. And we have several programs within our office that serve to encourage the development of pediatric devices. First is the Pediatric Device Consortia Grants Program that I will talk about at length here. We also do the Humanitarian Use Device Designation Program that we are going to have a separate session on later today. And we also have our Clinical Grants Program, the OPD Grants Program that I will talk a little bit about at the end of my presentation.

Okay, so what are some of the challenges to device development in general?

Sort of in a nutshell time, sweat, money, regulatory issues, and reimbursement are some of the commonly cited challenges that people face. Specifically related to pediatrics, there are some other hurdles as Jim had mentioned earlier, the small market size, the need to have multiple sizes of a single device in a given child, as the child grows throughout the lifespan, as well as a facility having multiple devices on-hand to use for various patients that may come in their door. And also the time line for use of these devices. If you put a stent in an 80-year-old, that may be in for a number of years, but then compare that to if you put a device in a child who is eight-months-old and is going to be having that potentially in them for up to 80 years. So the timelines for a user are different and that affects the way that you would think about some of the long-term safety effects.

Other challenges include the expense of trials. Enrollment challenges for children, the need to obtain both consent from the parents, as well as assent from the child. Whenever you are conducting a pediatric trial, you need not just the cooperation of the child but you also need the family involvement and family support. There are ethical complexities

involved in conducting research in children and overall a lack of a pediatric device trial infrastructure.

And as has been alluded to, some of our legislative incentives that have been effective on the drug side may not actually translate as well or apply to the development of pediatric medical devices.

So in response to some of this, in 2007 the Pediatric Medical Device Safety and Improvement Act was enacted and some of the things included in this act were an enhanced federal response to pediatric device needs, a call to track pediatric device approval. There were some incentives for development, including a profit exemption on humanitarian use devices, so that if something was developed for pediatrics, manufacturers could make profits. And that has since been expanded for adult humanitarian use devices as well. And Eric, I am sure, will touch upon that more later. The law established our pediatric device consortia and also permitted extrapolation of adult data and also called for enhanced post-market surveillance.

So, a little bit about the Pediatric Device Consortia Grant Program. We have been up and running since 2009. So far, we have awarded over \$14 million in our first five years. We have had three cycles of grant competition. As part of FDASIA, we were reauthorized through 2017. We are authorized to receive up to \$5.25 million a year. Currently, we received \$3 million by appropriations.

So, while Office of Orphan Products Development is responsible for carrying out the program, it actually encompasses devices used in all pediatric diseases, not just rare

diseases; although, certainly a large proportion of medical devices for kids are used in rare diseases.

Similarly, the program encompasses all aspects of pediatric device development, not just the regulatory aspects. And here at FDA, that is what we do. So, that is a lot of what we are used to thinking about but the program is really to think more broadly about all the different aspects that can go in to developing a device.

It is also a little bit different in that it is not a direct research grant. So, it is not like we are not intending to give individual researchers large sums of money to develop a single product but, rather we fund consortia that support pediatric device developers.

So, what do I mean by a consortium? I like to think of it as a network of individuals and organizations who are coming together to collaborate to develop medical devices for children. It is a network of business people, clinicians, manufacturers, engineers, and others. It is an information source, a place where if somebody has a device idea, maybe a clinician in practice that doesn't know the first thing about business or what does it take to come up with a prototype, a place where they can go and be connected with people that can help them solve those different aspects of their device development issues.

And so it provides experienced regulatory, business planning, and device advising and development services in order to advance medical devices for children.

And really the whole philosophy behind the consortia is based on this, that silos, I don't think they really help anywhere but they certainly don't help in device development for

children. And so that a lot of times we are all sort of used to thinking from where we stand. So, this is the perspective of engineers, basic science, legal, intellectual property, clinicians, business people, regulatory and we need to sort of try to break down some of those barriers, get talking to one another, and working together really from the beginning in order to get products for children through the process and onto the market.

And that is sort of summarized in this. Really beginning with the end in mind, realistically what it is going to be there, what it is going to take to get there, and that hopefully people can go to the consortia and get some of this frank advice up-front so that people can make an educated decision as to whether they are going to proceed down the path of developing a particular product.

One of the things that we have learned from sort of our first cycle and I think is true in device development in general, the Valley of Death is littered with prototypes. But a lot of times if you don't think of the market up-front or are there funding sources, where are you going to go to get the money to move this along through the different steps? A lot of us are clinicians. These are great ideas. It is going to help kids. Let's get going with it and develop it. But then if the market is not going to support it or manufacturers aren't going to step in to make it, some time, and money, resources have been wasted. And again, if we can sort of think of things up-front and take the long-term view, then maybe we can use the limited number of dollars that we have to develop products that will actually make it out there.

Also, one of the things in the consortia is that inventors need someone who thinks like a regulator, thinking in advance about what a potential regulatory path for clearance

or approval is going to be for a given device. And then again, what sort of data, evidence, studies are going to be needed in order to be able to clear through the agency.

So, here is what the law says about Pediatric Device Consortia. They are really intended to connect innovators with potential manufacturers and potential funding sources; manage and mentor device projects throughout the development cycle. So anywhere from when someone has a napkin concept or idea through coming up with the physical model, the prototypes, initial bench testing, being able to get advice on the best sort of animal studies to do, helping design clinical trials, in terms of thinking about endpoints, getting advice on where to go for funding for the various stages, help and assistance in putting together regulatory applications, and then continuing to support the products, once they do make it on the market.

And as part of this, the consortia will do sort of preliminary assessment of proposed projects for their scientific and medical merit, and then also provide business and device development support as needed.

This slide lists out the recipients of our 2013 PDC grants and I think, in our audience, we have representatives from all of our consortia. They have little orange ribbons on their registration badges.

So if you all from the consortia could just like raise your hands so that people know who you are and look out for these folks during the break to talk with them and bounce ideas off of each other. Because they have been in this business for a while, and are just a wonderful source of information.

What our program has accomplished so far. Over 260 projects have been assisted in their development by the PDC since October of 2009. I am always very quick to preface this doesn't mean we have 260 devices coming to market because of the program. The vast majority of these have been projects that are in the early stages of development, so concepts, early prototyping, and maybe some early bench-top testing in animals. The consortia are currently managing more than 110 active projects.

Some things that have come either onto the market or have remained as a result of the first few years: There is a brace for pectus carinatum. There is a component to an asthma management program for adults that had gone to one of our consortia for being put in contact with the pulmonologist who is able to then provide them the pediatric parameters that was able to be included as part of that program.

Dr. Geiger's pyloric clamp for pyloric stenosis, he has been doing some educational programming for physicians who are using this to treat pyloric stenosis.

Here are some other devices that are in the works. They haven't been approved or cleared but they have been reported in the popular press. There is a stent for the treatment of tracheomalacia, a remotoscope attachment to a cell phone that will, potentially, allow the diagnosis of otitis media, and then Buzzy for pain relief. It is a vibrational device that you can put on a patient's arm and that helps relieve some of the pain associated with immunizations.

And again, these haven't been cleared or approved yet by the agency but some of them have been reported -- they all have been reported. So, I feel comfortable at least

mentioning that those are some of the things that are coming through our program.

Other ways that the consortia have helped is to secure additional funding for pediatric research. The consortia from our first two cycles so far have raised over \$14 million of additional funding to support pediatric research, which is a fairly good return on the investment that has gone into the program. I think it has helped really raised some awareness about pediatric device issues and it has gotten people in the various communities rallied around supporting some of these issues. I think people really do want to help kids and children.

And there is one example of a software development program that donated over \$100,000 of programming equipment in order to be able to help one of our consortia do some of their work. So, finally, the consortia have created opportunities for outreach publications and research.

And that is sort of the nutshell summary of the PDC.

I had mentioned that Office of Orphan Products has other programs that support pediatric medical device development, Humanitarian Use Devices, as well as the Orphan Products Grant Program.

Our grant program has more than \$14 million annual budget that helps fund clinical development for products for rare diseases. We support, as I said, research that is in the clinical phase. So a Phase 1 Study is eligible to receive up to \$200,000 a year for three years; whereas Phase 2 and 3 studies can receive up to \$400,000 a year for four years and it can also support programs that are -- sorry -- devices that are coming through the Humanitarian

Use Device Program.

More than 50 products that have, ultimately, received marketing approval have come through our OOPD grants, receiving at least partial funding through that program.

An example of a recent pediatric device that came through is the Berlin Heart Device. And the program, overall, has a very practical goal and that is to advance approvals and relevant publications that impact the care for rare diseases.

Overall, the program receives about 100 applications per year. We fund about 10 to 15 new grants per year. Our application and review is similar to that at NIH. The RFA is available at our website. And most importantly, our next application date is coming up February 5, 2014.

In order to be eligible to receive one of our grants, it can be research that is done in a number of settings, including academic and industry-sponsored research. People doing their research can be domestic or foreign. They can be from public or non-private entities or for-profit or non-profit. And really encompass almost any entity, other than something from -- an entity with Department of Health and Human Services.

And we do have, as I said more information about our requirements available on our website.

And on my final slide, these will be available, all these slides from today will be available on our registration website and so you can always come to the Orphan Products website for more information.



So, with that, we can go on to our next speaker.

Dr. Francis: I am not Michelle McMurry-Heath but I will introduce her. So Michelle McMurry-Heath, she is Associate Director of Sciences at FDA Center for Devices and Radiological Health. Prior to joining the FDA, she was a founding director of Health Biomedical Science and Society Initiative at Aspen Institute and was an Adjunct Assistant Professor of the Health Policy at George Washington University.

Her Aspen Institute Team focused on creating new policy strategies for stimulating biomedical research, disseminating emerging healthcare technologies, and reducing healthcare disparities domestically and internationally.

Her sciences diplomacy work has included projects from Ruanda to Cambodia. From 2001 to 2004, she oversaw a social policy -- Health and Social Policy Issues for Senator Joseph Lieberman and was a Senior Health Policy Advisor for the Lieberman for President Campaign.

While on the Hill, she worked on homeland security, health disparities, healthcare quality, and transitional research bills, including the American Center for Cures Initiatives and legislation which was later enacted as the Cures Acceleration Network.

After studying biochemistry at Harvard, Dr. McMurry-Heath went on to become the first African American to receive both MD and PhDs from Duke University. She trained in pediatrics and molecular immunology.

Michelle.

## Medical Device Innovation Program

Dr. McMurry-Heath: Good morning again. So, I have been asked this morning to tell you a little bit about a new initiative we have been working in partnership with an external non-profit called the Medical Device Innovation Consortium. And one of the speakers earlier this morning talked about the importance of novel partnerships. And we think this is key, particularly for vulnerable scientific spaces, like the medical device space.

So let's see. So, I know we are here to talk about rare disorders, but I also wanted to impress upon you the extreme popularity and commonality of the use of medical devices throughout the healthcare system.

So, just looking in the adult space, you are looking at almost 50 million procedures per year that involve just the most high-profile medical devices like hip and knee implants, coronary artery stents, for example.

The Center for Devices and Radiological Health is responsible, as I mentioned, for regulating this space. And it is an extreme range of complexity, everything from Band-Aids and condoms and hospital gloves to MRI machines and long-lasting implants.

So, we balance this range and risk by taking a risk-based approach to the devices we regulate. And several of the speakers this morning, for those of you who are not in the device development field, have referenced how we have different approval and clearance pathways, depending on the potential risk that device poses for patients. Everything from a Class 1 device that might be very, very low risk to a patient and might not be required to come

to the FDA before it goes to market, to our more extreme and complicated devices that we consider Class 3.

So, this is just a quote from the recently revised Center for Devices and Radiological Health vision statement. And I like to start my talks with this vision statement because our Center Director, Jeff Shuren, has really tasked the Center with looking beyond our goalpost, getting new products to market, to really the ultimate goal post, which is improving the health of patients. And this is particularly important, I think, in the pediatric rare disease space.

So, our vision starts by saying patients in the U.S. will have access to high quality safe and effective medical devices of public health importance, first in the world. And that the U.S. is the world's leader in regulatory science, medical device innovation, manufacturing, and radiation-emitting product safety.

So, the key themes here are: Faster. We want our patients to have access first in the world to innovations. Cheaper. Access means that these products have to be available. They have to be manufactured as was referenced earlier but they also have to have the coverage paradigms in place to make sure patients can get them when they need them. And of course, they have to be safe.

So, we feel that this theme of getting devices to market to patients faster, cheaper, and safer, will improve the health of patients. And a key part of that is how we address the regulatory science hurdles in bringing new devices to market.

So, this is a very boring, almost required, Federal regulatory org chart. I am sure you have seen many of these in federal presentations. But the interesting thing about it and something that people don't often recognize about the Center for Devices is that we have a large research component in-house. So the CDRH consists of both the Office of Science and Engineering Laboratories, OSEL, which was referenced earlier which is our bench researchers really in everything from life sciences to physics and engineering and computer science and our Office of Surveillance and Biometrics, which includes our cadre of epidemiologists and biostatisticians, which spend a lot of time studying clinical trial design and providing assistance to manufacturers and clinical trialists in bringing new devices to market.

For us, regulatory science consists of all of the things that this team of researchers can work on and the teams of researchers in the audience have been trying to address. It is trying to improve the tools, standards, and approaches needed to both develop a new medical device, test whether that device is doing what you predict it will do, and then regulating that medical device to make sure it is safe and effective for patients from the time it is introduced until the time it is pulled off of the market or withdraws from the market.

So, we feel that regulatory science can reduce the time and resources needed to improve and design medical devices and will further our goal of trying to make device development faster, cheaper, safer.

About two years ago now, we unveiled our Center's list of regulatory science priorities. And I put it up not because the list as a whole is that relevant to our conversation today but that one of our key eight center priorities was improving the health of pediatric and

other special populations. And we remain committed to this as one of the regulatory science priorities that we promote, both within the center and through our collaborations externally.

Another thing that is unique about the medical device space, for those of you who do not work in medical device development, per se, but maybe patients or customers of these devices, is that devices are incredibly iterative. There has been some reference this morning to perhaps patent approaches to trying to improve the access and availability of medical devices and believe me, this is a space we have pursued doggedly. But it is very, very difficult because, unlike a drug, where you really need a huge team of people to create a drug and manufacture a drug and bring it to market, and once you have produced a patent on that chemical, it is really, really difficult for someone else to come along and make a small tweak in it and call it a unique, new drug. And so the patent is very, very salient and protective to that discovery.

And devices, it is much more like your iPhone. It is very, very difficult for Apple to protect the way they make their iPhone look. And so we have Androids and we have Google phones, and we have lots of different iterative changes that are called unique design and that come to market. And that makes it very, very difficult for our innovators and our creators to protect their new creative ideas using IP alone.

So, this iterative process, while it makes the patent protection piece kind of difficult, it also makes the medical device space very, very exciting because we have a very iterative design and creative process in the medical device space, much more iterative than you see in drugs.

And so in the Center for Devices, we refer to this as the Total Product Life Cycle. And we think that this entire cycle from going from discovery and ideation up to invention and prototyping and preclinical testing or you are doing your bench-top testing and your animal testing, down to clinical testing, where you are finally getting it into patients, not just leads to new medical devices that go through the regulatory decision-making process and then to post-marketing, but it also leads to new ideas that feed back into the creative process of creating new devices and new design ideas.

And so the medical device space is constantly changing and improving and this is wonderful, but it sometimes provides challenges to the market models that we traditionally use to try to incent new healthcare technologies in the marketplace.

So one of the approaches we have taken at CDRH to really address this is to say how can we form new partnerships so that no single company or federal agency or non-profit or patient group is trying to support this entire total product life cycle and trying to reduce the scientific barrier to innovation. How can we pool our resources and come together so that we are partnering with industry, with non-profits, including patients and providers and the other Federal partners. This circle cites FDA but actually the Medical Device Innovation Consortium also includes the Center for Medicare and Medicaid Services that addresses that coverage piece that is so important and the National Institutes of Health.

So, in this chart, is a very, very complicated slide and not that important, but it draws on an ideation pathway that NIST laid out a few years ago. And so when you are coming up with a new technological approach, you move from basic research to proof of concept, to

early-stage technology development, product development, and finally production and marketing.

Along the entire steps of this pathway, there are different sources for investment for each one. So in the early stage, you may go to NSF and NIH, corporate research, small business, innovation research grants to get funding. As you move to proof of concept, you may have access to angel investors or corporations or technology labs.

And then as you get to product development, there is often, hopefully, venture capital available and finally corporate venture funds, equity, and commercial debt that can be used to bring your product to market.

Each of these stages in the technology innovation pathway have clear, supportive sources of funding, except this early-stage technology development. All of these sources are a little bit allergic to investing in this piece of the puzzle. And it was this piece of the puzzle that we think is most clearly related to regulatory science, this pre-competitive space research and where we really need to join together in a more massive consortium, a more massive partnership, to say let's all work together and pool our people, our intellectual capital, and our fiscal resources, to try to attack the barriers at this stage and then bring those answers, both to the regulatory side of the equation and to industry, so that hopefully new solutions will come to patients.

So the Medical Device Innovation Consortium is an independent non-profit 501(c)(3) that was founded to do this very thing, to accelerate, align, and achieve. And the

public-private partnership that they have formed with NIH, CMS and FDA has these goals in mind. And we work together to try to reduce the time and resources needed for any single company or any single group of researchers to bring in a new solution to patients.

To date, the consortium was launched in December of 2011 and we have 35 members of the medical device innovation consortium, including some of the largest medical device companies, Johnson and Johnson, BD, Boston Scientific, Saint Jude, and a lot of the smaller startups as well.

We have got patient groups, including the National Organization for Rare Disorders is a member. We have got kind of non-governmental non-profits that are also involved including Pew and PCORI, the Patient-Centered Outcome Research Institute. So, it is a very large consortium and it is growing every day we invite folks to participate who are trying to define what are some of the key regulatory science hurdles, how they can all work together to address them and then, hopefully, eventually fund more research in this area with the goal of really bringing more medical devices to patients.

It is key that the MDIC is focused on medical devices and not medical products more generally because our industry is small. And often, when we sit at the table with Big Pharma, the dollars we have to play with and the people resources we have are sometimes a smaller universe and our questions and our issues don't always race to the top of the list.

But this consortium is really focused on trying to solve the needs and meet the needs of the medical device industry. And so our issues are paramount. And the first three



areas they have chosen to focus on are improving computer models and simulations for medical device development, clinical trial design and reform, and patient-centeredness in medical device development. How can you better measure patients' views on benefits and risks and incorporate that into the regulatory process?

They are coming up with new areas of focus every board meeting, which is pretty much quarterly. So, this list will be expanding. I know there has been a lot of talk among the board about how to focus more on pediatric issues. So, there is a lot more to be done but it is a very flexible mechanism and a way for us to work together in way that is on the time frame and relevant to what happens in the medical device industry, which is sometimes a difficulty when you are working with federal agencies.

So, we invite you to learn more about the MDIC. You can go to [MDIC.org](http://MDIC.org) to learn more about it or contact myself or the Office of External Expertise and Partnerships in CDRH. And Murray Sheldon, who is following me, will talk about some of the innovation pathway pieces we are doing internally in CDRH to also stimulate the medical device innovation eco-system.

Dr. Francis: Our next speaker is Gayatri Rao. Gayatri is Director of the Office of Orphan Product Development at FDA and that office is -- oh, sorry.

Sorry. Our next speaker is Murray Sheldon. After ten years as medical director of several cardiovascular medical device companies, Murray Sheldon joined the FDA at the Center of Devices and Radiological Health as the Associate Director for Technology and

Innovation.

Dr. Sheldon received his medical degree from the University of Michigan Medical School in 1975. He completed his general surgery residency with Kaiser Permanente Medical Center in Oakland and his cardiovascular fellowship at the University of California at Davis and at the Montefiore Hospital and Medical Center in New York.

In 1983, he entered private practice as a staff surgeon in several medical centers in Northern California, performing cardiac, thoracic, and vascular surgery. In 2003, he chose to become engaged in a highly productive career in the medical device industry, leading device development projects and providing expert consultative services to numerous device development firms.

From 2003 to 2009, Murray was the Medical Director for Arbor Surgical Technologies, which developed the unique two-piece, sutureless aortic valve for surgical aortic valve replacement.

Most recently, prior to joining FDA, he was the Medical Director of both the minimally invasive surgical program at BioVentrix, Inc. and developed a catheter-based procedure for surgical ventricular reconstruction for heart failure patients.

He also was a Medical Director for Solinas Medical, Inc. and was instrumental in developing a unique device for dialysis access.

Dr. Sheldon joined the FDA in 2012 and he oversees the Center initiatives to proactively facilitate medical device innovation, to address unmet public needs, and to align

what is traditionally done at FDA with what is required to support the U.S. medical device ecosystem. He primarily focuses in working with the staff, medical device industry, and clinical community, and others, on ways to facilitate bringing innovative medical devices to patients in the United States and the world.

Dr. Sheldon currently leads the Medical Device Reimbursement Task Force and identifies methods to streamline the path for FDA approval to reimbursement.

#### Innovation Pathway

Dr. Sheldon: Thank you very much. I realize that I am what sits between you and your first break and it has been a long session. So, I will go through this fairly quickly because I think your break was about ten minutes ago. Thank you for the introduction.

A lot of information that has been presented has been in preparation for what we have really considered to be very important, which is an innovation program. This program was developed a few years ago before I came, and I have had the opportunity to help pick it up and continue it, while I have been here.

The purpose of an innovation program here was to deal with specific issues that we saw that related to the FDA's mission and vision that, as Michelle pointed out, is to bring safe and effective medical devices to patients in the United States, first in the world. Well, as you all know, that simply wasn't happening.

In 2007, we saw a peak of investments in medical device innovation. And since that time, it has fallen by more than 70 percent. And this has been a very significant issue for

us in the United States. We now realize there is a lot of competition in the world for medical device innovation and we want to maintain our position as world leaders in this area.

In a survey done at the end of 2011, some of the factors that have been cited for having the highest impact on making companies having their decisions to go outside of the United States, 70 percent of that refers to things that are somewhat within our control. The greatest portion are regulatory challenges, but reimbursement concerns and clinical trial issues are also found to be very important.

So, what is the current landscape of medical device development? So, CDRH acknowledges that there are either real or certainly perceived problems in medical device innovation development. That begins with the initial clinical development and in non-U.S. sites, in animal labs overseas. And this often leads to device innovation that continues overseas and actually there are several devices that are totally ignoring the U.S. market. They just don't want to get involved with what goes on here at FDA. They think it is too challenging and it is too difficult.

And FDA's requirements are seen to be an impediment, specifically to the early clinical testing of new devices. There is a growing concern regarding the time lag between available products in the United States and in other parts of the world. A clear example of this is percutaneous heart valves, where more than 30,000 were implanted over a five-year period in multiple countries, in Europe and other areas, before the first patient in the United States was to be given the first device. So, these are problems.

So, what are we doing about it? Several years ago an innovation initiative was actually presented out of the White House, and our Center Director, Dr. Shuren developed this program, the Innovation Program. And we have certain principles that allow us to do things a little bit differently. What we primarily need to do is understand the problem. So many times we deal with solutions that don't at all relate to the problem. The methods to create solutions can almost always be found, but it is key to understand what is actually the problem.

And we have looked at these situations and felt that it is okay to experiment, to take some risks in problem-solving and that it is okay to fail, as long as one fails fast and fails smart and then picks up the pieces and continues in the forward direction.

So, we have three goals that we try and achieve in the Innovation Program. The first is to shorten the time from initial concept to commercialization. Now this takes into a lot more than just regulation. We need to understand the issues of preclinical testing, clinical trials, reimbursements, marketing, manufacturing, et cetera. But some of the particulars that we try to emphasize is in earlier contact. We believe that medical device companies for innovative products need to connect with FDA earlier and more often, and we are open to this. Pre-submission programs are available for discussion about the eventual development process.

We also want to improve our benefit-risk thinking, primarily based on the patients' perspectives, recognizing that there are a lot of differences within a variety of diseases. There are alternative therapies and unmet needs. And that there can be mitigation strategies that we can put in place so that we can help reduce risk and support the benefit of these medical devices that can lead to earlier approval.

Just recently, we have been able to publish our early feasibility, first in human studies guidance. These are for medical devices that have not yet found their proper iterations where bench testing and animal testing have reached maximum, where you can no longer learn anything and you have to go into humans to see how this device is going to work, understanding that these devices are still going to undergo redesign and redevelopment.

So, we have been able to support early feasibility, clinical trials here in the United States, which we were simply unable to do until very, very recently.

Our second goal is to transform the user experience. And this is really important. You have heard a lot about collaboration. We feel that this is one of the keys to really develop innovative medical devices is to form one team between a medical device innovator, and the FDA, and payers and reimbursers and manufacturers to say how can we work together to solve this problem? How can we create a roadmap that will allow a sponsor to understand the pathway that they are going to have to take to get eventual regulatory approval of clearance and eventual reimbursement and eventual marketing and success.

And we have also tried to update our IT tools with the use of platforms such as Sales Force to enable to us to communicate more effectively.

And our third goal is that it is critically important to always make decisions that create forward momentum, even if we are going to say no to something, to say no quickly, to have a manufacturer understand why it is no right now and to come back and to fix it so that we continue to move down the field in that forward momentum.

So, as Dr. Geiger mentioned this morning that there are some success stories and I will just mention a few of them here, very briefly. We have heard about some of these things. With regards to benefit-risk principles, we have been able to change how we deal with pediatric-sized heart valves. Instead of having initial or original PMAs, to use PMA supplements to make the pathways easier. The Berlin Heart that you have heard about has been brought to the United States specifically, and approved and helped through OOPD specifically based on an unmet need that we simply didn't have here.

The PumpKin Project that involves VADs and ECMOs have been brought to the United States.

Under early feasibility studies for pediatrics, the transcatheter pulmonary valves have been able to be studied here in the United States before other countries.

The Innovation Pathway has also developed two specific programs used as pilots to understand how we might be able to be involved in specific device developments and, perhaps, it can be used for pediatric. So far, it has not. The first is the End Stage Renal Disease Challenge and the second was our Entrepreneurs-in-Residence Program.

The End State Renal Disease Innovation Pathway Challenge began in 2012, actually before I arrived, with the notion that end stage renal disease is a major issue. Devices and care for patients with end stage renal disease accounted for six percent of CMS's budget at the time. Now I believe it is up to seven percent. And the numbers of patients with end stage renal disease are just going to be continuing to rise and are a major, major issue.

So, we issued a challenge to say come to FDA first. We can try to help you and work with you in a different way to get devices onto the market. We had 32 applicants. We were overwhelmed. We selected three with three different stages of development. The direct access device system had actually already been studied outside of the United States and we helped bring this product into clinical trials in the United States a lot earlier. A wearable artificial kidney was just in the process of development. We accelerated the approvals of their IDEs and their clinical trials, and currently, we are in the process, actually, of helping support some reimbursement through CMS and national coverage.

Lastly, in a very, very early stage, a project coming out of UCSF for an implantable bio-artificial kidney we have been working at. This project is still in the prototype stage. Yet, we have had multiple collaborations with the company, developing pathways for eventual regulatory approval. It turns out it is a combination product that has both mechanical filtration, as well as renal cells. So, it is a very highly complex system and we are involved very, very early in the development.

Our Innovation Pathway has also instituted an Entrepreneurs-in-Residence Program. And this is a new program. It has had two iterations. The first one was for six months in 2011-2012, and the second just finished in April 2013. It is a limited time public-private interaction between selected FDA participants and entrepreneurs, venture capitalists, engineers, academics, that come and we work side to side to think about and understand specific problems that we are facing, and to develop solutions.

This past Entrepreneurs-in-Residence tackled three areas. You might notice that



these happen to be the three specific challenges that lead companies to go outside of the United States: streamlining clinical trials, streamlining a pathway from approval to reimbursement, and striking the correct balance between pre- and post-market evidentiary requirements that could potentially lead to accelerated access of medical devices for patients in the United States.

All three of these programs are now developing specific processes and have been put in place throughout the center and we hope that this will play a significant role in improving the way we do business here.

So, that is a little overview of our innovation program here at CDRH and we hope to see you all involved in medical device development here in this country. Thank you.

#### Participant Questions about FDA Initiatives

Dr. Francis: So, we are running a few minutes behind schedule. So, we are going to have five minutes for question and answer and I would like to ask that anyone with questions or comments please come to the microphones to present them.

Participant: This is more of a comment than a question. I am a dad of two little boys that have Hunter Syndrome. My boys are Jason and Justin and are the ages of seven and four.

There is, thank God for my hope, that there is a drug that, if you ask the parents, that is actually working for their brains. Unfortunately, there is a clinical hold right now on the medical device.

Now my son, Jason, his IQ is at a 71. The threshold to get into this clinical trial that is on hold because of the device, is 55. Typically, a child with Hunter Syndrome can drop 10 to 15 points per year on their IQ level. Now, this device is on clinical hold, as we have been told as parents, approximately around maybe August or September. Well, unfortunately, I have been hearing that the clinical trial is on hold because they are looking, either the FDA or the pharmaceutical company, needs more data on the device.

Unfortunately, I have been hearing this for approximately about two years. So I sit as a father at home watching my children die. And what I mean by saying that they die is that if this device is not approved so the pharmaceutical company can move forward with the clinical trial, my son's IQ at 71 might fall below that threshold of a 55. If he falls below that threshold of 55, he is as good as dead because he is no longer eligible for the trial.

So when we sit here and talk about that we need speed on getting these devices approved, if you take it from a parent's perspective, it is very important to me that if he was able to get this device approved quicker, he would be eligible for the trial. And I have been told by a few doctors already if my son Jason would get the drug today, he would be a perfectly normal boy.

So, I ask this to the panel, and I say this to myself quite often, where do I live? Do I live in a third-world country or do I live here in the United States? And I feel that every child that suffers from Hunter Syndrome should have a right to live and I think there should be a better way from a parent's perspective to have a direct line of communication to try to get these devices, especially in my situation approved much greater. Because basically, if they

open up this trial, let's say in August, September or at the beginning of 2015 and Jason goes and takes this test for his IQ and he fell below that threshold, who is actually there to blame? And there is somebody that my child would die.

Now, my other son, Justin, who is four is not greatly affected by the disease yet. He is not as progressed as Jason is. Hunter Syndrome, they usually pass by the age of 10 to 15 years of age. Justin is four. His IQ is still at 102. Thank God, he is doing well. I know where he will end up. He will end up to be Jason and unfortunately, he will also pass if things are not developed much quicker.

Now, I understand with Justin if this disease was a slow progression disease, I understand, let's take our time. Let's figure out what the data is. Let's try to figure out what the bugs are to fix it to make it right. But in some cases, like my son, Jason, time is against me and time is a word that I do not like to have in my vocabulary.

So, I think going forward and I will leave you with this point is that we need to figure out a way that I am months away of losing my oldest son dying. But if I gave him the medication today through a clinical device, he would survive and be a perfectly normal boy.

Thank you very much for your time.

Dr. Francis: So, I know Gayatri you are not really on this panel, did you have any comment about this? I know you are not on this panel but did you have any comment on that question?

Dr. Rao: I wanted to thank you for your comment. I know a lot of parents with

children with Hunter Syndrome are here and have expressed similar concerns yesterday, as well as today. And I thank you for sharing those concerns.

These are tough issues. It is difficult to talk about the specifics in a large setting like this, particularly in terms of working with the sponsor. However, I know that there are active discussions underway to deal with these issues and we are very sensitive to the concerns that you have raised.

But thank you very much for raising them.

Dr. McMurry-Heath: And I would just add we will never be able to answer your question as satisfactory as you deserve and as you would like. All I can say is that we know we are under a time crunch to try to get more solutions to patients and to do it as effectively and reliably as possible and we are trying to put the systematic changes in place to make that process more smooth.

Last May, the Center for Devices was the first FDA Center to release the guidance that said for the first time we will take data that measures whether a patient is willing to tolerate a risk, or is really interested in a benefit, into our regulatory decision-making when we are deciding whether to approve a new PMA or de novo application.

This is revolutionary. We are saying that the very data you so eloquently gave at the microphone, the data that you are willing to accept the certain risks that this device may pose for the benefits that it potentially holds, should be part of the regulatory decision-making process we do every day. And we are trying to move in that direction. Unfortunately, federal

agencies move much more slowly than patients would like.

All of us here at the table are clinicians and we have sat across from patients that are in dire need at that particular moment and we cannot do enough to help you. But I would like you to know that we are trying to put changes in place, to make sure that that story changes over time. And I am sorry that that time frame is not shorter than it is.

Participant: Thanks. I would like to just rebut that. You mentioned about risk. I know my children are going to die. Okay? So, as a parent, I would take any necessary risk there may be.

Now, looking at a parent's point of view, not as a doctor. I don't know all of your vocabulary as well as you guys explained yourself up here. But if I had to take a device and put it in my child once every single month because it is not working, take it out of him, insert it, put it back into him, I think I would rather have those risks and put him through that to give him the opportunity to live.

So when you just slide about risk, I could care less about risk because you know what, he is going to die anyway. So, at least give me the opportunity for my children to make it. And I will take those risks. I will take it.

You know there was a device out in Phase 2 of this clinical trial. The device wasn't working. It was breaking, replacing the devices, but these children were still getting the medication.

You ask these parents about this device that was breaking while their children

were getting the medication, they are doing phenomenal. These kids' IQs were going from a 70 up into the hundreds, able to go back on the potty, having them go to special needs class, and no more aides, while they were getting these devices removed and replaced because they were breaking.

So, if you would ask as parent that is facing death in their children, a risk? What do you mean? I laugh at a risk. I will take that risk because he is going to pass away anyway. So, give him a chance. Give him a chance. Let us try to do something to get these things approved a lot quicker. Let us worry about the risk. It is our children. If we don't care about the risk, I feel that nobody else should care about it.

Because ultimately, we are the ones that are in charge and we are the ones to take care of our children. And if we don't care about it, why should anybody else? And that is just from a parent's point of view. And I might not have said it correctly and the medical device as a parent, I will take the risk.

Give him the chance to survive. And if something happens, at least I know I did everything as a parent to try to save my children and that is what we -- when we have children is to let's try. Your responsibility is to what? To take care of your children. To do the best you possibly can as a parent. And if you don't do that, you are doing an injustice for your children. And I think that we need to be able -- let me take that risk. I don't care about the risk because he is going to pass away by the age of 15 anyway. So, let's do it. Let's just give it a shot.

And I thank you again for both of your comments and I don't want to take up

anybody else's time but thank you again. I appreciate it.

Dr. Francis: Well, thank you. And we still have run over our time. So, I would like to thank the panelists for speaking today and participating and hopefully, you can continue to participate.

We will take a 15, maybe 10-minute break and we will resume at 10:26.

(Whereupon, the foregoing meeting went off the record at 10:16 p.m. and went back on the record at 10:30 a.m.)

#### HUD/HDE Discussion

Ms. Wagman: Hi, I'm Victoria Wagman. I am with the Office -- Center Director at CDRH and we are going to start, if you can grab your seat. Thanks.

Our next session is on HUD and HDE discussions. And I am going to go through because we are running very short on time, a little bit of the bios of the next three speakers.

Eric Chen is Director of the HUD Program. And that is all I want to say, actually. We will do that really fast. And Nicole is the Director of the PMA Staff. And then we are going to get to Skip Nelson is the Deputy Director of the Senior Pediatric Ethics at the Office of Pediatric Therapeutics.

So, I want to then turn it over to Eric. If that wasn't fast enough, I don't know what is. Thank you.

## Humanitarian Use Devices

Mr. Chen: That was excellent. Thanks.

So, I am the Director of the HUD Program and I sort of wanted to give you a brief overview of this program. This program comes out of the Office of Orphan Products Development. So as Gayatri had mentioned earlier, our office is separate from the centers sort of set up as a purpose that way.

So why was this program even considered? Well, usually as people have heard, devices when they try to go on the market, they have to be proven to be safe and effective. So, they have to go through either a 510(k) program, which is the Pre-Market Notification Program or they can go through a PMA program.

Now, the data that is required for both of those applications is very rigorous and is sort of abundant, depending on the patient population the device is designed to treat or diagnose.

So, to encourage the development for devices for rare diseases or devices for pediatrics, Congress had developed this program in order to decrease the level of burden and the level of data necessary to get these types of devices to market.

And the program was developed in 1990 but there have been some legislative changes in the recent past, in 2007 and 2012. And what these legislative changes have allowed is to incentivize the way that manufacturers can now make a profit for these devices. In the past, manufacturers were only allowed to recoup the amount of costs necessary for



manufacturing, development, and marketing. But now, manufacturers are now able to make a profit.

So the HUD program, it is designed for niche populations. And what I am indicating with that or saying is that the device has to be designed to treat a population that occurs in less than 4,000 patients per year. So, this is a very small population and primarily designed for rare diseases or pediatrics.

It is a two-step process. The first process for people who may have been part of the workshop that we had the first two days that talked about the Orphan Drug Act, this is very similar to that pathway except that in order to receive approval for the application or the device, you have to come to the Office of Orphan Products Development to get a designation, which is the HUD designation. After that, the company is allowed to apply for HDE application for the Center for Devices of Radiological Health or to the Center for Biologics, depending on if it is a combination product that includes a biologic.

Once you obtain the HUD designation, you can then move forward into submitting that application.

So the process of how our office reviews these types of designation requests is we always try to evaluate what the disease or condition is, to make sure that it is either rare or pediatrics, or that it qualifies based on the population.

Our office can either choose to approve the application, disapprove it, or we can request for additional information, depending on what is necessary in order to designate that

product.

We have a 45 day review clock. So these are applications that we try to do on a quick basis because we recognize that these are devices that could potentially help the rare disease population in pediatrics. So, we try to accelerate that process.

When applications come in, the first thing that we do is we try to again identify what the disease or condition is. And we try to identify this based on the prognosis of the disease, the course of disease and et cetera. And what we do is we try to consider how the device works, whether it is a diagnostic device, or whether it is a therapeutic device.

Some of these designations that we give out may not be specifically for a rare disease but could be for an orphan subset of rare disease. So for example, what I am saying there is, there may be a common disease for but for some reason, there are certain patients in which the device would be designed specifically for that patient population. Then, we would be able to designate for that niche patient population.

For pediatrics, I think you have already heard from other speakers is that for devices, we will consider the population for pediatrics to be from birth up to the age of 21. So, inclusive of the age of 21. This is different than how the Center for Drugs and the Center for Biologics views the pediatric population.

I just want to touch a little about the difference between prevalence and incidence. As I mentioned before, for HUD designation, we look at the incidence of the disease. So we are looking at the number of patients who would be newly diagnosed with this disease or

condition, as opposed to looking at the prevalence. We, in the orphan products, generally interpret statutory legislation that came out of 4,000 patients per year as incidence because I think, from the standpoint of being overly burdensome, if we looked at the prevalence, I think we wouldn't have too many of these devices going on the market, just because a prevalence of 4,000 is a very small population and I don't think any of these devices would ever move forward.

There are different types of devices that we look at. We look at therapeutics and then we can also look at diagnostics. There are subtle differences between the way that we look at or we count the weight of the population. For diagnostics, we look at the number of patients who would be subjected to the device. So, it is not the annual incidence of the device, it is more of how many patients per year would be subjected to the device. And as long as that number is less than 4,000, then we are able to designate it.

So, in some cases there could be a rare disease that exists in the patients but because of certain characteristics of the device or characteristics of the disease, the device may not be able to be designated.

And I think as you had mentioned, as we heard from earlier from the presentation from Gayatri, the agency has approved 58 HDE devices that have come through the market. And a small number of them are diagnostics. And that is just because of the fact that we look at the number of people who are subjected, as opposed to the number of people who would be newly diagnosed with the device. So, there is a subtle difference and I think that subtle difference makes it difficult sometimes for diagnostic devices to be on the market.

We know that devices can be used for repeat or multiple uses. That doesn't come into consideration when we look at the patient population eligible for diagnosis. We don't consider how many times the device will be used per year. We always stay with the number of new patients that would be diagnosed.

I had briefly talked about the orphan subsets. So, in some cases when a company is designing their device, we would consider the entire population that would have the disease. So for example, if there is a certain disease in which the incidence occurs in 8,000 people per year, from a general standpoint, obviously, that wouldn't qualify for the HUD designation program. However, if there are certain individuals in which they would be able to use the device, then we would count that population. We know that for pediatrics, size is always a big issue. So, for example, if there was a device that was relatively large and would not be used in infants or neonates but would be able to be used in the adolescents and, what I am going to call sort of the larger pediatric population between 18 and 21, then this orphan subset characteristic is able to play a major role because the fact that large devices is not able to be used in small patients; therefore, we would not be considering the smaller patient population during the incidence calculation.

The orphan subset is an interesting and tricky way, and no, I am not doing its due diligence in explaining it, but I want to get through a lot of the other information and also be able to have an open discussion.

So the program has been around since 1990. The first designation that we gave out was actually in 1996. It took a couple of years in order to get the program up and running

and develop the regulations for it.

But as you can see, we do very well. We average around 20 to 25 HUD designation requests that come in for a year and we designate about two-thirds of those. Out of those two-thirds, they move forward into the Center for Devices. So the number of 58 approved HDEs, it is a small number but I think we are doing a benefit to patients who have rare disease. And those 58 approved are not only for rare diseases, they are for pediatrics. They are inclusive.

And most recently with the changes in legislation, the last bullet that we have is we currently have eight devices on the market that are allowed to make profit. So, we are interested in seeing if the changes in legislation are going to increase the development of pediatric devices that come through this program. We have actually seen a significant increase in the number of Humanitarian Use Devices that have been designated by our office for pediatrics. So, we know that this process is working. It is just going to take some time to for these devices to get on the market.

So, as a summary, HUD designations allow these types of devices to be used in patients with rare diseases. And having pediatrics as a subset is very beneficial for that patient population. We designate devices for a disease and not for a specific indication. And lastly, we have a guidance document that is on our website that can assist in better understanding this process.

## Humanitarian Device Exemptions (HDE) Overview

Capt Wolanski: Hello. I am Nicole Wolanski and as I was introduced, I am the Director of the PMA staff. And we have recently taken over the HDE program management of that program, so it has moved to my group and I am happy to explain to you the basics as far as I understand them.

The HDE pathway to market is a regulatory pathway for devices intended to treat rare diseases, as we have been discussing all morning. And my objectives are to go over the HDE program; to discuss the statutory changes that have happened over the past several years to allow a profit for those devices; to review again the two-step submission process for HDEs, because that is much different than what there is for 510(k)s or PMAs; to briefly discuss the HDE submission content and what you need to remember to consider including in your HDE; and other interesting HDE facts.

HDE is our marketing application. It is important to know that because approval of an HDE grants you the authority to market a device. That being said, there are some limits to that marketing approval that differ from our other types of applications. Once you receive HDE approval, you will still need to have IRB approval for using that device in accordance with its approved indications for use prior to using it, except in emergency situations.

In addition, the labeling for HDE-approved devices must include a statement that it is an HUD device and that effectiveness has not been demonstrated. Because the bar for approval is a little bit different for HDEs than it is for PMAs and 510(k)s.

In order to qualify for review as an HDE, you have to have, one, been designated as a Humanitarian Use Device, as Eric mentioned. In addition, that device cannot be otherwise available through a 510(k) clearance or PMA approval, and there can be no other comparable device available with 510(k) clearance or approval.

And that threshold for approval is safety and probable benefit, which is to say that that device does not pose unreasonable risk of illness or injury and that the benefit, the probable benefit, outweighs the risk.

An HUD is now eligible to be sold for a profit if it meets certain criteria. In 2007, that is when that first came into play through the Food and Drug Administration Amendments Act of 2007. And at that time, these were the criteria for being able to earn a profit on an HUD device. It had to have been intended for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric subpopulation, and it had to be labeled as such. Also at that time, it only applied to devices that were approved in 2007 or later, and not prior to 2007.

When a company qualified for this, we assigned an Annual Distribution Number to that submission and informed the company in its approval.

In 2012, we expanded the ability of HUDs to obtain a profit after approval. And the first criteria remained the same. The second criteria was added, which is that the device is intended for treatment or diagnosis of a disease or condition that does not occur in pediatric or that occurs in pediatric patients in such numbers that the development of the device for such

patients is impossible, highly impractical, or unsafe.

In addition, we allowed, through FDAAA the ability for HDEs that were approved prior to 2007 to also request the ability to obtain a profit in the marketing arena.

As Eric explained, the HDE submission process starts first with request for a HUD designation from his group, the Office of Orphan Products. As he also explained, it is a separate group from CDRH. It is outside of our office. So you have to go there first and make that request. And after you have received that designation, you submit your HDE to CDRH.

Some of the incentives for going through this pathway include that there are no user fees associated with that process, like there are for 510(k)s and PMAs. And there are -- I lost my train of thought -- no user fees and it has a 75-day review clock, which is shorter than PMAs and 510(k)s as well.

The HDE submission content includes in your HDE you would have to reference your HUD designation letter, which is granted by OOPD. You have to explain why the device was not otherwise available or comparable devices are not legally marketed.

In addition, your content would include a device description which includes graphics, chemical composition, specifications, device drawings, bench and animal testing, which includes software, biocompatibility, mechanical testing, chemical testing, electrical testing, anything that is applicable to your device.

It would also include whatever experience you have had with that device, whether it has been within the United States or outside of the United States, any data,



literature, any marketing experience whatsoever.

Of note is that the clinical data experience with HDE devices is often quite a bit smaller than that for PMAs and 510(k) submissions because it does impact such a small group of patients and there are no comparable devices. So, the data is not randomized or controlled in any way, typically.

An HDE submission would also contain manufacturing processes and procedures. The quality system regulation still applies. It would include any labeling for patients and physicians and it, as I mentioned earlier, must contain the HUD statement and a statement that no effectiveness has been demonstrated.

An HDE submission would also be the appropriate place for an applicant to request an ADN, if they are eligible and we will review that information.

One place where you can go to get more information about the specific content requirements for an HDE is our HDE filing checklist, which is online at the link included here.

To give you a little bit more information about how the ADN is calculated, it is calculated by multiplying the number of devices reasonably needed to treat, diagnose, or cure an individual each year by 4,000. So, if an annual incidence for a specific HUD is 3,000 but the number of devices that would be reasonably be needed per patient per year is two, we actually multiply two by 4,000 and your ADN is 8,000. So your ADN is always going to be a multiple of 4,000, even if 4,000 devices are not intended to be used each year.

Again, the approval threshold for an HDE is safety and probable benefit. This is

different than PMAs which is reasonable assurance of safety and effectiveness. So, we carefully review the devices. And it is a different mindset for a reviewer to be looking for this type of information than what they are used to looking for, so we focus on that. We have to make sure that the device does not expose the patients to unreasonable risk of illness or injury and that is a probable benefit.

We do complete a risk-benefit form to have a better understanding of what the risks and benefits are for that device and put it into the framework of probable benefit versus reasonable assurance of effectiveness.

As has been mentioned, there are 58 approved HDEs since 1996. We keep a list of all the approved HDEs on our website at the link on my slide. When you go on that link, you can go for each HDE approved and see our summary of safety and probable benefit. You can see our approval order and you can see the physician and patient labeling that was approved as part of that submission.

Some of the key points I want to reemphasize is that HDEs are exempt from the effectiveness requirement, that HDE is a marketing approval; however, IRB approval is required. Informed consent is not required by FDA but it may be required by the IRB.

And there is not a requirement for an HDE applicant to eventually submit a PMA or 510(k). It is certainly an option that they have if they wish to pursue that, but it is not something that anyone has to do.

And we can have multiple HDEs for the same indication from different sponsors.

Just because we have one HDE approved does not mean that we can't have another. But if a PMA were to get approved or de novo were to be appointed, that would have an impact on the approved HDE.

Thank you. And if you have any questions, feel free to follow up with me after this directly or we can discuss it in the session later.

IRB Oversight of Humanitarian Use Devices (What's an IRB to do?)

Dr. Nelson: Moving right along, I wanted to see the slides because I hadn't seen them before to make some adjustments to what I say, so I could not create the orthopedic problems relative to my neck.

So, what I am going to cover is some IRB issues. I am going to shift a little bit on the timing I was going to spend on different slides. But basically I was going to note that you need IRB approval to use an HUD except in emergencies. You have heard that twice. I wasn't going to say much more than that but that is similar to the use of drugs in emergencies if it is a life threatening disease and you can't get IRB approval.

I am going to review the distinction between using the HUD in the course of medical practice and in a clinical investigation and then discuss the IRB review procedures. And then conclude with a summary of regulations.

But what I am going to do is go through this a little more quickly than I was planning to because I chose that because that is the source of confusions for IRBs. Any IRB members in the audience? One. All right, former IRB chair. So, probably you are more

interested in the fourth point. So, I will go through those points a little more quickly and spend time on the fourth point.

There is a guidance. There is a caveat that there are parts of that guidance that are now -- that require revision after FDASIA. You heard some of those points made around how it has been broadened. But I will suggest I don't think any of the IRB stuff in that guidance was changed by FDASIA. I'm not aware of anything. So, the guidance is probably still useful for that purpose.

You have already heard the distinction about a Humanitarian Use Device and a device exemption around probable benefit and the point that it can only be used in a facility where the IRB has approved it.

In that guidance, there is a decision tree. And I still think this decision tree is useful. I am not aware of any conversations to revise a decision tree but you know, we will see. But basically across the top here, it says this is the emergency use. Can you get IRB approval in time? Yes/no? If the answer is yes, you have got to get it. If it is no, then maybe it is an emergency use life threatening.

But then it comes down to this question about what is the use of that device? Is it a clinical use or is it an investigational use? And you will see this tree again so that you don't have to look at it in detail.

So, this is the basic distinction. You can use it in medical practice. So, you have an HUD that has an approved HDE. In other words, it has already gone through that process

and it is sitting in the device room and the surgeon wants to pick it up and use it. You can use it according to approved labeling or you can use it off-label, maybe modified in some way. That is medical practice.

Clinical investigation would be if you are collecting safety and effectiveness information or in fact if you are doing the necessary studies to get your HUD into an HDE application to submit to the Agency for approval, that would be a clinical investigation. So, that is an important distinction.

How does this play out? Well, it says first of all, are you going to be -- are you studying it on its indication? Yes or no? If the answer is yes, are you going to collect any data about it? No, well, then it is clinical practice. An interesting issue here. Clinical practice means we don't collect any data about what we do. I mean we could debate that as a physician whether that is a good frame of mind to have about the use of what you are doing.

If it is not being used according to indication, again, the same question. Is it being used as part of a clinical investigation? If the answer is no, that would be off-label medical practice.

Now, I am going to walk through what does the IRB do if that is the case, either on-label or off-label clinical practice. And I will move quickly through this and there is not a lot of IRB people here. How many of you have already approved HUDs that are out in clinical practice? Very few. So, most of you are in the pre-practice space. So, that is why I will go through this quickly and you will see what is confusing to an IRB.

IRBs are supposed to review research. Well, must an IRB review a protocol? No. Must an IRB monitor the number of HUD uses per year? No. Must an IRB audit the medical records of patients who receive the HUD? No. Should an IRB ask for justification of the HUD charges? No. Does an IRB function as a data monitoring committee? No. Do the requirements for IRB review shift if you have to apply the HHS as opposed to the FDA regulations? No. Must an IRB approve an informed consent document? No.

What are they supposed to do? Most IRBs wonder that, which is why they say what are we supposed to do with this?

Well, the FDA has some advice and, arguably you could say that maybe the proper committee to review HUD use after an approved HDE would be a Medical Device Committee that exist. Most large institutions will have device committees similar to drug use committees. But whatever it is, IRBs were written into it. So, the FDA does have some recommendations, basically which says that the IRB, do sort of what you normally do about evaluations, risks, and benefits, basically and sort of look at these documents. But it is not meant to be the kind of protocol review that takes place in the context of a clinical investigation. All of this is in the guidance. I went through it rather quickly but the point is you can see why IRBs get confused when you bring an HUD to them. After approval, they go, "Huh? What are we supposed to do here?"

So, the other use is in a clinical investigation. And the bottom line is when it is a clinical investigation, all of the basic rules apply for a clinical investigation. And that is really the slide where I want to spend a little bit of time.

So prior to HDE approval, so you are in the position where you have got your HUD designation from the Office of Orphan Products and you are then developing it to submit to CDRH for HDE. That is a clinical trial.

So, you could collect safety and effectiveness data after its approval without an IDE. So, the bottom line is if you are basing it on its indication, the assumption is that the risk is really no different. The FDA has already made a decision about the appropriateness of that use. And so that doesn't require an IDE. So, the IRB ought to be able to just move forward with that approval without getting overly exercised about CDRH signing off on an IDE application.

They may ask that question. You could provide them that answer. And this is in the guidance so that you could use that to support that.

A clinical investigation for a different indication, though, the question is, is it a significant risk device or not? Now, basically as a former IRB chair, the way I understood this designation is CDRH sort of delegated to IRBs a decision about whether something is a significant risk device or a non-significant risk device for the purpose of deciding whether they need an IDE application, or an IDE, to the FDA. So, if it is a non-significant risk device, the IRB could say you can go forward without the FDA being involved.

Now, in this space, it turns out that all HUDs have been, at least historically, considered significant risk devices. But that is why this other category exists. So, the IRB needs to make that determination. Most likely, I know of no examples where it wouldn't be a significant risk device and IDE would be required. So you would go through that process of

getting the IDE.

And then the IRB approval is required under Parts 50 and 56. Now, let me talk briefly about this slide. We heard a little bit of discussion about risk and there was a discussion yesterday in the session that we had on pediatric drug development around risk tolerance.

Basically, devices are under the same regulations. You do a clinical trial in pediatrics, the risk that you put that child to must be justified by the prospect of direct benefit. And so there is that assessment of risk and possible benefit and then you put it in the context of the available alternatives. It's that risk assessment that I think is important -- and that is 21 CFR 50.52, for those who are keeping score. It is within that context that I think one could begin to frame how we understand the risk of these devices and how we understand the appropriateness of making decisions within all of the various stakeholders as part of the discussion yesterday about how we justify the risk to which we are putting a child in hopes of the potential benefit that we intend to achieve.

And I just make that comment, particularly given the comments that were made following the last session that it is sort of within that space that there needs to be a conversation between parents, investigators, sponsors, device developers, FDA regulators, et cetera, about the appropriateness of the risk to which we are exposing a child in hopes of that potential benefit.

So, I will stop there. A whirlwind tour of IRBs. But again, there is a guidance out there which I think on the IRB side is accurate, even if it is not accurate on some of the other



device issues that were updated by FDASIA 2012.

#### Moderated Discussion

Ms. Wagman: So, it is time for questions. I am going to ask that you use the microphones. I want to thank Skip and Nicole and Eric. And I also want to remind people if we can't answer all your questions that there is an open docket. So, please make sure that you submit it. If you think of things afterwards, please make sure you submit those questions and comments to the docket.

Questions? Yes.

Dr. Snyder: Hi, I am Brian Snyder. I am a pediatric orthopedic surgeon at Boston Children's and then I represent Pediatric Orthopedic Society of North America and then I sit on study section for NIAMS for several study sections.

One of the problems that I want to address is IRBs. If you want to try to do multi-center studies, each IRB at each of the parent institutions interprets the mandate in very specific and different ways, that becomes a real barrier to getting studies done. And an example would be the VEPTR device which is used for thoracic insufficiency does have an HDE but if you want to compare to growing rods, which are completely off-label use, that is the common clinical practice now, I can't and we can't, organize a multi-center study because these are small numbers of patients, so you need multi-center so you have adequate power.

IRBs won't allow you to compare to a device that we are all using off-label and yet the HDE which is approved maybe a better device for that purpose. So, you have a situation

where the IRB is actually a barrier to getting things done.

And then on the tissue engineering side, that is the section multi-center studies can be problematic in that every IRB has their own little political set of standards that they apply and interpret the mandate in their own way. What would help would be then, almost a universal IRB for these kind of multi-center studies.

So, when you are writing your NIH grant that gets approved or when you have your HDE device and you are now going to compare it to whatever the clinical standard is that you can basically bypass the individual interpretations of the mandate at these multi-centers.

Dr. Nelson: A couple of quick comments. I don't disagree with anything that you have said. I do think, I mean and the issue is common across both the drug and device world.

One thing I would say, though, is you will never bypass the local IRB. What you have to do is you have to get to the point where they are willing to accept the judgment of another IRB and the like and be able to delegate that decision.

In clinical trials networks, and I heard some discussion about the need to develop a sort of device infrastructure for clinical trials and, to some extent, I would suggest maybe that needs to be sort of grafted on to some of the discussions that are going on quite vigorously in the drug world because large children's hospitals that insert these devices are really the same hospitals that are getting involved in the clinical trials infrastructure as well. Within that space, there is discussions about how to streamline IRB review and how to get to the point where one IRB could make a decision where all of them would then be willing to accept. Part of that is

building trust and setting up mechanisms by which the decisions are transparent, one to the other.

And one final comment, I mean there is variability and some of that variability is unjustified. Just on the face of it, it is hard for me to understand why someone wouldn't let you study an HUD against something you are already using that is off-label. I mean we do that in drugs all the time. It is a little unclear to me why that would be a problem. But if you propose that to CDRH, they can always involve me, and I can advise you as a sponsor.

Dr. del Nido: Pedro del Nido from Boston.

Just as an additional comment about the last question, I am involved in a Pediatric Heart Network, which is sponsored by NHLBI. And they actually deal with those issues ahead of time, which may be a helpful way to address. In other words, they contact all of the IRBs ahead of time as an NIH-sponsored network and that sometimes works. And that certainly has worked for the Heart Network. So, it may be a way to get around that issue.

My question is a broader question, though, and more aimed at Eric. Sorry to put you on the spot. But the number 4,000, that legislation and that number came up a long time ago. A lot has changed since then but the number hasn't changed.

Is there any thought or any effort to relook at that and see? Because especially now with the 2012 legislation where profit is a possibility, now we are talking about potentially greater interest on the part of manufacturers in pediatric devices. And I think revisiting this number may be timely.

Mr. Chen: And I think that is a very good point. It is something that internally our office, in conjunction with CDRH and stakeholders have thought about. We haven't performed a formal analysis of applications that have come into our office, compared to the ones that we have granted. So, trying to look at the ones that have been denied because the population was over 4,000, comparing it to the ones that do qualify.

In the past, we had heard that the 4,000 limit was the rate-limiting step as to getting devices on the market for rare diseases and pediatrics but most recently, we have heard of other reasons being reimbursement and clinical trial design and getting data.

So, I am not sure if it is because the tides have just changed and that is the case but it is something that we would be interested in looking at. But at the moment, I am not aware of any potential reasons for changing that number.

Dr. del Nido: Well, it has been around long enough that I think almost everybody just takes it for granted. And I think it may have been embedded in the thinking already. But if we are starting to look for other ways to get all the stakeholders interested in pediatric devices, that may be one mechanism that -- I mean let's face it, it is a bit of an arbitrary number. And you know there were justifications at the time but a lot has changed since then.

Mr. Chen: Yes, I would completely agree with you.

Participant: So, I think Dr. del Nido and I should have spoken before we come up here because I had a very similar comment to him but I will take it a step farther. In my simplistic view of things, the HDE process is the CE process, essentially with cap. Is that not

true? And if the HD process is working so far, why in pediatrics can we not have a specific approval process that looks like the seed process? Because essentially med device companies are only going to get interested in this space if you give them a tax deduction or if you create some way for them to get a device to market more quickly. And if you can do this by actually developing a pediatric device first, that may be an incentive to bring the devices that Dr. Geiger was talking about to market sooner.

Again, I am not a regulatory expert but, to me, it seems like you already have the CE process and it is working well pediatrics.

Capt Wolanski: I don't know if I would equate it with the CE process. We have some differences. But I do take what you say to heart and will certainly share your comments.

Participant: Just quickly, could you describe how it is different than the CE process, other than the IRB?

Capt Wolanski: I don't have an analysis in my head of this. I am not familiar with the CE process to its specifics. But I know that we have certain ways of doing things here that are not identical to the CE process.

Mr. Chen: Yes, I can briefly just in simplistic terms talk about the difference. The CE mark is, for people that don't know, it is the approval process for medical devices in Europe. And unlike the approval process that we have in the United States, individual countries within Europe were able to give CE mark for manufacturers to get their devices on the market.

So, it is not like an entire European Union approval to allow a device to be used

in Europe. Individual countries are able to give CE mark. In actuality, individual manufacturers can actually give CE mark to other devices for other manufacturers.

So, there is differences there. One of the other differences is that for CE mark, a manufacturer only has to show that the device is safe and the device meets the device specifications that the device manufacturer has put forward for that device.

So, there is very limited data to support a probable benefit or effectiveness hurdle for medical device. So, those are some of the two differences. And I have heard people say the HDE pathway is very similar to CE mark, as you have said, because of the fact that the safety part is there and they know that they are exempt from the effectiveness.

But for HDEs, we do require because of the legislation, the safety, and probable benefit, the data is lower. It doesn't meet the hurdle that is needed for a PMA but I would say it is, to me, personally, I would say it is in-between the CE mark and a PMA.

Participant: So, sorry. Quick follow-up, then. Who exactly is responsible for changing or eliminating that 4,000 number? Is that within the FDA? Does that require something going to Congress?

Mr. Chen: It is in the statute, so we would have to -- I mean not me, not FDA, but legislation would have to be changed in order to do that.

Participant: Okay, thank you very much.

Dr. Nelson: If I could just add one comment, one of the more interesting panels I

served on before my FDA gig, was on a CDRH panel asked to decide whether a device was approvable as an HDE. And I would say, having listened to this conversation, the main issue was around probable benefit. It was not a CE determination. And it was around whether the data met a probable benefit cause. I wouldn't see them as equivalent at all.

Participant: No, I just meant from the standpoint of looking at safety and probable benefits, which --

Dr. Nelson: Yes, but there is no probable benefit in Europe around devices. I'm just saying the CE process is different. But the probable benefit standard is different.

Operator: We also have a question from the webcast for the panel.

What are issues for IRBs if a HUD is being used to monitor an investigational drug? For example, drug companies may be hesitant to include use of an experimental device to monitor a drug for which they submit an NDA. Can you answer that?

Dr. Nelson: Well, that is sort of a combination question. I don't have a lot of experience with that. But part of the hesitation might be that when you incorporate both drugs and devices into your clinical trials, you fall under the jurisdiction of two different centers. And so if it is a combination product, per se, with a drug and device or really like a drug-eluting stent, then the Office of Combination Products makes a decision that it falls under one or the other Center so that that process is simplified.

But if you have, for example, an in vitro diagnostic device paired with a drug development program, I know there is a lot of coordination between the two centers and I

don't know if someone else would want to comment on that, but it is not a simplification from the standpoint of one center per se having all of the sort of decision-making authority delegated to them around that device.

So, there are complexities. But my understanding is there is a real attempt, particularly given the development of targeted drug therapies and the fact that that, by definition, has an in vitro diagnostic device tied to it to try and simplify those procedures as best as possible for sponsors coming in so it is transparent and the sponsor is not the only person sort of running between the two parties, much like a sort of negotiation between two centers.

Ms. Wagman: This is going to be the last question.

Participant: Thank you. Hi, Chris from the National Heart Lung and Blood Institute.

If a company were seeking to develop a pediatric device that would, as Dr. Geiger pointed out earlier, might need to grow with the patient as they progress through their disease and yet it is a rare disease and they are going through the HDE process, would they need to seek HDE designation and approval for each size of that device or would there be some way for them to seek a blanket approval for the concept of the device?

Capt Wolanski: All sizes and models are considered part of the submission and would have to have some data to support the different sizes to make our determination of safety and probable benefit.



Dr. Nelson: I think the question was could you get an HUD designation for each size of the device.

Mr. Chen: You could. I mean a company could come in and request for individual HUD designations for each different size but we generally will give designation for the entire range of sizes.

So for example if there was a blood pump that has sizes between 10 cc, 25, 30, 40, and 50, we will give HUD designation for the entire range. We won't give designation for each individual size because we find that that would just be overly burdensome for the manufacturer to have to keep track of everything. And as mentioned before, when you go into the HDE application, you have to provide a letter saying that you have received HUD designation.

So for example, if you gave five designation letters, it would just be overly burdensome for a manufacturer to keep track of those five and then submit five different HDE applications. It is more of we would just combine all of those together into one.

Ms. Wagman: All right. I would like to thank the panel again. And we are going to move on. I see Christy has arrived and so we are only a little bit off schedule. So, thank you.

#### Engineering Considerations

Mr. Chen: So, I am actually staying on the panel. I am going to be the moderator for this session. So, I wanted to welcome Christy Foreman. Christy Foreman has been with the

Agency for over 15 years now. She has different roles within CDRH from the compliance to post-market and now she is currently the Director of the Office of Device Evaluation within the Center for Devices.

So, I will turn it over to you, Christy.

Ms. Foreman: Good morning, everybody. I am going to talk a little bit about the engineering considerations for pediatric devices. Some folks would say well, you just build a smaller version. In some cases that it is true. In some cases, that is not quite exactly what we would want to do.

So, I think we have covered some of the basics already in this talk but I will talk about the pediatric population, device and design considerations, unique and unmet needs, and some creative approaches that we are trying to do within the pre-market review process.

So, I think we have covered the pediatric population but you can see the pediatric population is a very wide ranging population. So, are you dealing with neonates, the really, really small folks? Are you dealing with adolescents? There can even be differences in the subpopulations within pediatrics that you need to take into consideration as you design a device.

Pediatric populations are a particularly vulnerable group. The general principles of device review would apply to pediatric devices. So, we are going to make sure that the devices are biocompatible. We are going to make sure they are sterile. We are going to look for electromagnetic compatibility. Design controls and good manufacturing practices also

apply. But it is the bench testing and the specific design testing that needs to really probe the use of these products.

So, additional considerations for pediatric populations include the height and the weight of the patient. So you are going to look at how small do you need to make the device.

Pediatric patients will also grow. They may grow in general or they may have an unpredictable growth in development issue.

So, if you have an implant, you need to take this into consideration: the disease or condition, the congenital problems that may occur, any hormonal influences, anatomical and physical differences from the adult population, the activity and maturity level. We have cases where approved devices have been used in pediatric patients, particularly pediatric patients with cognitive problems and their activity level has caused some problems with the devices. So, you need to take that into consideration. The injury and recovery from the use of the device, and also most importantly, the difficulty in conducting clinical trials, which in turn means that most of our question may need to be answered on the bench.

So typically, modifications to an adult device would include a reduction in size or, for example, attenuation in electrical output.

So, I have here an endotracheal tube. One of my many positions in the Agency was as a reviewer and I used to review endotracheal tubes. And in this case, this is a case where you typically look at differences in sizes. But there are not a lot of other considerations that may take place for a pediatric use.

Designed specifically for pediatric populations, you may want to look at the specific condition and you may want to address pediatric limitations.

You need to consider factors specific to the pediatric population, such as the stresses on the device due to growth. So, there are some creative approaches that have been used. You don't want to necessarily have to go in and resize the device through an additional surgical procedure, although that may be the way to resize the device but some folks have been very creative in that you can do the resizing externally with the use of magnets, which would be a much preferable options, so that you don't have to have another surgical procedure.

As I mentioned, the activity level can cause additional stresses on the device that you need to take into account.

We are going to look at the impact of the treatment on the smaller patient and the effects of treatment on development. So, we don't want the device to have any adverse consequences on continued development of pediatric patients.

So, I am going to go through some specific device examples. AED manufacturers have recognized the need for lower output for children. So, we have different design options. We have pediatric pads that attenuate the signal. And the user input to the AED will signal that it is a pediatric patient, as opposed to an adult patient, so that you are actually delivering the right energy level. Because an adult energy level delivery would actually be catastrophic to a pediatric patient.

So, here is a device that is a, we call it the VEPTR, the Vertical Expandable

Prosthetic Titanium Rib, and it is indicated for the treatment of Thoracic Insufficiency Syndrome. This is for use in skeletally immature patients. It is a curved metal rod that is attached to the ribs.

So, the device is lengthened or replaced at specific times to allow for the patient's growth and to further correct any deformities associated with TIS.

So, this is a device that must take into account the fact that the patient is going to change size and shape and the device must accommodate that.

So, the Berlin Heart is another example. This is a Ventricular Assist Device that is designed to assist patients who cannot pump enough blood with their own natural heart. This is the first FDA-approved pulsatile mechanical circulatory support device specifically designed for children.

So, in this case you are going to need a smaller device because the adult version is going to be simply too large. But what you need to really worry about here is when you make a smaller device, you may have increased risks. Thrombus formation may be catastrophic in these devices because of smaller diameter, smaller lumens. So, you really want to make sure that you have some patient experience but you are not going to get a sample size large enough to fully validate this device. And I think that is the one point that we really need to consider with pediatric indications is the amount of uncertainty that we will allow in our knowledge of the device, to allow the device to market.

So we are only going to typically be able to get a certain amount of clinical data.

We then must rely on bench testing. In some cases bench testing will be pretty good. In some cases, bench testing will be imperfect. And we have to decide how much uncertainty will we allow before we allow the device to be marketed, knowing in many cases we have an unmet need.

So, we have to look at how creative can we be in our bench testing methods to give us the amount of validation that we would need to comfortably put a device on the market with the minimum amount of information to make sure it is safe and effective but we also want to make sure time to access is not unduly delayed.

So, FDA wants to work with manufacturers in the clinical community to bring to market more devices designed for and evaluated in children with appropriate labeling. So, often times if there are limitations in our understanding, we will communicate that through the labeling so that patients can make and caregivers can make the appropriate informed choices.

It is hard to say that there is a one-size-fits all model. So, we encourage manufacturers to work with the agency so that we can develop a tailored approach specific to the needs of each particular device.

We are willing to work through pre-submissions. We are willing to work through IDEs. We will work through endpoints. We will work through the bench testing that is needed. The first step, though, is that manufacturers need to come to talk to us so that we can work these issues out as early as possible.

So, I want to thank you. And now we are going to open it up to probably the more informative part is kind of the discussion, question and answer period.

## Moderated Discussion

Mr. Chen: All right, so if we have any questions for Christy, please come to the mike. Please try to identify yourself and ask your question.

So I don't see anyone rushing to the microphone. So as the moderator, I will take the liberty in taking the first shot at Christy.

So, we have heard many people say that pediatric patients are just not small adults. And you can't just miniaturize a medical device from an adult population or an adult size down to a pediatric size.

Can you describe what CDRH is doing in terms of developing guidance documents or working with standards groups to develop sort of guidelines on the type of preclinical testing that would be necessary for pediatric device development?

Ms. Foreman: So, we have the guidance on extrapolation of pediatric or adult data to pediatric indications, which really talks about clinical data. We don't currently have any general guidance documents on bench testing because in most cases, the bench testing will be very specific. So, it would be hard to write a general principles guidance document because of the specificity for each device type.

So generally speaking, we will try and incorporate that in any device-specific guidance that is being drafted.

One thing that, as an agency, we are also looking at is the concept of what we

call a leapfrog guidance document. And this is a concept where we will put out guidance before we review products. Our typical life cycle is we see several of the devices. We kind of establish what are the data requirements that are needed. We then take that knowledge set and we put that in a guidance document and publish that.

Well, that means the first few folks that went through the process had to kind of figure it out or work individually with the Agency. What we want to do is for some of these tough issues, we want to think about it ahead of time and we want to put out these leapfrog guidances so that we can say if you are thinking about developing a product in this space, here is what you would want to think about. And we prospectively communicate that to make device development a little bit easier.

Mr. Chen: Okay, great.

Ms. Cocanower: Hello. I am Carolyn Cocanower. I am one of the engineers in the Pediatric Device Consortium located in Washington, D.C. And one of the major challenges I have had as an engineer developing medical devices is developing bench models and animal models for pediatric situations, which I am sure most of you all are aware of, just pediatric models don't exist. A model of an animal that grows with the implant patient just doesn't exist. And sometimes creating those animal models or creating that bench shop model is more costly and the time to validate is sometimes extremely lengthy.

Are you all doing anything in CDRH to work with developing these animal and/or bench models, as well as helping work with people to validate these models, since it can be so



costly? Neonatal tissue, you can go buy synthetic adult tissue but buying synthetic neonatal tissue is more difficult. So, you have to be a little bit more creative.

Ms. Foreman: So, in working with pediatric devices, creativity is really the key. One of the things that we are working on is medical device development tools, which is a way to qualify tools for the development of medical devices. We have just started this effort but we are hoping that we can use animal models. We can use surrogate measures. We can use even computer modeling, computational modeling to kind of help facilitate device development without the need for as much clinical trials.

In terms of clinical data, we may need some clinical data but really, I think the key is how can we efficiently and effectively develop surrogate models that can give us information so that we may actually gain more information than we would from a clinical trial. Because if you look at a clinical trial and especially for rare diseases, you are just not going to get a lot of data. So, as I said, that is where you have to put a device on the market with probably a large amount of uncertainty. And we may rely on our post-market data collection to help answer those questions.

But we are trying to look at, we have some concerted efforts underway for computational modeling, which you are right, the validation of the model is probably for any one individual, it is probably harder than doing a clinical study but I think what we really want to focus on is let's validate one model that everybody can use, as opposed to asking everybody to do a clinical study, looking at the same question.

So, we are in the early phases but that is where we are putting a lot of emphasis.

Dr. Berul: Charlie Berul, pediatric cardiology here in Washington, part of the National Capital Consortium.

It is actually a pretty quick question. How do you classify fetal research and device development? Does that come under pediatrics or is that a different committee or classification?

Ms. Foreman: So, we don't have a lot of fetal research. We would probably consider that a pediatric indication. We have some devices. We did have essentially a pulse oximeter that was used pre-birth and we did have a clinical study for that product.

We do have some imaging devices that would look at devices -- look at patients before they are born. We don't have a lot of, as I say, clinical studies in that area but I think it is something that we would, once again, have to develop a creative approach if we were approached. You mentioned you are from cardiology. So, if somebody came in with a device that is to be implanted in a fetal patient before birth to correct a heart defect, we would consider that a pediatric study and it would obviously be one that we would try and be creative with, to make sure that we have safety measures in place but we would have to look at the patient population, which is probably going to be pretty small.

Dr. Berul: Pretty small. Less than 4,000 for sure.

Ms. Foreman: Definitely less than 4,000. Maybe less than 400.

Dr. Basu: Sujit Basu, Shire. You mentioned, Christy, that activity level is one consideration in the area of design. I wonder if you have any guidance because we often struggle in literature to find the clinical element forces on device. And this is also complicated by a child with a normal development and those going through rare genetic diseases.

So, do you have any guidance or documents that we should refer to? Obviously, understanding that different devices will undergo different forces but what should be the starting point that we should think about?

Ms. Foreman: Well, I will give you the official Agency answer. It depends.

You know it really is going to be. In most cases I would say your smallest patients are going to represent your worst case scenario in terms of many issues. You know you have size constraints. You also have the forces and kids are very active. They are going to bound around and if somebody is going to break a device, it is probably going to be them.

So, I think you would start with what you know about the device in general, the device in the adult patient. And then I think you would have to scale it to the best you can. I think we are open to reasonable, rational conclusions that if you look at your device testing and you say we did a factor of safety of 2X because we looked at the adult patient. We put in some additional activities that we think a pediatric patient would be likely to do with this device and then we put in a factor of safety, I think that would be a reasonable approach.

Certainly, if there is clinical testing, it would validate some of those assumptions. I think that is part of the reason why we look at clinical studies. And I think what we would do

is, if we were unsure of those assumptions, we might look at some clinical data, along with the bench data and we would say okay, the bench data has basically validated the device performs according to the assumptions. The question is, are the assumptions appropriate for the clinical use? We might give you a few patients and we would say how does that work in a few patients? And if it works okay in a few patients, then we will say okay, take a few more patients.

If we are pretty comfortable with the assumptions that you made for your device, we might say you can have the whole patient population but we might put in some stopping roles.

So, there are a few things we can do to try and work through those issues but I think it is really going to depend on what the device is.

Mr. Chen: Okay, let's have two more questions. Dr. Del Nido.

Dr. del Nido: A couple of questions. Maybe I will just stick to one.

There is a great interest right now, particularly in the cardiac and vascular world for resorbable materials for devices for children. And that comes in with a lot of questions because most of these are meant to either restrain parts of the heart or to expand vessels but only for a short period of time and with a concept that there is growth involved.

There is still, at least it seems to be, a lot of questions about how that is going to be managed or at least how that is going to be addressed by FDA, whether it is going to be treated as a device or whether it is going to be treated as some sort of a drug. Where do things

stand on that? Because, obviously, it is a different world.

Ms. Foreman: So, once again, the official Agency answer applies. It depends.

If the product works by chemical action, it is going to be considered a drug.

Now, the real question is for some of these resorbables, the question is actually going to be is it a biologic or is it a device. Because if it is a cell-seeded scaffold, it is probably going to be regulated as a biologic.

If it is a device resorbable material where it actually has no biological material but it is resorbable, it would be a device.

So, we do have a process where you can have a designation in terms of if you are unsure where your product will be regulated, you can submit what is called an RFD, a request for designation to the Office of Combination Products. They will tell you if you have, A, a combination product or if you have a single entity product and they will tell you where that single entity product will be regulated.

Dr. del Nido: Well many of these devices, particularly if they are resorbable materials that just go away by hydrolysis, which is where a lot of the devices are. Is that considered a chemical reaction? I mean because hydrolysis is something that just happens. But I mean theoretically, it is a chemical reaction. That is how the polymer breaks down.

Ms. Foreman: So, we look at the product for what is the primary mode of action. And is that primary mode of action achieved by chemical action?

So, resorbable materials have been regulated as devices and I can think, you have resorbable pouches for pacemakers and some of them are actually antibiotic coated. Those are put in the pocket when you put in a pacemaker, not necessarily a pediatric product. It could be but not necessarily. Those are regulated as devices because it is a pouch for the device itself and it does have a drug on it, which makes it a combination product in some cases. And, so we regulate it in conjunction with our sister center. But the resorbable material is a secondary function. It is performing the primary purpose of containing the pacemaker or the defibrillator. So, that is what we look at is what is the primary mode and then how does it achieve that mode? The resorbable nature doesn't necessarily mean that it will be a drug.

Dr. del Nido: But something like a stent, for example, a vascular stent, which would be probably the biggest application for kids.

Ms. Foreman: So the primary purpose is to keep the vessel open. So that is the primary mode of action. That is a device function, its patency.

Dr. del Nido: Okay. Thank you.

Participant: Hi, my name is Fadi. I am a biomedical engineer.

My question is regarding bench testing. With regards to making the regulatory process easier, is there any efforts considered in making bench test data public through Freedom of Information Act or something similar? So that if we are developing a new device and we mention that development is often incremental in reducing the cost of testing by having access to that data.

Ms. Foreman: So, certainly information is available from Freedom of Information. Get in line, wait a couple of years and you will get it. That doesn't help you today, though, if you are trying to figure out what to do.

So, we do recognize that transparency is important. So, we have taken several steps to try and improve our transparency processes.

So one is, if you look at our 510(k) summaries, for 510(k) devices, if it has a summary, we have been trying to make sure that the data included in that summary is sufficiently robust, that you can actually figure out what the agency looked at to make their determination.

For our de novo applications, we actually are publishing a de novo transparency memo associated with each granting of a de novo petition which is a device that has no predicate but we feel that it could be classified in Class 2 or Class 1. So, we put our memo on the website, so you can see what the Agency looked at and it contains a sufficient amount of information so that, hopefully you can understand kind of what the testing was and what the parameters and what the results were.

Another effort that we have is we have memos associated with PMA supplements. Right now, it is in two branches. We are piloting that trying to optimize that process, with the hopes of eventually making more PMA memos available, so that you can actually see the Agency documentation.

Then as I mentioned, we have our MDDT, our Medical Device Development Tool

process, where we are looking at blessing medical device development tools and that could include bench testing. And that would be a public process and it basically gives you a blessed test method or a blessed tool that you can use in the development of your medical device.

So, I would say that we are not there yet but we are working to try and improve our transparency.

Mr. Chen: Great, thank you. Thank you everyone in the audience for your participation. Thank you, Christy, for giving us a good insight on the engineering prospects that the CDRH for pediatric medical devices.

So, that will conclude the session today. And I think I am going to turn it over to Linda. I think she has some housekeeping for the luncheon and for the rest of the day.

Capt Ulrich: Yes, I just wanted to go over what our plan for the noontime hour is. We are going to break for about the next ten minutes. You all can go out and pick up your box lunches.

And when you all signed in today, you signed up on a specialty -- on the sign-in sheets for a specialty-specific lunch table. So, the tables are located at the sides of the room and there are also three other tables will be in break out rooms.

What you can do is go to the group that you signed up for and then for each table, there will be a moderator, which is generally a medical officer from the review divisions in CDRH. And we also have people who will be taking notes, our scribes.



And there were two questions in our Federal Register notice that we wanted to really try to focus the noontime discussion around. And just to review what those questions are, the first is for any given specialty area. What existing medical devices appear to have the best potential for modification for rare diseases that affect pediatric patients? And if possible, please prioritize existing medical devices in terms of the amount of changes they would need to have in order to be able to be used in kids. And if you could rank that according to like minimal change, moderate amount of change or significant change.

And then the second question to consider is what are the best ways to foster efficient networking across agencies, academia, professional societies, and patient groups, in order to address medical device needs for pediatric patients with rare diseases.

And each of your moderators should have those questions at the table as well, and we will probably raise those again at the beginning of the discussion, but I just wanted to put that out, that that is really what the input that we are seeking for the noontime discussion.

So, with that, we can break. And after our noontime discussions, we are a little off schedule, so let's plan on starting the afternoon up maybe at 12:45. Okay? Thanks.

(Whereupon, the above-entitled matter went off the record at 11:41 a.m. and resumed at 12:51 p.m.)



Afternoon Session

(12:51 p.m.)

Clinical Trials Issues Panel

Dr. Luke: It is really nice to see the turnout at this meeting. This is an area that is of profound interest to many of us here at FDA with regards to the development of medical products for our pediatric population. This is the youngest, the folks that are least able to care for themselves and having the availability of these products, specifically designed for them with them in mind is great.

I know there is a lot of hurdles and barriers to development. Some of them are real. Some of them are perceived. Some of them we can work together to reduce. And so this is great and this is part of what this meeting is about.

I hope you all had a good chance to chat with fellow colleagues in the area of interest to you with regards to product development. I sat through a few of those sessions and listened to what some of the issues were and it looked like those were very productive. And hopefully you have made some connections and saw who you might be able to reach out or chat with, people with similar interests to yours, where it is important that no one be an island here in that FDA is able to help you and you have colleagues and you have other folks in other agencies like NIH and CMS to help you.

So, with that, we are going to get into clinical trials. This specific panel is focused on clinical trial issues and we have three presenters. I am just going to start with, I think, John,

were you going to speak first?

So, our first presenter is John Laschinger. John, I knew him when he started here. He joined FDA in 2010. He had 20 years in cardiac surgery. He is our pediatric thoracic surgeon but he will, of course, will say oh, I also treated adults. But I like to think of him as our pediatric thoracic surgeon and whenever I have questions about that area, he is our go-to person.

He was in practice in Maryland at Hopkins and he has done a variety of things, including heart and lung transplants and aortic surgery.

So John, with that, please.

#### Trial Design Considerations

Dr. Laschinger: Hello. Okay, I am in charge with keeping everybody awake after lunch. So, I hope I am up to the task.

Basically today I am going to talk about clinical trial issues, specifically trial design considerations and mostly from a clinical perspective but also I will throw in the requisite regulatory considerations as well.

Really at the FDA we have a dual mandate. The first is, obviously, to protect the public health and that is to provide for safe and effective medical devices. But also to promote the public health and that is by facilitating device innovation. And what we are here to talk about today is really the field of device innovation, especially in areas where there is not a huge

market but there is a huge need.

The current state of medical therapy for pediatric/orphan diseases are shown here. And really few are supported by randomized clinical trials. Most of it is off-label use supported by expert opinions or single institution observational studies, extrapolations from adult cardiovascular medicine, or evolutionary historical literature-based comparisons.

However, especially in the last five to ten years, there is a desire for innovative, less-invasive treatments, which drives a need for more targeted therapies which require disease or lesion-specific devices and more rigorous comparisons for approval or clearance of those devices. And it is also the use of hybrid approaches, which are also driving some of that need.

From a device company perspective, randomized clinical trials are a barrier because of their very high cost. Other high costs that contribute to that prohibitive nature of pediatric device development are R and D cost, trial cost, FDA regulatory cost, getting it through the FDA, and of course there are marketing costs, all complicated by small end market and limited returns on their investment.

As you know, medical device approval is a risk-based paradigm. And for the most part, I am going to talk today about what we call significant risk devices, which are Class 3 devices. On the left, an example would be a stent is shown there, that has a large market. It goes through the Pre-Market Application process or PMA process and on the right, would be a Humanitarian Use Device, which is also a significant risk device but really affects less than 4,000

patients per year or a plausible subset of 4,000 patients per year. And it goes through the process called the Humanitarian Use Device Exemption.

The Humanitarian Use Device designation, I think that you have heard a lot about already so, I am not going to spend a lot time on this slide, to keep on schedule. But it is really 4,000 patients per year is the cutoff you have all heard about and that includes medically plausible subsets for either the population or a condition.

An HDE application really is an application very similar in form and content to a PMA application that is not required to contain clinical data demonstrating effectiveness. It is for significant risk devices. It requires an IDE for clinical study, designed to collect safety and effectiveness data. And it must contain information in the final application to allow FDA to conclude the device would not otherwise be available. There is no comparable device available for therapy, and also justifying why a PMA application is not feasible or why it is cost prohibitive.

Once an HDE is approved, it has to come in front of what is called the Pediatric Advisory Committee or PAC every 12 to 18 months but it can be sold in pediatrics to recoup all costs and profit is allowed for pediatric use. And the device has to be administered, as you have heard, at sites with a local IRB.

On a time line basis, actually the HDE and the PMA process are shown on this slide and the real differences are highlighted in red between an HDE and a PMA. Really the main difference is that for an HDE you need to go through the HUD submission and designation

process first to designate your devices as a Humanitarian Use Device. And then at the end, where it goes to market it has to be implanted in places with an IRB approval.

Otherwise, the processes are remarkably similar and really are divided into two phases, preclinical and clinical phases. The main difference is shown on the bottom. The approval thresholds are markedly different, which changes the level of data you need to get through the process substantially.

Pre-clinical phase is designed to show that the device is safe. And basically what we are looking at is a combination of bench tests, animal studies, biocompatibility, toxicity, and all those things shown in the white box on the right are present in a test device that goes through several iterations until a final test device is ready.

Then some clinical data is collected on a test device to make sure that it is safe, it is not going to be put in and immediately degrade or break or whatever. And then because of that preliminary data, that sufficient safety exists with the device to proceed with a clinical trial.

So, that is the preclinical phase.

Then once you get through that, what awaits you is the pivotal clinical trial, which is about the acquisition of valid scientific evidence. It really comes down to three phases: the design, the conduct, and the analysis of the trial. The more you come in and talk with us ahead of time in pre-IDE meetings, the easier that process is because it gets everybody onboard as far as what you as a sponsor want to do, are expected to do, and what we, as an agency expect to see to make the approval in the end, whatever process you take, go very smoothly.

So, it doesn't behoove anybody for you to go through a whole IDE study, get to the end, and the FDA say well we really want to see this. So up-front communication gives us the data that we believe we need and the interpretive results will allow adequate clinical assessment of the device to meet the thresholds for your particular application.

Again, the goals of the pivotal IDE trial for adequate clinical assessment for a PMA is reasonable assurance that the device is safe and effective and for a Humanitarian Use Device is reasonable assurance the device is safe and provides probable benefit to the patient, which is a different threshold than effectiveness.

Depending on the device and the need of the patient, there are characteristics of the device, the conditions of use, adequate other therapies available and they are not how big of a clinical need there is for the patients. It really depends on what kind of evidence you need.

And this on the right just shows the evidence hierarchy that is typically presented. We tend, with pediatric devices and HDE trials to work well down that pyramid, never expecting to see prospective randomized trials because the patient numbers are too small but usually trying to work with the sponsors and the statisticians to come up with a way for us to get meaningful clinical information that allows us to make the judgments we need to make in the least burdensome way possible, using various data that we can ask for them to acquire.

Safety is basically defined in the FDA regulations as probable benefits outweigh the probable risks. And you can see that the benefits are things that have to be clinically



meaningful and are really dependent on patient factors as well as available treatment options.

The risks we look at are harmful events, including their type, number and severity, their probability, their duration, and whether any mitigating factors are -- mitigations are available to decrease those risks. And really that is one of the key factors in evaluating all of these devices is this benefit-risk relationship.

Probable benefit is an explanation of why the probable benefit to health from the use of the device outweighs the risk of injury or illness. And it also takes into account the probable risk and benefits of currently available devices or alternative forms of treatment. And also, the explanation should include why this device should work.

So, it is basically a known or postulated mechanism of the disease and the action of the device should match up. So, the device that treats pulmonary stenosis should be something that matches up with the pathology you are trying to treat and have a mode of action that makes sense in context with that disease.

Overall, when you look at it, it kind of looks like this on a scale. Basically, you look at everything as a continuum. If you look at the outcomes of the current standard of care therapy in the middle, and that might be nothing, and the outcomes of that as denoted by the dotted lines, the boundaries of the outcomes of that, we look for the device. Obviously, if it is in the lower right quadrant, it is a great device and everybody is going to use it. But if it is in the top left quadrant, it is a terrible device. Nobody wants to use that. And then in the middle there are some gray areas, and basically that is where judgment comes in, depending on the

need and the patient illness.

And shown here are two different diseases, Disease A in the green splotches or whatever you want to call them on the slide, is a severe disease with no other treatment options. And for those, we would likely not accept the bright green one that adds only risk but not real benefit. But for the two lighter green splotches in the right, we would accept some increased risk versus current therapies, if the benefit was substantial enough. And the degree of risk we are willing to accept and are willing to look at carefully depends on the amount of benefit that is offered by the device.

For Disease B, shown in the blue splotches on the bottom, this is a severe disease with other proven therapies that are available. Certainly, we don't want a device that has less benefit as shown on the far left. But a disease that might not have any benefit but be much safer than the device that is already on the market or the treatment that is already on the market would be certainly something that would be looked at as favorable, as would be a device that has substantially more benefit and no additional risk.

So, really it is a risk-benefit threshold and a risk-benefit determination and we look at it with the factors of not only the device and the results from that device but what else is out there on the market and whether it is available to the patient.

So, I would like to thank you for your attention and hope I have kept you awake after lunch here. And obviously, if anybody has any questions, they can feel free to contact me anytime.

Thank you.

Dr. Luke: Thank you, John. And we will have a chance to discuss a little bit more about how best to do clinical trials, given all of what you had discussed and how to design.

And speaking about clinical trial design, we have Laura Thompson, who is a doctor in statistics. She has -- we have been working with her from the Office of Biometrics and Statistics here in CDRH for many years. She is the co-author of an upcoming draft guidance document on extrapolation of data for pediatric uses of medical devices that is coming out soon. So, stay tuned.

And I think Laura is going to talk a little bit about some of the statistical tools that we have with regards to clinical trial design for pediatric studies focusing on rare diseases.

Laura?

Extrapolation Issues: Bayesian Methods for Making Inferences about Rare Diseases in Pediatric Population

Dr. Thompson: Thank you. Okay, so I will be talking about Bayesian methods for making inferences about rare diseases in pediatric populations. And I am going to start with mentioning some special problems with studying rare diseases in pediatric populations, including small sample sizes and studying rare events.

Bayesian methods can be nicely used as solutions to these issues and I will discuss each of them in turn. For the small sample size issue in particular, I am going to spend a little bit of time talking about the forthcoming pediatric extrapolation draft guidance and then

bring up some other issues and then conclude.

So, the special problems I will be talking about are given on this slide. The first is one that we all know about, that the pediatric population available for clinical trials is limited, even when the condition or the disease is not rare. In addition, there might be issues with informed consent or finding an appropriate control. As a result, with smaller sample sizes, high variability can affect conclusions, making them more -- making them less reliable and studies lack power.

When conditions are rare, the small sample size problem is compounded because rare events may not even occur in a finite collected sample of pediatric patients. And estimating an event rate is difficult when you have no events.

So, in this talk, I will be explaining how one might use Bayesian methods to help with these issues.

So here is an overview of the Bayesian approach, for those of you who may not be so familiar with it. The Bayesian approach, it is a statistical approach. It essentially describes a method for learning from evidence as it accumulates. The method combines prior information with current study information on an endpoint of interest. For example, an adverse event rate from using a device, in order to form conclusions about the endpoint.

Prior information typically comes from results of previous studies and often there are previous studies done on a related device, a previous generation device, or sometimes the same device used on a different population, which we will later see with the

pediatric extrapolation.

The Bayesian approach can be helpful because often prior information can be used to estimate rare event rates and gain power for small populations. And I will expand on each of these later.

In short, it is way to combine the past, the prior, with the present, the current study to make decisions about the future, which we call posterior conclusions.

I would like to bring your attention to a guidance document released in final form in February 2010 entitled "Guidance for the Use of Bayesian Statistics in Medical Device Trials." It is available on the website.

So first, I would like to talk about the first special problem that rare conditions or events may not occur in a finite collected sample of patients. And this is often referred to as the zero numerator problem. This example comes from a paper in the Journal of Data Science in 2008. These authors describe the following, hypothetical, but not uncommon situation.

A standard test or device has been shown to cause a serious reaction in about 15 of every 10,000 patients exposed to it. A new improved test or device was used on 167 patients and none of them reported having the reaction.

What can we say about the probability of a serious reaction for the new test or device? Is it really zero percent or, more likely, do they just not have enough subjects to get any with a serious reaction?

A typical ad hoc solution to the zero numerator problem is to estimate an upper bound of a 95 percent confidence interval on the true rate. And this is called the Rule of Three. It is a conservative approximation and it is computed as  $3/n$  the number of subjects.

In this case, it would be  $3/167$  or 180 out of 10,000 subjects. Of course that is incredibly high. Of course we know that the rate is probably lower than that. So, it is not very useful in this case.

The approximation holds better with a larger sample size. But of course that is our problem in the first place with rare events. And in addition, it doesn't provide a point estimate of the occurrence rate.

Bayesian methods can obtain this, even with small sample sizes, as well as uncertainty intervals with direct probability interpretations.

And before I get to how that is done, I want to mention that the zero numerator problem has occurred in submissions and this is just one in particular. This is the Essure System for Permanent Birth Control. And the SSED is given in the following URL. This was a micro-insert that occludes the fallopian tubes, hence, achieving permanent birth control.

Out of 632 subjects, zero pregnancies were observed at 12 months. However, because no birth control is 100 percent effective, except abstinence, an estimate of a zero percent fertility rate at 12 months appears somewhat inaccurate.

We will see that Bayesian statistics can help, so that the estimate is not zero percent when that is unrealistic. And we can do that by incorporating prior information and

then combining it with the study result and getting a posterior estimate.

So, in this situation, a prior distribution is placed on  $p$ , the probability of experiencing the event. Some examples for a rare event rate might be setting a prior distribution so that the prior mean is equal to the standard rate. And if we use the Chen and McGee example from a few slides ago, the standard rate was 15 out of 10,000. And you can also set the prior distribution so that there is a high chance that the rate is less than a particular value. In this case, they chose 75 out of 10,000. If you didn't have prior information, you might choose a vague uniform prior distribution, which gives equal probability that  $p$  falls anywhere between zero and one and note that with this prior distribution the prior mean is 0.5, considerably higher than the previous prior mean.

A common method used in the Center for Devices is to use a hierarchical model, which combines several study results in order to construct a prior. And I will have more to say about that in later slides.

So, if we use a prior distribution on the true event rate, we can get a posterior or final estimate when we combine it with the observed data. And this posterior mean rate is not zero percent but something more realistic and satisfying.

So for the Chen and McGee example, using the prior mean that was set to 15 out of 10,000 and then combining it with zero out of 167, the posterior mean is 2.2 events out of 10,000, which is much less than the standard rate. And you can get posterior probability statements as well. There is also a 96 percent posterior probability that the rate is lower than

the standard rate. So, that looks very good for the new test.

With the uniform prior, the posterior mean is 16 out of 10,000 and there is a 39 percent posterior probability that the rate is lower than the standard rate of 15 out of 10,000.

So, these were sort of simple examples but it is a nice way to show that if you have reasonable prior information, then you can actually study rare events without having thousands and thousands of subjects.

The second problem I want to spend more time discussing is that the pediatric population available for clinical trials is limited and we end up with small sample sizes. Again, Bayesian methods can be used to gain power by combining prior studies with a current study. And we can refer to this as borrowing strength or statistical information from prior studies. And we will see that by borrowing from appropriate prior information the same decision might be reached with a smaller sample size.

The extent of borrowing from prior information depends on the similarity of the previous or prior studies with a current study. To the extent that prior study results are different from the current study result, then borrowing strength weakens and can go to zero.

Bayesian hierarchical models are a common and useful way to borrow strength across studies. The models allow a sample size boost by borrowing strength from prior studies that are similar to occurrence study on an endpoint of interest.

And the reason why we effectively get a sample size boost is because we borrow some of the total information provided by the subjects in the prior studies.



We don't know how much we will borrow until the current data become available, however. So, it is important that when we are choosing prior studies, we do so carefully so that they can be considered exchangeable with the current study. And I will have more to say about exchangeability in the next slide. The model lets the current and the prior studies determine how much to borrow.

So, as I mentioned before, in order to use prior studies with the current study within a Bayesian hierarchical model, the studies must be assumed to be exchangeable.

Exchangeability of studies in practice means that the study results are comparable. Technically, it means that knowing your result from one of the studies would not divulge which study it came from. So, if you saw one of the results and you saw that it was particularly high, you couldn't say oh, yes, I know that is the one done outside of the United States or whatever.

Ideally, it is decided upon before seeing any study results, even the prior study results. Of course, in practice, that really doesn't happen many times because we often already have the prior study results.

To decide whether exchangeability of prior and current studies can be assumed, we need clinical input and we need to think about some of the factors that are similar across studies. For example, the device used should be the same or similar, similar protocols, patient population, inclusion/exclusion criteria, et cetera.

A nice application of the use of hierarchical models is in the pediatric

extrapolation effort described in the forthcoming draft guidance document, "Extrapolation of Data for Pediatric Uses of Medical Devices." And it explains the Center's implementation of the Pediatric Medical Device Safety and Improvement Act of 2007. The intent is to introduce a framework for decisions about whether borrowing or extrapolating from adult data is appropriate. And the draft guidance explains in detail some factors to consider when deciding whether extrapolation is appropriate and to what extent it can be done.

I list here general factors that are described in detail in the guidance. The considerations for extrapolation, the first is the similarity of adult population/response data with future pediatric response data. For example, will there be differences in device characteristics, disease, process or patient characteristics that will likely make responses to treatment with the device different for the pediatric population than adults?

And second has to do with the quality of the adult data. And this has to do mostly with study design issues and sample collection issues. So, how are the data collected? How are the subjects assigned to treatments? And both of these factors will be considered together to make decisions about the extent of extrapolation. The higher the similarity and quality, the more likely extrapolation will be appropriate for regulatory submissions.

So, in order to use adult and pediatric studies within a hierarchical model, they need to be exchangeable. But of course, there are many reasons why we might predict very different results for adults than for pediatrics. There are obvious differences in physiology such that the measured outcome from the device would be expected to be not the same. There may also be study conduct differences in terms of enrollment, informed consent, or treatment or

handling of the trial, which might be expected to make outcomes differ.

So with these dissimilarities, how can we still borrow from adult studies?

One thing we can do is manipulate the structure of a hierarchical model so that we are not assuming exchangeability between studies but assuming exchangeability of studies within patient populations.

So, and in doing so, what happens is that the borrowing is tempered to some extent. We are not borrowing in the same way we would across studies. So, in this figure we have two patient populations, adults and pediatrics. So we have two studies done on adults and those are considered exchangeable. Study 3 and then a future study, which may be used to predict a future pediatric patient's outcome in a future study, those are considered exchangeable.

And so we have this three-level model and exchangeability is then sort of brought up to this top level, instead of this bottom level. So, we temper the borrowing somewhat.

Then to deal with -- to incorporate physiological differences between adults and pediatrics, we can explicitly measure the variables in question and then just put them in the hierarchical model. So, we need to know how the growth or the size of the patient might influence effectiveness of the devices versus how it would influence the effectiveness of the device on adults. And if we have that relationship, then we put it into the model. And so that is all this slide is really saying.

So, I do want to talk about a simplistic example of how this might be done, where we have just one covariate and we have single arm studies. So, this is a hypothetical example, SlimFix Device for weight loss. And say the goal is to determine how effective this device is in adolescents. Unfortunately, we only have 20 subjects and we can only collect 20 subjects in the adolescent population but we have two adult studies and we want to borrow information from them.

The primary effectiveness endpoint is average excess weight loss in percentage and we can see that the adolescent study, the mean percentage is much lower than the other two adult studies. Well, we can see from the next slide that the difference is due to a baseline covariate that has to do with the size of the patient. And here when I say baseline size, it is a made up variable, the higher the baseline size, the bigger the baseline size. But it could be something like BMI, baseline weight, whatever.

So we see that size appears to be related to percent excess weight loss and you have different colors for the studies. Adolescents tend to have a smaller size than adults but it also looks like the relationship, even though it's positive and increasing, it may be a little bit smaller for the adolescents than in the adults.

So, we have put this information in a hierarchical model and we can still use the hierarchical machinery. The details of which I omit for this talk but you can ask me about later.

So, what I want to do is compare what happens when we look at the adolescent study by itself and then what happens when we borrow. What are the gains? Really what we

are looking for is a more reliable estimate.

So, when we have covariates like baseline size, we need to report posterior mean estimates at given baseline sizes. And here I chose a baseline size of 0.85 and one that is 0.6. And so, the 0.85 you have a lot of adult data and 0.6 you don't have that many. So, we get the following estimates and note the posterior standard deviations.

Well, look what happens when we borrow from the adult studies. Well, for baseline size of 0.85, the estimate moves up a little bit in the direction of the adult means and that is a feature of the hierarchical model that mean estimates will tend to shrink together. But the estimate is much more reliable. The standard deviation went from 5.1 to 3 percent. A similar thing happens with the 0.6. The estimate doesn't change much but we gain a lot in terms of reliability. So, we have a better chance to get a significant result.

If we wanted to have a numerical measure of how much we borrow from prior studies -- Markham Luke is chomping at the bit. He wants me to finish but just a couple more minutes, please.

We can use a measure called the effective sample size. And remember that when samples size goes up, variability goes down. So, when we are getting a more precise estimate, we can talk about that in terms of how many samples we are gaining.

So, if we compute that for each of the two different baseline sizes, we see that we borrow 38 subjects' worth of information from the adult studies when the baseline size is pointing at five. So, about ten percent of the information. And when the baseline size is 0.6,

we borrow about five percent of the information. So, we are still getting some information, even though we are talking about a variable that we expect to have a -- or a device we expect to have a different result in pediatrics and adults, we are still borrowing information.

The last couple things I want to mention is the adaptive/flexible designs which are discussed heavily in the -- maybe not so heavily, but they are discussed in the pivotal trial guidance, they can be used to make gains in pediatric studies. And the Bayesian predictive probability can take advantage of adapting the sample size. The Bayesian predictor distribution describes what unobserved outcomes for future patients will be mid-course in a trial, given observed patients' data. And so you can use predictive probability to predict the trial success before all patients finish the trial.

For example, Bayesian predictive probability might be used to predict a clinical outcome from a valid surrogate. It might be used to stop a trial early for success or futility. It might be used to stop accrual of patients into the trial and then follow those patients to the end of the trial.

So, the key point is, they often lead to shorter trials or smaller trials.

So in summary, Bayesian methods can handle difficulties with studying rare conditions in pediatric populations. They provide more realistic estimates of rare event rates. We can borrow strength from adult data to make decisions about device performance in pediatrics and adaptive designs and predictive probability may shorten lengthy trials.

Dr. Luke: Thank you, Laura. You can see Laura is very excited about the

statistical tools that we have that enable us to take a look at rare diseases. So, thank you, Laura.

(Applause.)

Dr. Luke: I just want to say that unfortunately in the rare disease environment, many of the pediatric patients with rare diseases don't make it into adulthood and that is very unfortunate. So, this is something that we are very interested in making sure that we have products to help them at least get there.

So, some of that what you have talked about may not be applicable to some diseases but clearly it is applicable to some pediatric-specific devices that are important for development.

Our next speaker comes from the NIH. I see my contingent of rare disease patients, patients with rare diseases at NIH. NIH is the Mecca for bringing patients with rare diseases to a central location for clinicians to look at and study to look at how they progress and look longitudinally at their outcomes. And in the dermatology clinic there, we see rare diseases from every spectrum because almost all the genodermatosis are associated with some sort of rare disease or rare disease syndrome. So, it is a great thing.

And with that, Steve Groft is the Director of the Office of Rare Disease Research over at NIH and he is going to come and talk to us a little bit about what they do at NIH and how the NIH can help with clinical studies.

Patient Registries as a Prelude to Clinical Trials and Post-Approval Studies

Dr. Groft: Thank you very much and it is always a pleasure to come back to FDA after working here for a number of years back in the middle '70s. So, it has been a number of years but it is always a pleasure. I will try to get this all to work. Okay, this actually came up pretty good.

What we are going to talk about today really will be patient registries, a natural history study leading into the natural history studies and the whole process of trying to provide a good pathway for better recruitment of patients to get into clinical studies and to move the research forward.

And I think it really does, the patient registries probably reflect as much as anything else the evolving role of the patients, the patient advocacy groups as research partners. And over the years, we have seen this tremendous evolution and welcoming effect of an increased role of the patient groups. And so if any of you are dealing with rare diseases and you are not working with patient advocacy groups, my real recommendation would be find out who it is, the leaders of the patient advocacy group and have conversations with them immediately because they will, and to a large extent, determine the success or failure of your studies. They have access to the patients and they become your greatest advocate, not only to the patients but to the public, to members of Congress, to regulatory agencies. And so please, I just put a pitch in for you to gain access to them and they are such willing partners. They want to participate in research. They want to participate in development, as you heard this morning from one of the parents how important it is. So, we look forward to that.

I am going to start, we don't have a pointer but let's see if the mouse works.



Okay, great. And actually I probably could go through about two slides and then the presentation is over. I will be on a short leash here as far as the time frame.

We are going to talk a little bit about the patient registry, how it evolves and include obtaining information from biospecimen repositories. And you will find in here different activities such as a contact registry that we use within our rare disease clinical research network and you may have heard about the CTSA program from NCATs that has research matches that try to link up patients with clinical studies. So, there are things to be aware of and to utilize.

And so we are going to go around the circle a little bit, including access to biospecimen repositories and biospecimens in studies. And many of these evolve into natural history studies. Because of the nature of so many of the rare disorders, we don't have a good understanding of the disease and we are really trying to expand the knowledge base of the individual diseases.

And we think that by following patients over a number of years, even if there are no interventions available, no clinical trials ongoing, we think it is important to begin to understand the disease, perhaps identify clinical endpoints and maybe even do some biomarker studies leading up to clinical trials. We also have found that patient registries and natural history studies are good indicators of off-label uses. I think I can say that here at FDA. Can we do that? Is it okay? Okay, we won't talk about any specific ones. But yes, it is a very, very useful process of really trying to identify what the patient is doing and how they are reacting to their disease.

We also think that the natural history studies and the registries help develop both basic and clinical research hypotheses to move research forward. And if everything works well and we begin to identify potential compounds, we move into the clinical trials. And here, I think, is where the registry really comes into be a great deal of helping to recruit the patients.

And we move through the process and I think as a result of the FDASIA amendments and other activities, we have a greater role now. Both the patients and the researchers here at FDA that the possibility of meetings is very, very important as we move through the process of the different phases of research.

And of course, if everything goes well and the approval is obtained, we move into Phase 4 where we have to follow the patients. And I think it is sort of interesting that many of you as device manufacturers probably do a lot of this already. And so I think it would be good for us to hear from you as well what your experience have been with these post-marketing approval and monitoring of devices after implanting, sort of to gather your experience and knowledge about how they all work and how the collection of data actually works.

And so this Phase 4, actually brings us right back to the patient registry. So you see a little bit of a circle. You start here and we sort of end up back here. And all working with the patient. So, we think it is a good model to sort of look at to begin early on working with the patient groups to develop the registry.

So, the value of registries and some of the things I have already talked about is

improving the recruitment of patients, identifying of possible patient cohorts for different studies. And while this may be more indicative for the therapeutics, the drugs and biologics, it is still very important, I think, when it comes to all interventions.

We think the registries are very, very helpful in integrating patient-reported data and clinical data from different sources into a single repository, along with biospecimen repository information, biospecimen information into a repository. And we really feel that the registries can be used to stimulate new research into different interventions that we are talking about.

And we think, as we go along, if we are able to successfully implement these registries that we will enhance the data mining within the disorders, whether they are related or not and we find that there are many, many groups involved now with developing patient registries. And two organizations, particularly patient organizations, the National Organization for Rare Disorders, Diane Dorman will be speaking later from that organization, and Genetic Alliance, are two groups that have had active roles now in developing patient registries and, along with a number of other vendors and different healthcare systems here in the United States and throughout the world that are looking for the globalization of rare diseases research and gaining access to patients and patient information because we do find, of course, like so many other things, that rare diseases don't respect the borders.

But there are a number of considerations that you run into and that you really have to think about before you begin that registry. There is a lot of interest in develop registries, as I mentioned, and I think really trying to establish the purpose of the registry, who

is going to control the data, who is going to control the access to identify and de-identify data, all major issues. Who will be the curator? What will their role be? What type of informed consent do you need? Is it restricted or broad access to data? And I think it is something we have to be careful about and to realize that the data might be deposited into a de-identified database or repository. So you really do want to think when you construct the informed consent that this is not just for this study or this registry, that de-identified data, and I think we have to let the patients know in all likelihood this data will be used in other purposes as de-identified data to move forward.

Where we have run into particular some difficulties is meeting not the IRB requirements but the FISMA, the Federal Information Security Management Act. As a government agency involved with developing registries, you have to go through certain other requirements and this takes a considerable amount of work to really document what you are doing and how you are collecting data, how you are protecting the privacy of the individual and it does take a considerable amount of work.

So, if you are going to be dealing with people and organizations and vendors, you want to ask do they have a FISMA compliant system. Very, very important as you go along.

As you can see, there are different sources of data from the patient, the family, the caregiver-entered data, the healthcare provider could enter the data in the electronic health record. So, you are going to get different sources of data coming in from different people. And so we rely upon a lot of different things, including the common data elements, unique data elements which are disease specific questions, look at data mapping strategies,

develop data sharing policies for the collaborators who participate, consider options for data updates, how frequently will the information be updated, who will be responsible for this, especially in pediatrics where you have to have the caregivers, the parents, other family members providing that information. So, you go through a lot of different processes.

Okay, I've got three minutes.

Okay, we in the Office of Rare Diseases recently have come up with a list of about 70 different common data elements that are available and I will have a slide coming up in just a minute or two from the NIH of a different website that you can go and find these data elements to help guide you. Many of these are disease specific or organ specific. So, it is sort of important to look at these.

But you can see we are trying to bring a standardization into this whole picture of patient-entered data and to a large extent, the success of the registry will be developing the questions and the data elements that will be useful and really help to provide cohesive approach to the entry of data and then to the analysis of data.

So, you can see there are some of the data elements, the common ones, that are available and perhaps should be used for most rare diseases, just as a starter. And then you get into some of the very unique data elements or disease-specific questions.

Here is the portal and this is not live but it does give you the portal to the NIH common data element initiatives that are in existence. And if you have an interest in different patient registries or information, there is a great deal of information here on different registries

and information on specific diseases, questions, and data elements that you might want to consider, if you are constructing your own registry in the future. So, it is something to look at.

And even for clinical trials, I think, helping to identify various questions that you might want to consider integrating into your trials.

So, future needs, I what we are looking at is developing, sharing, and agreeing to use common data elements and unique data elements by the various partners who are involved here in the rare diseases community. So, it is important to gain that acceptance that we are going to be sharing, we are going to be contributing data elements. If we construct a new set of data elements that are useful, we would like to have those deposited into the library, so to speak, at NIH and to work with the various institutes in developing them and sharing them into the portal that I mentioned for the data elements.

I think one of the things that we really do need is to have a regular forum for the registry developers to share their experiences and how they are going about developing their registry. It seems like many times they are using a different platform and we really do need to have that consistency a little bit better identified and adhered to. So, it is very, very important.

And I think the key to all of this is really developing the partnerships and the collaborations with the patient organizations, the academic researchers, the biopharmaceutical medical devices industry. It is key to everything we have been doing with orphan drugs and rare diseases since the 1980s and I think it still holds true today that success is gained when you do establish these partnerships and these collaborations.

And I will just mention two organizations going global, the approaches, there are many, many partners now throughout the world. We started a couple of the organizations, more recently the IRDiRC group, International Rare Diseases Research Consortium in about 2011 and we now have members from European Union countries, the United States, Canada, Japan, Korea, China, Latin American countries. So, it is a growing group and if you have an interest and you want to sort of see what is going on on a global basis with rare diseases, please take a look at both IRDiRC and ICORD resources to join what is going on.

So, I will end it with that and be available for questions later on. And really, as you go on if you are thinking about developing a registry and you have any questions, please contact the office and we can discuss with you in greater detail what you would like to do, who the potential vendors might be to help you if you don't have a vendor in mind, and just some of the procedures that you should go through. So, we are available to provide that assistance.

I will jump out of here and keep things moving. Thank you very much.

Moderated Discussion

Dr. Luke: Thank you, Steve. Thank you so much.

So I think we heard this morning that not every medical device needs a clinical study but many devices for rare diseases, given the complexities of rare diseases and the types of devices we are talking about do require clinical studies.

And what we heard from today were our three panelists who have given a lot of thought to clinical studies, how they are designed, and what possible tools might help.

I mean we heard from John about how FDA is working to help with regulatory incentives to help move clinical studies along and product development. We heard from Laura, who talked about statistical tools that could help work with data that you have and small studies to put forward a reasonable package to help us look at some assurance of safety effectiveness. And we heard from Steve about registries, which is a great tool. I would say NIH is a great tool not just for patients but also for academic expertise from the researchers themselves. If you have an area of product development that you are working on and you need some clinical help, the NIH does have federally employed physicians who would be very interested, probably in seeing what you have and discussing with you, frankly, about the possible -- about the prospects for that device.

So, let's take questions from the audience. And if you can line up at the microphones and use the microphones, that would be great.

If you can address --

Capt Ulrich: Yes, Markham, if you could just go over the questions in the *Federal Register* just to sort remind people of that as well.

Dr. Luke: Should we start there first?

Capt Ulrich: Yes, thanks.



Dr. Luke: Yes, the questions were ordered in the -- I was looking at the questions and they were ordered in basically what was presented at the thing. The first question was the most challenging barriers in the process of designing protocols for devices used to treat and diagnose rare diseases. I think John covered some of that. We only have a little bit of time.

The other thing is the unique challenges for identifying appropriate endpoints. I think that is very much the case with individual endpoints for specific areas. If any of you want to chime in on the endpoints, John maybe, from the clinical perspective, how to identify endpoints, you touched on that briefly in your talk, I think.

Dr. Laschinger: Yes, I think the endpoints are best decided, obviously before you start, and it is best decided in what we call pre-IDE meetings with the FDA. Because I think it gets everybody onboard as far as what your goals are, what you are trying to look at, and then we try to determine what are the most appropriate endpoints that are needed to get the information that we need and that you want to generate, so that we are not all working across purposes.

So, I think the key to the endpoints is not exactly what they are but how they are derived and there should be a collaborative process between the FDA and the sponsors or the sponsor investigator so that everything is done most efficiently and with the least amount of burden.

Dr. Luke: Right. And it is disease-specific. I mean I think maybe Steve you want to touch on a little bit about the registries and the long-term prospects of the total disease

lifespan and how do you derive endpoints from that.

Dr. Groft: That is very important because, as you know, there is variability in the rare diseases, whether it is a genotypic relationship or changes in different patients. But I think what we are thinking of with the registries and natural history says that if we are able to follow the patients over an extended period of time, that we really begin to understand the disease better, see what changes over a period of time and what is the appropriate clinical endpoint.

What we think an endpoint might be at one point in their lives may not be the most appropriate, as the events evolve and life changes. And so I think we are trying to gather enough information that we really can make better informed decisions about appropriate endpoints and about the disease, caregiver information. There are many other aspects, I think, in working with the registries and determining the prevalence of the disease, identifying patients.

So, it is quite necessary and quite important as we go along.

Dr. Luke: Right. And as we come to understanding of a disease, I think we can talk about performance outcome goals and things like that for clinical study design based on the longitude information that we derive from patient registries, potentially.

And we can factor that into statistical design, which brings us to the third question in the *Federal Register* notice about what barriers related to statistical analyses must be addressed in order to promote device development for rare pediatric diseases.

Laura, do you want to answer that one briefly?

Dr. Thompson: Yes, well I did mention some of the barriers. I mean the small sample size is the one in particular. Did you want me to go further or have them --

Dr. Luke: I did want to hear from the audience. I think we have ten minutes now.

Dr. Thompson: Okay.

Dr. Luke: And then the last question from the notice, how can new registries be developed or current registries to be leveraged. I think you have addressed that question already, Steve.

So, let's take questions.

Dr. Rodriguez: Yes, hi. Bill Rodriguez from the Office of Pediatric Therapeutics.

Dr. Thompson, I really enjoyed your presentation, amongst others. And one of the questions that comes to mind is the fact that we did have a working group on extrapolation, which we had representatives from all over the CDER and looking at hundreds of studies that were done, looking at the various ages.

And one point that we came upon was, number one, yes, we love to extrapolate but one area where there could be a problem could be in the area of safety. And essentially, even though the extrapolation may look good, when you actually went into the data we figured that that would be one area that had to be documented in the pediatric population. I didn't

hear anything about the safety but in the guidances for the CDER, we do not extrapolate safety in that age group, okay, in the pediatric age group.

So essentially, we are happy to have the fact that the effectiveness of the disease or the drug can be extrapolated, fine. But we still look and see whether there is safety evaluated in the process.

So anyway, I just wanted to share that, that that is part of what the drug area is very much connected with.

Dr. Thompson: Right. And our draft guidance follows sort of that same logic, although we don't -- we do say that we will consider extrapolation of safety on a case by case basis. But certainly, there may be many cases where we would have to get as much data on pediatrics and safety as possible.

So yes, I think we are on the same page.

Dr. Luke: I think there are certain aspects, clinical aspects of devices that you can extrapolate safety for, such as biocompatibility, things like that. Certain implanted devices we can look at certain aspects of safety and have some shortcuts there.

Dr. Rodriguez: And it may be associated with the age of the patient you are extrapolating to.

Dr. Thompson: That's right.

Dr. Rodriguez: That is a very important point, too.

Dr. Thompson: That's right. And with the extrapolation guidance, it is not just from adults to pediatrics, but also within pediatric age groups as well. And of course, as the age gets closer to the group you want to borrow information from, then it would be assumed to be easier.

Dr. Luke: So it sounds like we need to stay tuned for that guidance document. When it comes out, we expect comments from each and every one of you in the audience.

Dr. Thompson: Luckily, we all got an email today that we are setting up another meeting. So, that is good.

Dr. Luke: Thank you. Who is next?

Dr. Tarachandani: So, my name is Anil Tarachandani. I am from Usin'Life and we do a lot of data mining.

Dr. Luke: Where are you from? I'm sorry.

Dr. Tarachandani: From Usin'Life. It is a startup.

So a question about registries. Is there a common list that is archived for the registry that follow the CDE standards?

And a related question, and the access to these registries is always a problem within the diverse areas. There is diverse registries. Is there some way to make sense out of all these different registries and also have access to them, good access and look at some of the data?

Dr. Groft: Yes, I think that is part of the purpose of the portal that I put the slide up on, that the information trying to get the commonality of language, mapping that information. And that is very, very important to SNOMED or LOINC or different acknowledged databases of information and methods of mapping data. It is very, very important as you go along. Because we can get lost in the specificity and differences that people would like to have the different terms for the same disease or the same symptom. And so I think that is one of the reasons why we are trying to get the standardization and trying to get people to look at what has been created and say okay, how can we change.

But yet, in your data construction and your mapping, you can put in five, six terms for essentially the same term and it will come out however you would like them to have it digested and be brought out to you. So, there are ways of doing that.

Dr. Tarachandani: What about data access?

Dr. Groft: Pardon me?

Dr. Tarachandani: What about data access? I mean just accessing some of that data. I am sure there are security issues and patient issues.

Dr. Groft: Yes. Again, in gaining access to the data, it really is -- we have looked at it as the responsibility of the curator to work with the requestor to determine what access they are going to go. We advocate for total free access to the de-identified data so the investigators can go in and mine it. But if they went to recruit for a clinical study, we do ask them to work closely with the developer of the registry to gain access to the patients and yet

protect their privacy as much as possible.

Dr. Luke: Steve, does your office act as an intermediary for say a company that wants access to a registry to help them contact the curator?

Dr. Groft: We are not that far yet. But generally, for each registry there is a contact person and we would require that as well. I think for most registries you can find the curator. If you have any difficulties, you could call us or if NORD is doing it with Genetic Alliance, they are also very helpful. So, we are going to help you however -- whatever is necessary.

Dr. Snyder: Brian Snyder, Boston Children's. A comment and then a question.

One of the dangers with registries where data's being collected for data sake without a specific research question being asked is the tendency for people to take associations of data elements and imply causality, when the original design of the registry was not to look at that research question. And sometimes people then jump to conclusions and you see that with data mining.

My question is, in certain rare diseases where it is very hard to come up with a control group, from a statistical point of view, when is it permissible to use data registry data as your control set, so if you are doing a case control study you cite that historical control data as your other comparison, assuming that the same outcome in your dependent and independent variables line up.

Dr. Thompson: With historical controls, really what you would like to do is

emulate what a randomized concurrent control would be. And so to do that, you have to construct a control group from the historical control population, as though it had an equal chance of being in the control group as in the treatment group.

And there are statistical methods to emulate that as best as you can. But aside from that, some other things that are important when you consider an historical control are the timing, like when historical control information was collected.

Sometimes there is information about how it was collected that could introduce biases, what types of baseline covariates are measured. And those can be used within the statistical modeling to emulate your randomized control group.

It seems like an easy way to get a control group by just using historical data and it is, but what makes it easy is that you don't have to actually collect the data yourself and run it or run the trial. But that is the only thing that is easy about it.

It has to be a good match. And so if everything you do doesn't end up being a good match, then it doesn't become easy for you because then things don't become believable.

Dr. Snyder: The problem is, a lot of the registries you can't dissect out those specific issues. So you have data elements that you can't in fact look at that.

Dr. Thompson: That's right.

Dr. Snyder: But yet it is very difficult to then do a non-treatment group or to compare to another treatment. Patients will not consent to randomization, especially where



you have small numbers to begin with.

Dr. Thompson: Right. If it is a case where getting a randomized concurrent control would be virtually impossible, then historical control or performance goal, or objective performance criterion, those would be options. And I believe FDA usually tries to entertain those other options when it really is an impossibility or really is a great problem to get a randomized --

Dr. Snyder: And then the registries start becoming an option.

Dr. Luke: Well I think you can see there is a synergy here between the registries.

Dr. Snyder: Right. I mean that is why we would want to use these.

Dr. Thompson: That's right.

Dr. Snyder: So what we tend to do is go to the registries. The problem is the data. When you go to the data registries, the information is not always consistent, especially if it is entered from multiple sites.

Dr. Luke: Right, that's true. I think what is important is that that feedback needs back into the registries. That yes, if there is an endpoint that is missing or there is a data point that has failed to being tracked in the registry, then the curator should not want to know -- would want to know that to be the case.

Of course, we need to be careful that these endpoints are not minuscule things that -- I know some of them are important for daily lives of patients but then again, some of

them may not be. And so in the context of how does this benefit a patient, it is there a meaningful benefit to the use of that device, as Dr. Laschinger pointed out, to use the device in the life of the patient? Does it prolong the life of the patient? Does it improve the quality of the life of the patient? Those are the important pieces that will need to be tracked and considered as we look at the registry, as we look at the clinical study data.

Dr. Laschinger: Yes, and when people do come to us and use registries as the control group and what we recommended in the past is that if there is a good chance the propensity score analysis might not work out for some reason that they also have an alternative performance goal they can fall back on if that analysis doesn't work. And that process gives you at least a fallback position.

And sometimes we just have to use judgment. If there is a disease where there is no other treatment option and there appears to be a probable benefit and reasonable assurance of safety, then sometimes we just have to use clinical judgment based on the totality of the data.

Dr. Luke: I think we might have heard this morning that our Agency or Center is interested in developing medical device development tools. And along those lines, those could include patient-reported outcomes. Those could include a variety of tracked outcomes that hopefully the registries will have enough of that data to address those pieces as well, if we are talking about historical data comparisons.

Dr. Groft: If I could also respond. You know you really do bring up the

significance of working together in a partnership with a patient group with the curator, whoever is developing the registry, with the experts, with the research community so that you do have the appropriate questions and you don't subject a patient to questionnaire fatigue. How many questions are patients and families able to complete? Is it 200, 150 or what have you. So, there are some limitations I think you have to look at.

So, all these things that go into the planning and pretesting are very, very important but really the key is developing good questions that will give the information that can be useful to the investigators and to the community.

Because the patients when they do enter the data and the families, they want to see the summation of that data coming back out as well. So, it is not just a one-way street. We like to project that information coming back to the patients and families so they can make that comparison themselves of what their disease is looking like to them as a patient or as a family.

Dr. Luke: We have almost no time but Mike 1 says he has a related comment and we will get to comment and Mike 2.

Participant: Yes, and my comment was on registries and my concern is that we are overselling it a little bit. Because to the extent to which the registry does not include information on the end points of interest and have not been collected using the instruments that would collect those endpoints, as was pointed out by the previous comment, would be relatively useless as a comparator group.

And so that is where registry studies then trend over into natural history studies

where you have a prospective collection or at least even a retrospective collection of data done on those endpoints whether it is patient-reported outcomes or others. And so I, personally, think registry data is important but they don't include the endpoints that are generally of interest for regulatory approval and that is part of the difficulty.

Dr. Groft: Well, I think what you are trying to do is identify those endpoints. I mean, we don't have that information for most of the rare disorders now and I think that is the basis of the registry and we are moving into trying to gather information that will lead us into natural history so that we can identify those endpoints. And that information doesn't exist right now.

Participant: But it only becomes that control group once you have done that. I'm not arguing that that is not important in the process but you need the endpoints in there to make it useful.

Dr. Groft: Yes, I know, but for how many diseases? We have, what, 250 diseases that have treatments available? And so we have to start somewhere to gather this information so that will lead us into this. And it is an evolutionary process.

Dr. Luke: Like I said, there is room for --

Participant: There is a lot of discussion of this over the last two days as well and there are ways to do it.

Dr. Luke: There is room for synergy there. I think there is room for NIH curators to look at our guidance on patient-reported outcomes to then design into context their

registries and their long-term data, patient tracking, having patients volunteer to do diaries, to say, this is how I feel about this specific aspect of my condition.

It is more difficult than the pediatric community, just to let you know, the pediatric patients with self-reported outcomes, you get into the issue of accuracy and understanding, especially with younger patients. And so, care provider, other possible approaches to pediatric reporting and I think there will be a guidance addressing those tools as well coming out soon.

Ms. Hogan: I have a separate comment. But I think to his point, maybe, and I might be overstating it, that it is a whole lot easier to use natural history data as a control instead of registry data, obviously.

My name is Melissa Hogan and I have a six-year-old son with Hunter Syndrome. And three years ago, he entered a Phase 1-2 clinical drug and device trial and experienced multiple device failures. So, this is particularly interesting to me.

But I just wanted to say that I think a lot of times there is theoretical information. There is controlled information de-identified. But when it really comes down to it, these are complex diseases that affect neurological function and muscular function and these kids are not theoretical or controlled or don't follow averages that might be in a registry. And in pediatrics, I think we are dealing with a lot of times first in human or first in pediatric device trials. So, it can be described on paper in terms of behavior or lifestyle, or cognitive effect. But I think we can't consider it in a vacuum of a registry of other information,

specifically in a context of a particular either type of device or actual particular device.

So, I will ask the panel and I would pose this, I guess to the sponsors in the room as well. In the initial evaluation and/or discussion or selection of devices, what mechanism or experience do those have with involving patients and caregivers in that evaluation discussion and ultimate selection before you get to a clinical trial and potentially spend too much time on a particular device and then have to go back to the drawing board or reevaluate?

So, I put that to you and to sponsors to think about as well.

Dr. Luke: So does anyone on the panel want to address it or do you want me to start with that? Why don't I just say that device development, we talk about iterations and total product life cycles and early device development, early feasibility. You have an idea. You put it on paper. You design a little bit of a prototype device. You look for a patient to start that study in and FDA has worked through some great strides to help get those early feasibility studies underway for devices. We have a guidance out there on early feasibility studies.

What is learned from that study will, hopefully, feed into the following iteration for a larger device study or more robust device study that then can lead to an HDE application or a PMA application, as Dr. Laschinger had pointed out.

Dr. Laschinger: Yes, I think there is a couple of components to your question. The first one is I guess -- did I understand you correctly? Do we seek direct family input from the FDA as far as designing these trials go? And that is, unfortunately, that is not part of what we do.

At panels, we do have open comment sessions for families to come in and talk about their experience with both the disease and possibly the device under consideration. So in the approval process, we have it at the tail end but not at the beginning.

At the beginning we rely on the sponsors to do that work and to bring in that information to us, what kind of need there is out there, what the unmet clinical need is. And hopefully, a good sponsor is going to be able to transmit that information to us or physicians in the agency will have experience dealing with those patients directly and know what the unmet clinical need is certainly from the literature.

So, it is not that we ignore what the unmet clinical needs are. We certainly pay attention to them but if you are asking if we actually bring families in to talk to about it, that has not been part of the process up until now, no.

Dr. Luke: There are persons out there that know how to design the clinicals, how to develop a product and move them along. A lot of times a company or person might have a great idea for a product but would lack that regulatory knowledge and they will seek a consultant or they will come to us and ask for a meeting to discuss how to develop their product, in which case we can provide so much information but in the end, it really behooves the sponsor companies to find someone who can really help them along with the process or have someone who can work on -- who knows the disease and knows the outcomes to be expected for that patient population.

And we see companies come in with just the engineer who designed the device

but does not have a good understanding of the disease, the person aspect of what the patient deals with. And that is something that is lacking. We think that is real important that that particular informational piece be added into the device development process.

Dr. Laschinger: And we certainly do look at the personal aspect when we are looking at what kind of bar we need to set to approve the device. I mean, obviously, where there is a situation where it is a terminal disease where what is out there doesn't work and our bar is not going to be set as high as one where there is three approved therapies that are known to work well and has many treatment options.

Dr. Luke: So with that, we have our next session, which is Debbie and Eric. Is Debbie and Eric in the house? Great.

Mr. Chen: So thank you for that. So, we are going to move on to our sixth session for the day. It is about needs assessment. So, this is a project that the Agency, along with NIH has recently started to tackle. So today I wanted to introduce some of the colleagues that we have today that is going to serve on the panel. These are individuals from FDA and NIH that are going to join in on this.

On my left we have Debra Lewis. Then we have Gayatri Rao. We have Heather Agler, Scott Freeman and Kui Xu. And from NIH, as you have heard already, Steve Groft is helping with this, as well as Rashmi Gopal-Srivastava. I don't think she is in the audience today but she has been working us on -- oh, hi, Rashmi. There you are. Sorry. So, she is joining with us on this project.



So, what I will do now is I will turn it over to Gayatri. She is going to give us a presentation on the project and give us an update on the current status.

#### Medical Devices for Rare Diseases: FDA/NIH Needs Assessment Project

Dr. Rao: Thanks, Eric. The goal of this session I want to keep my talking to a minimum. So, what I really want to do is just give you a brief overview of a project that we are undertaking, as Eric mentioned, in collaboration with a number of different stakeholders but we really want to spend a good chunk of this session really getting some input, since all of you are here and you have expertise in the device arena, to sort of give us some input into how best we are going to do this, we should do this.

So, like I said, I am going to spend very briefly giving you an overview of what we are doing in terms of our needs assessment project. And then I want to talk, open it up for discussion that will be moderated about ways we can be doing this and getting your input.

So, why are we doing a needs assessment now? Why now? And there are some really good reasons for it. I mean, one of the first questions we get all the time when we talk about device needs for rare diseases is what is the need. Has anyone actually looked at it? I mean we hear anecdotal stories about what the needs are.

I mean, just this morning when we listened to Dr. Geiger's presentation, he rattled off a bunch of devices that were needed just in his practice. But in terms of sort of systematically trying to identify what those needs are, as far as we know, publicly, there hasn't been a whole lot done.

So why are we doing this now? In 2010 IOM issued a report on rare diseases that really essentially says, and the language is up here, but it essentially says that it tasks FDA and NIH to conduct this needs assessment. It says the assessment should focus on the most plausible areas of unmet need, identify impediments to meeting those needs and examining options for how are you going to overcome these impediments.

That is a tall order. So, our goal right now is actually just to focus on the first piece of it, which is to identify the most plausible areas of unmet need.

A lot of conversation has already happened and is continuing to happen on what are all the barriers and how do we overcome them. But in terms of actually identifying the needs, that is really what we are focused on.

So, what are the goals? You know at the 10,000 foot level, why are we doing this? We are doing this because we really want to try to address unmet needs for rare disease patients. But sort of on a more granular level, the reason we are doing this is one, we want to try to identify what those unmet device needs are for rare diseases and we want to have a sub-focus on the pediatric population. What are the unmet device needs for pediatric patients with rare diseases? And what are some of the Humanitarian Use Device considerations? We have heard this earlier in the day that the HUD/HDE process, given sort of the 4,000 number, it may not be accurately capturing the full spectrum of the rare disease population. So, we are trying to capture what some of the unmet needs are, even outside of the HUD population.

We want to understand what the extend of the need is in the rare disease

population. Again, to answer the question, is there a need? I mean again, anecdotally, we understand there is one but we want to at least be able to say yes, there is a need, we have looked at it and here it is.

But the goal, ultimately, of hopefully starting to provide some of this information so that it can really inform patients, practitioners, and developers to sort of take this information and inform patient advocacy groups to mobilize them or inform legislative initiatives that folks might be interested in taking. I mean, these are lofty goals, I understand that, but you have got to start somewhere.

Really quickly, there are a bunch of stakeholders involved in putting this together. Our office, the Office of Orphan Products Development, has been taking the lead in sort of putting this together but we have been working very closely with our CDRH colleagues, as well as our colleagues in Office of Planning and Policy and, of course, NIH. And we have come together with a number of stakeholders, many of whom are in the audience from AdvaMed, AAP, AMA, MDMA, NORD. I mean this is sort of a laundry list of acronyms.

But certainly one of the things we would be interested in are there other stakeholders we should be reaching out to? This is sort of the list that we have generated to try to get a holistic perspective.

One of the threshold questions we had to answer in wanting to conduct this needs assessment is how are we defining what a rare disease is. And again, it really comes down to the earlier conversation about the 4,000 number. Did it make sense to use that 4,000

number in sort of conducting this needs assessment? And we thought we might be a little too limiting if we just use that number.

So, we are actually looking to apply the less than 200,000 persons in the United States number, that prevalence number. And where did we come up with this number? This is the number that is used to define what a rare disease is for purposes of drug designation -- orphan drug designation. It is more expansive.

So this is the number, like I said, we use on the drug side. It is also the number we use in our grants program. When we are evaluating whether or not to fund clinical trials for devices, we don't use the 4,000 number. We use the 200,000 number.

And again one of the reasons we decided to do this is one, it allows us to really kind of determine whether the HUD criteria really addresses rare disease needs and it also allows for us to think about diagnostic devices because often diagnostic devices, when you look at the 4,000 number get excluded. So, we are hoping that when we look at the 200,000 number, we are able to bring in diagnostic devices necessary for rare diseases and be able to identify what some of those needs are.

Another threshold question we had to ask is how are we defining what an unmet need is? And this is a tough question.

So, one of the potential definitions that we are batting around is this one, which is when there are no approved devices for the treatment or diagnosis of a disease or condition, or when a novel device could provide a significant clinically meaningful advantage over existing

approved devices. Now, this is a working definition but there are some limitations to this definition.

For example, if there are no approved devices for a certain treatment but say there is an approved drug or an approved biologic for that same condition, are we still going to view that as an unmet need?

Similarly, if there is already a device on the market but there is another device that provides a clinically meaningful advantage, for purposes of our project, does that make sense in that case to still consider that to be an unmet need?

And this is really one of the questions, as I sort of race through this presentation, this is really something we want to get your input on. What are your thoughts? Does this definition make sense?

We have done quite a bit of work to date. It is a pretty big lift to try to do this but we are trying to be as methodical as we can in our approach and we have really appreciated the input we have gotten from our stakeholders thus far.

So just to give you a sense, I mean because it is a pretty big undertaking, we understand that this is just going to be the tip of the iceberg. If our goal is to come up with this comprehensive list of unmet -- this comprehensive list of needs across the broad spectrum of devices, across the various systems, I mean, that is a huge lift. Our goal is to start that conversation and to start identifying what the needs are.

So, one of the threshold questions we had to ask is do we want to do sort of a

broad look across the different body systems in terms of identifying what the needs are or do we want to look at specific areas and do more of an in-depth dive in those specific areas, like for example cardiovascular or orthopedics?

And what we have decided is for our purposes for now, we would really like to sort of take the broader look because then there are certain areas, for example, in cardiovascular in orthopedics while there are still lots of need areas in those specific specialties. Those are also the areas where most discussions tend to happen, whereas other areas, no one is really talking about. So, we are trying to look across broadly. It may not be as deep of a dive but we want to look across and at least get the conversation started.

And again like I said, we are really looking on identifying what the device needs are, instead of focusing on barriers.

We held a kickoff meeting with our stakeholders to sort of start this process and get this input about how do we do this. What should our goal be? Who should we target for this information? How do we obtain it? We had a really good discussion but certainly one of our takeaways from that discussion is there are lots of different ways to do it. No one way is going to be perfect but we should just go ahead and try to do it anyway and come up with some information that, hopefully others can continue to build on.

So based on the information we have received to date, we have come up with a proposed plan. And I just want to spend a minute or two talking about this because, again, just like we talked about how we defined what unmet need was and we wanted your input on that,

this is another area where we would really like to hear your thoughts on this, in terms of how we propose to move this forward.

Now, bear in mind that because we are a federal agency, we are somewhat limited in how we can conduct this needs assessment. The most obvious thing that comes to mind is hey, if you do a needs assessment, send out a survey and survey the heck out of everybody and get that information. That would be great except we have to work under the Paperwork Reduction Act and we need clearance in order to be able to do that. And obtaining the clearance to allow us to just send out a huge survey to everybody is challenging. So, we are trying to work around some of those constraints and still be able to get really meaningful data.

So, this is how we are planning on doing it. We are in the process of sort of developing a plan and we hope to have that plan done by the end of this month. And as you will see by this time, it is a pretty aggressive time line.

So instead of doing this broad survey, one of the ways we were thinking about doing it is conducting a focused, specific targeted focus group interviews. So, taking that kind of information that we would put into a survey and conducting a targeted focus group interviews with relevant stakeholders to try to generate some of this data.

And we have identified some of the groups that we were thinking of targeting. An easy reach for us or a relatively easy reach for us is FDA already has a number of advisory committees where there is a broad range of expertise and we wanted to try to take advantage of the expertise within the advisory committees. So, we wanted to do focus groups to certain

targeted advisory committees.

Similarly, there is expertise within FDA and NIH on devices. So, we wanted to try to target internal expertise within FDA and NIH.

You have heard a lot about the consortia, the PDC Consortia, whose members are here, as well as the medical device innovation consortium. We wanted to try to target those because these are already existing groups with expertise and, quite frankly, interest in these issues. So, we are hoping they are going to be engaged.

But we'd love to hear from you in terms of whether there are additional stakeholders that we should be targeting. One of the stakeholders we have talked to was AAP to try to see if there are folks within AAP that we should be targeting as well.

To sort of supplement this focus group approach, we also wanted to have a public meeting at the end of 2014 to sort of solicit larger input from folks who we may not have been able to reach out in a focus group to get input from them in terms of needs.

And then our goal is to sort of take all of this information and hopefully have something that is useful that we can publish next year that can then be shared with a broader audience. And that can then be used to either further build upon or be used to start additional conversations like mobilizing patient groups, having conversations about legislation and the like.

So, just to summarize, we are really, like I said, we are really looking to work collaboratively with all of the different stakeholders to identify unmet medical device needs



and our goal is really to generate meaningful data. I mean, this is not even part of our day jobs. Our offices have a number of programs that we are legislatively mandated to do. This is something that we are doing in addition to running our normal programs because there is just a real need to do it. And if we are going to do it, our goal is to do it in a practical way that will really generate data to further the rare disease conversation.

So with that, I am going to stop so we can -- so here are the questions that we want to try to address with you. And Debra, should I turn it over to you? Okay, I can go ahead and introduce the questions. All right.

So the questions you know when we were thinking about putting the questions out in the *Federal Register* notice, you have to bear in mind the *Federal Register* notice came out months ago and we since have done some additional thinking. So, the questions are more broadly worded. So, we are hoping to drill down more on these broader questions.

So the questions in the notice were describe the parameters that should be used in determining priority areas of development of devices for both therapeutics and diagnostics. So, our challenge, obviously, is how best to formulate and prioritize key questions as we conduct this cross-cutting assessment of needs.

And the second is, what is the best approach to conduct this needs assessment? So, again, the challenge is how do we perform a cross-cutting analysis but use a sub-focus on pediatric devices and HUD-related questions?

So with that, I will turn it over to Debra, who can start moderating some of this

discussion.

## Group Discussion with the Rare Disease Devices Needs Assessment Team and Participant

### Comment

Ms. Lewis: Thank you, Gayatri and thanks everybody for participating in the whole day. I really do look forward to your participation in this project.

As Eric said in the beginning, we are going to try to co-moderate this but people may have questions right now from Gayatri's talk. So, if you have clarifying questions, we welcome those now. So, come forward. There is microphones about. We can help with that if people have questions.

And I see someone coming up. But while you are coming up to get started there, I can focus on one of the things that came from Gayatri's talk. She mentioned that the unmet need question was one of the things we are struggling with. That came about in October. We brought our stakeholders together and they said, you have got some tough questions. And one of them is how do you define unmet need.

And Scott, what we have got here is a part of our team. We have been working on this for a while. We are not going to make speeches, we want to hear from you instead but we thought it would be good to clarify. Scott maybe can tell us where we came up with that unmet need definition.

Dr. Freeman: Yes, so for the definition for unmet need, it is basically a modified version of the criteria for priority review in the premarket submission for devices from that

guidance document with the same name. We considered other sources as well, such as the guidance document for expedited programs for serious conditions pertaining to drugs and biologics but this one for priority review for premarket submissions seemed to fit the definition of what we were looking for better than others.

The obvious difference is the other one was for drugs and biologics and this pertains to devices. And while it doesn't state specifically within the guidance document that this is the definition of unmet need. It really fits the definition of what we are looking for really well.

Ms. Lewis: Thanks. And so our team is here. We want to hear from you but I know Gayatri you had a concern about whether drugs should be in that definition. So perhaps you want to just elaborate on that. So, if you were answering that question, you can keep that in mind.

Dr. Rao: Sure. And I referenced this in my talk, which is if there is an approved drug that is out there and is sort of treating the same condition, if you will, is it still considered an unmet need for purposes of a device unmet need?

And similarly, if there is already an approved device out there, it might not be the best device on the planet but you have got something and there is another device that really provides a significant clinically meaningful advantage over the existing device. Is that still an unmet need?

So these were questions, like I said earlier, that we were struggling with and we

would like your input.

Ms. Lewis: So just for that part, let me just go ahead and start getting some of that input with everyone. We will start over here on the right.

Dr. del Nido: So just to follow up on that on a couple of thoughts, one, drugs are different than devices. One, it is you can change the dosage of a drug much more easily than you can change the size of a device. And often, the clinicians have gotten very, very good at taking adult designed devices and sticking them into children. But what they have to do in order to get that device in carries a significant risk and that is often ignored in this process of looking at unmet needs.

Yes, I can put a valve in a small child, an adult sized valve, but what I have to do to enlarge that outflow tract in order to get that valve in has significant risk and has significant complications. We don't consider that often and I think that has to be taken into consideration that what are the current workarounds that we use? They are effective but they are at a certain level of risk that we can drop if we had a device that we didn't have to do that for.

Dr. Rao: Can I try? There is a really good point that I didn't bring up, which is off-label use. And would we consider so if there is a device out there that is not approved for that use but you can construct a workaround and use it in an off-label fashion, is that considered unmet need?

And I am going to look at my colleagues here. We talked about that. And from our standpoint, we were going to consider off-label use as there still being an unmet need. So,

in order to have the need be met, the use must be an approved use.

Dr. del Nido: Right. I think using the broader definition is going to be very important.

Dr. Snyder: Brian Snyder, Boston Children's. So I think the problem here is you can identify unmet needs but really this requires research to define and identify potential solutions.

You know, coming up with the device is sort of many steps down from the initial R21, R01 and basic research that you have to do to identify what is the problem and then how will you solve it. And then to do the important basic science and applied science to then do you have a good solution.

The unmet need is funding at NIH level to be able to pay for that rare diseases as an institute is one of the lowest funded institutes. And so I would almost make the argument the unmet need is making sure that you fund the research so that it can get done.

Ms. Lewis: I want to see if people want to talk about the -- there are a lot of good solutions, whether they be about funding or about incentives. And we talked a lot, and Gayatri mentioned in her presentation, that we have heard a lot today, and they are important to hear about, these challenges and the policy types of issues that create challenges and the possible solutions to them. And we want to incorporate a part of that in our work.

But the focus of this is going to be really to try to answer that one part of the question about needs, which is, can we at the end of this, what we are proposing is having

some sort of listing of what are the categories of need and the actual priority device needs.

There may not be the solutions there, just as you are saying, but I don't know if people want to elaborate on that. But it has been something that we talk a lot about and we feel very deeply about being in orphan products with our own grant program for rare diseases. So, we know that those are important issues.

And I don't know if you want to talk about our scope any more, if anyone has anything. Deb?

Ms. Lewis: I don't know. I think you have talked about it.

Dr. Rao: If that is in any way not a satisfying question -- I mean not a satisfying answer but at least to let you know our scope. We are trying to be able to come up with that listing approach.

On this side?

Dr. Gray: I'm Darryl Gray from the Center for Quality Improvement and Patient Safety at the Agency for Healthcare Research and Quality, another division of HHS.

One of the things I just wanted to mention is the availability of our administrative database, specifically with the Healthcare Costs and Utilization Project has a specific database, the Kid's Inpatient Database, which actually captures 80 percent of the pediatric discharges to non-federal hospitals in the United States. And so that, given the fact it is inpatient, so has coding based on ICD-9 diagnosis and procedure codes. However, that can

be certainly a way to identify the magnitude, at least of discharges, for given conditions. And so that is something that is potentially useful for identifying potential targets for looking for unmet need.

And so if anyone is interested, there certainly is information on our website about that and I am also certainly happy to discuss that with anyone who is interested.

Ms. Lewis: Thank you. I'm looking -- obviously, you can see we haven't rehearsed how we are going to respond to questions but we definitely want to have these types of models that are out there that may be able to help us as we go forward.

And we don't want to recreate wheels. We are not trying to duplicate wheels. We are trying to use the resources and that is why we appreciate. And I see people who have been working in these areas of needs for a long time in line and we welcome those resources.

Dr. Agler: Yes, I was just going to say the same thing. Just basically, if there are resources like that that maybe we are not aware of or even if we are aware of them now but you want to make sure, we would be happy to hear that type of input.

Dr. Rao: And please don't go away. We want to get your -- no, no, no. You can go back to your seat but we want to make sure we get your contact information.

Mr. Chen: Well, I will take the liberty of being also being a moderator to ask the panel. You know, we have heard from just now with the Kid's Database and then also with Dr. Geiger earlier that the clinicians are the ones who are seeing the patients who have this type of

rare disease. What steps do you think from a panel, where is the priority? Should we go to the clinicians first or should we go to the patients? Should we go to industry? How do we know who to go to first to figure out what is the priority in figuring out where these needs are?

Dr. Xu: Can you hear me? Yes, I would say actually device development is a collaboration between all the stakeholders. First and foremost, the patients are the sources of information, they are living the diseases every day. So, they have first-hand knowledge of the disease, while industry has the resource and experience of developing these devices.

So but the clinical investigators, they have medical knowledge. So, in most cases, they hold the key to the diagnosis of the disease and by interacting with patients, they are actually observing the disease and observing the natural history. And hopefully, they also know what is needed for successful therapy.

So, I would say in general I agree that clinicians actually, if we focus on clinicians as the main target for this needs assessment project, we might yield some valuable results.

But of course, we have to take into consideration the patient industry perspective because the patient is the person that we want to help.

So industry would make it a reality. So, I think it is a collaboration but clinicians might be all we want.

Ms. Lewis: Thank you, Dr. Xu.

Mr. Mindrebo: My name is Scott Mindrebo. I am the Senior Director of Clinical



Regulatory Strategic Planning at Cyberonics.

I want to commend FDA on using the definition under the priority review for the unmet need. I think that is a very wise choice.

We have received approval of a product that was given a priority review, based on the fact that there are patients who are resistant to drugs. So, they may try all of the approved drugs that are on the market and that creates the unmet need. They cannot be treated because the next drug isn't going to help them.

So, I think that is something that should be taken into consideration when you are taking into account should a drug be counted as an on-market product in this definition.

I would also like to recommend, maybe using the priority review process, manufacturers could submit a priority review for a pediatric application to be able to address your first question. That might be another way for us to begin putting together a list of what products, what unmet needs are out there for the pediatric market.

Ms. Lewis: Thank you.

Dr. Gnanashanmugam: Hi, my name is Swami, I am a surgical resident, and I am currently in the Stanford Biodesign Program which I don't know if you are familiar with that. And I would hope that I am seeing some nodding, so I would posit that a great way to figure out how to identify and assess unmet needs is our process, because we have been doing it for like 14 or 15 years now and it is an academic process but generates a ton of needs.

I would like to echo the previous person's comments, though, that I think the biggest unmet need is figuring out better incentives for the development of pediatric and orphan, you know and rare devices. I think the bigger issue is having a bigger pull so that clinicians, innovators like myself, when we figure out that it is a rare disease and that there is no market and so on and so forth, we don't just shelve the project in favor of something else. I think that is really the biggest thing.

And the other thing that I would say is as a physician, in my limited experience, what I have discovered is we don't tend to diagnose problems that we can't fix. So, if you are going to produce a huge list of all of these conditions, I hope that you also provide some sort of guidance about what to do after the fact because it is going to be extremely frustrating, I think, if you are going to identify all of the unmet needs but don't have any cohesive plan about how you are going to move forward.

That being said, I would like to offer some suggestions. What we do in terms of needs assessment is we do exactly what you mentioned. We go to the hospital. We go to the patients and it based on primary ethnography. And I am sure that if you would like, there is possibilities to explore collaboration where we could generate a list of needs for you through Stanford or through Northwestern, which is another institution that I am involved in that has a similar program.

And essentially, when we, as fellow, look at those needs, we kind of more or less subjectively rank them on the basis of four different things. Most importantly, is morbidity and mortality to the patient. Beyond that, we look at the incidence and prevalence. So, in this case,

usually the more patients the better but I suppose in your case, the fewer the patients the better. We look at the cost to the healthcare system. And then we kind of look at the overall gestalt on how feasible it would be to develop a solution to this or how difficult it would be.

So, in some sense, I think what you are looking for is maybe high per capita cost, high morbidity / high mortality, a low number of patients and extremely difficult, I guess, to develop a solution or not.

But I am happy to talk more about that or if you guys want to come out to Stanford where the weather is considerably warmer, give you a whole workshop on it and go from there.

Ms. Lewis: You know we do welcome our interactions with these resources. So, if you are one of these people who have these experiences, there is a couple of ways. There is the dockets and we want you to participate in the docket that you heard about earlier but you can contact us directly. There is contact information on this next slide that I will have up here momentarily.

But please do feel free. At the end of this, don't make this the end of our interaction on this project.

Dr. Geiger: Hi, Jim Geiger, University of Michigan.

I think this is a challenge. So, I think you recognize that. And some of the cautions that you have heard. I think the first one, which was sort of the cyberonics comment, you know if you had asked patients or neurologists treating seizures or they would say I would

want a better drug for seizures, they wouldn't have said I wanted a drug to stimulate the vagus nerve in my brain.

So, it is a little bit tricky to ask people what they want. And so focus groups is definitely, I would say a concern or a little bit caution about what you are going to get from asking people. And that is where the direct observations really come in.

The other thing is you have to, I think, really be careful about what your goal is for this database or what is your number one goal. What do you want to accomplish with it? Because when we, similar to Stanford's program, when we understand a need, our fellows will spend six months filtering needs down. They have a very organized process to filter those needs. It is very intensive.

As you go down each step of the way, you put in more time in understanding the need. So literally by the time they get down to the needs that they actually then start to look for a solution, which is after months of work, they have spent hundreds of hours understanding the need.

So the question is you know to what depth do you want to understand these needs. How much information do you want? How validated do you want it to be? That sort of thing. It is really important.

And I think like I said, direct observation is something that does add a tremendous amount of value, which is going to be, of course, difficult in this process.

But anyway, I think it is good to see, I think, this sort of effort. But I think I have

some cautions there of what you want to accomplish with the information and really then what information you need. And I would try to come up with a process of how you are going to filter these things, process them, group them. There is sort of a process that I think needs to be in place. Otherwise, you are going to end up with a lot of information and maybe not know exactly what to do with it.

Ms. Lewis: Thank you for those cautions. Anybody would like to remark on these cautions? Or are we short on time so we should get -- we will go ahead and take another.

Dr. Levy: I am Bob Levy from the Children's Hospital of Philadelphia.

I wanted to comment on Dr. Chen's remark about contacting clinicians for the survey, which I think is a good idea. I think all the specialists involved in the care of children in terms of pediatric devices, the surgeons, and the interventionalists who are organized in national organizations, I am sure that if they received a survey from the FDA, those organizations would be responsive in terms of distributing them.

I think the same is also true for the hands-on allied health personnel who take care of the patients. The ICU nurses, the operating room nurses, physical therapists, occupational therapists, all of these individuals, in my experience, have ideas about things that would be much more helpful for the patients than they are able to get their hands on.

Ms. Lewis: Thank you.

Mr. Moran: Hi, my name is Tim Moran from an organization called PediaWorks. We have actually done a pilot on this and we are involved in a second pilot right now. I know

you have reached out to me and provided some feedback on this already.

But a couple of comments that I would make about this is that in our experience, we took the approach per what Dr. Geiger said of saying the value of this data is to get a device onto the market. So, that is how we structure the questions and that is how we structure the data that we gather.

The one thing I would say is you absolutely have to do a broad market survey. If you just use small focus groups, you are going to get the feedback from small focus groups.

What we ended up doing to make sure that we didn't just do a shotgun approach is we actually convened small little hit teams of a focus group. We took that information, structured questions, brought in industry at that point to find out what sort of data that they would like to include or ask questions about.

It was at that point that we went out and surveyed the broad community. And what we did was actually very simple and cost-effective. We worked through the specialty organizations. It was all web-based. It was all done within a couple of weeks at minimal cost.

And what I would offer to you is that we, as an organization, since we are already doing it, would be happy to provide that aspect to you, since you are not able to do that. And certainly, we can tie together the information that you want and we want.

But I think the key to all of this, too, is you let the market determine what the priorities are, so you don't have to wrangle back and forth to say how should we rank these. You ask the market, the users, the allied health, the clinicians to say what are the biggest

challenges you face from a device standpoint? What devices do you want to see in the market? They will tell you what they want to see. And that is your ranking right there.

Ms. Lewis: Thank you. I know we have heard that this has been an area people have been working in for a long time. This is not coming first with us. We understand that and we appreciate the ability to work with a variety of folks who have experience in these areas, who have good cautions for us to consider. Our stakeholders who met with us in October, that was a fantastic experience for us but we are about --

Oh, I have one more question, I guess, then we will turn it over to Gayatri for closing remarks for today. But, please.

Dr. Purucker: Hi. My name is Mary Purucker. I am actually with NCATS, which is the same NIH institute as the rare disease program is with. But I am actually with the Clinical and Translational Science Award Program.

And I just have a comment and maybe a question for the group that has more to do with the issue of capacity building. And I would like to know whether the group thinks there is a sufficient number of individuals who are clinical investigators, who have the technical skills and the regulatory expertise and the capability of moving these types of products forward.

The reason I ask is because the CTSA programs trains a significant number of clinical investigators and we are focused on translational research, which is clearly what this group is interested in.

Ms. Lewis: And I appreciate that and we appreciate the support that NCATS is

giving us on this project, as a partner on that.

And so, the capacity and experience that NCATS has, together with our team here and our other stakeholders, it is a daunting project. It truly is. But we have some capabilities that we have talked about already with our Pediatric Device Consortia. We want to tap into that capacity building aspect. A lot of different things that we have touched on a little bit earlier and don't have a lot of time today. But I hope that our conversations with NCATS, whether it is through Rashmi, yourself or others at NCATS, we can continue that, too.

Dr. Purucker: For us, we can talk offline about this because I mean in terms of looking forward to capacity.

Ms. Lewis: Yes.

Dr. Purucker: Thank you.

Ms. Lewis: Yes, I think it is an important concept and there are so many stakeholders in the rare disease community and we know that whether we are starting with clinicians or starting in any particular are, we have to take into account those cautions that we have heard about.

So, given our timing, I know people are expecting their break soon. So, Gayatri, if you just want to go ahead with closing.

Dr. Rao: So just to echo what Debra said, yes, this is a very daunting task. And we so appreciate just even in the limited amount of time that we had, the feedback that we



have gotten.

We would like very much, particularly for those folks who have spoken up who have experience with needs assessment to really be able to get additional advice, information, and perhaps collaborate with you on how best we can do this.

We understand that there are real challenges in doing this and we understand the point was raised earlier, well, you are going to put this list out there. And there will be limitations to this list, how robust it is, how complete it is. You know, I am going to put right out there that it isn't going to be complete and there will be limitations to how we are collecting the data. But we at least wanted to take a stab at it to start the conversation or, in many cases, to continue some of this conversation.

And I agree, at the end of the day, once this list is out there, what do you do with it?

And our goal is this is step one. At least put the list out there because, again, one of the constant refrains that we hear is is there an unmet need for devices, for rare diseases? And while that might be a pretty self-evident question to the people in this audience, it is not largely understood or accepted in terms of what the need is. So, our goal is really to get the broader conversation started.

So, we really look forward to working with all of you on this. We are going to do our very best to try to do as good a job as we can. So, please be kind, once we put this out, in terms of your criticism. However, we do want to get as much input as we can. So, if you didn't

have a chance to say anything or obviously we were limited, please, please, do submit your thoughts to the docket. We will be looking for information. We are looking for feedback on what is the best way to do this.

So, please do submit comments to the docket.

Mr. Chen: And maybe I can make one request, Gayatri, if you can go to the next slide. This is another way that you can provide information to us. We have a website here that will -- I mean not a website -- an email address here that will let those who did not get a chance to provide comments or those who did provide comments to elaborate on those. Please provide your additional comments to the email address and we can look forward to using those when we move forward with this project.

Dr. Rao: Thank you. And with that, I guess, Linda we are at break now?

Okay, so come back in ten minutes. Okay, so break time for ten minutes and we will see you all back here.

(Whereupon, the foregoing meeting went off the record at 2:54 p.m. and went back on the record at 3:04 p.m.)

#### Diagnostic Devices

Dr. Luke: Our next session is on diagnostic devices. And our speaker for this session, which is a relatively short session but that is not to belie its importance because, as you all know, for pediatric patients with rare diseases, diagnosing these rare diseases is very

important and the earlier you diagnose, the better, in many cases. So, how does the Agency approach this clinical need?

Alberto Gutierrez, Dr. Gutierrez is the Director of the Office of In Vitro Diagnostics and Radiological Health. He is a laboratorian and he has over ten years of experience in research in chemistry and he has been a researcher and reviewer in FDA since 1992. He is currently the Director of the Office of In Vitro Diagnostics and he is going to be talking about the considerations for diagnostics in this environment.

Alberto.

#### Considerations for Diagnostics

Dr. Gutierrez: Good afternoon. This is somewhat of an unusual talk for the rest of these because even though, and as you will see, diagnostics do form part of the equation. In terms of the regulatory issues and how the agency deals with diagnostic devices in the area of pediatrics and rare disease is somewhat unusual from the rest of the paradigm and there are many good reasons for that.

So, I don't have to tell you that rare diseases vary with regard to severity and organ systems affected. And the diagnostics play really a pretty important role in determining both what therapies are going to be used in diagnosing the disease itself and identifying what needs to be done.

So, even though I am going to be speaking mostly today about in vitro diagnostics, many of the same issues, actually cut across some of the other diagnostic

modalities that we have with the agency.

The approach is sometimes different. So for example, the way that we regulate imaging devices has tended to be much more tool-like. But some of the issues are similar. I will, though, focus mostly on in vitro diagnostics for this talk.

And so, what is an IVD, an in vitro diagnostic? And I just have a picture of a whole bunch of things there. Actually, anything that is a test on a sample that is taken from a human being. And so they go from things that people can use for themselves, as direct consumer type of devices such as glucose meters, to fairly complicated arrays and devices that actually help diagnose or help even do entire genomes, sequence entire genomes or sequence particular genes to determine particular mutations.

So it really is a fairly broad range. The type of devices that are useful for determining a particular rare disease could be just as simple as a chlorine test for cystic fibrosis to actually being able to sequence the whole gene in determining what mutation exists. So, it varies as a whole range.

And it is a very broad and diverse world. We believe that more than 70 percent of all medical decisions, actually, required some type of diagnostic testing, in vitro diagnostic test. And it is a fairly large portion of our medical care, if you like.

Now, the way we regulate in vitro diagnostics is the same way we regulate all medical devices is really based on the amendments in 1976 and is based on risk. And in general, for most in vitro diagnostics, most of them fall under Class 2 Risks, what we consider

Class 2 and that is, determining that there are substantial equivalent to something that is on the market or that if there hasn't been anything on the market that we find a way to put it into a Class 2. And we do do some PMAs, some Class 3 devices. In general, though, in the review part, the pre-market part is actually very similar.

What is it that we look at when we look into these devices? The essence of it is very similar. You heard earlier today about HDEs. It turns out that in diagnostics, we don't see many HDEs and there are actually some good reasons for that. In determining a risk of a diagnostic device, what we look at is the risk of an erroneous result, a false positive or a false negative. If you think about it, that means that the safety of the device and the efficacy of the device are intricately linked. So, it is very difficult to determine safety in a sense, without determining some kind of efficacy. And that makes the HDE process a particularly difficult one for devices because all the stuff that you need to do to do analytical validity, which is what we require, essentially, of an HDE is just about all you need to do also to determine the medical usefulness of the device. So, we don't tend to see many HDEs. In many ways, it becomes easier to just get the devices through 510(k) process or down-classification to a Class 2. And if you end up there, you end up without having to do all kinds of things that you have to do with the HDE.

So, in general, the packages that for PMAs, 510(k)s or HDEs are very similar. And really what we do is we actually determine, we have the same type of scientific questions and those are divided into two. One is what is the analytical performance. Are you measuring what you think you are measuring? If you think that you are measure certain mutations in a gene,

are you actually picking up those mutations or not? And how well, how precise and how accurate are these measurements?

And are there anything that is going -- are there any interference that are going to create problems or how sensitive are you? How well can you pick it up? Do you need to worry about the sensitivity of the test?

And then the clinical performances. Is there a link between what you are picking up and a clinically relevant -- some clinical relevance? So if you think you are picking up a CF mutation, are you linked to CF? And is the fact that there is a mutation, is there disease that is associated with it or not? Or is this a mutation that actually does not result in any disease outcomes?

So, those are the type of questions that we ask and the data that we look at is really towards the finding that how well do you detect -- how many positives when something should be positive? How many negatives when they should be negative? Are you detecting the right things?

So in general, all these things are important. In general, let me just talk a little bit about what kind of things do we see in terms of pediatrics and rare disease. It is clearly becoming the area of in vitro diagnostic testing is becoming increasingly important. The number of newborn tests that states typically do are increasingly all the time to screen for rarer and rarer diseases, so that we can know early whether kids are being born with a particular rare disease.

The ability to start actually testing and even doing screening tests in the prenatal area is actually increasing. And we will be seeing in the next few years a simple blood test that will lead to the ability to actually screen for most or many rare diseases actually. It probably won't be too long before we can actually do whole genome sequencing in the prenatal of babies before they born.

So, we are moving into an area that actually has many issues that need to be resolved. Some are technical. Some are ethical. And some are really clinical. What are we going to do with lots of findings that we may not actually understand? What are we going to do with testing for things that may not cause either immediate disease or that could have adult onset type of issues.

So, there are lots of issues that we deal when we deal with in vitro diagnostics and rare disease and it is that type of issues that we do.

In general, if you think about it, a lot of the testing that is being done now in in vitro diagnostics, just about all of it is rare disease testing because we are actually testing for all kinds of mutations. And the more -- the better that we get to test the mutations, the rarer the mutations, we actually see this problem. And the problem for us is well, I can divide it really into two areas that we need to worry about. One is analytical ability and the problems that we have with sample or specimen, and clinical ability, that is, what kind of studies we need to do and what kind of risk assessments we do.

So in specimen, the problem with availability is somewhat that is similar to other

areas in which we do, either therapeutic testing for things for rare diseases. In some ways it is a little bit different.

There is an inability to get specimens that actually have the disease or have the connection to the disease that you want to test. It is typically not as difficult as getting patients that have those diseases, partly because we can actually store samples. But how accessible those samples are depends on how well stored and in some cases it depends on whether there are patient groups that actually help determine or help push for storage of samples and availability of samples so the new test can be run.

And not only are there samples available but is there enough sample so that you can actually do all the type of tests that you need to do?

The type of things that we typically do to get around the number of samples that are available is that we actually mimic those samples in one way or another. We can do things like use cell lines. We can use plasmids or enriched samples. We can, sometimes, have to go down to using fewer samples than we would really like but that is the number of samples we can get or manufacturers can get to test their devices with.

Sometimes we can do pooling and it is a type of -- it is one way to get around the issues of exactly do we have enough samples and can we get the right samples.

The challenges that we see in clinical studies are, in some ways, similar to the challenges that you all typically see in this area. Can you get adequate representation across the defined groups, specifically in pediatric groups?



You have a limited number of patients and you have ethical issues, sometimes, including patients. And with extremely rare disease, you may not have too many people or too many samples that you can use. And always, how do you get to clinical truth?

And the type of solutions that we have typically found so that we can actually clear or approve these devices is there are lots of well-recognized pediatric reference intervals, that helps. A lot of times, we tend to use literature support, things they have done in literature, and then we tend to bridge to the devices that were used in the literature.

We have the luck of actually being able to use a lot of retrospective samples. And again, that depends on having the correct, the sample stored correctly and having the appropriate sample, appropriate data banks -- sorry -- sample banks that can be accessed.

And we do have ways to try to mitigate the biases that occur with using both retrospective samples with missing data and with lots of issues, as long as you can prospectively plan for many of these, you can actually take into consideration many of the biases.

So in general, what I can say is that the issue of rare disease testing, the issue of testing for mutations that occur rarely, the issue of pediatric testing actually is one that we face just about every day that we actually see these type of issues all the time. And we typically find ways to get around the problems and, of course, the solutions are never ideal. But we weighed the benefits and the risks and, usually, if you use samples that are in some way doctored, you are increasing the risk that you may actually miss something or that you may not represent fully the samples that is going to be tested. Yet, you have to weigh that against not being able to, in

some way, detect a specific disease or not be able to get some information that would be useful to the patient.

And I think that is all I have.

#### Moderated Discussion

Dr. Luke: So, we will take questions from the audience but first, I think Linda wants us to make sure that we cover the question that is in the FR notice. And that question is what is the major issue or problems that you see with development of diagnostic medical devices, from your experience with companies coming in.

Okay, right. We are going to bring the audience to the mike if anyone has questions for Dr. Gutierrez, please stand up at the mike and we can take those questions in order.

And diagnostics is important, as we pointed out, because it really gets at the heart of picking out those patients for which you are going to give the drug therapy or the device therapy for. And that is primary to what we do and this is how wide the rare disease environment has changed so much is that we are able to diagnose earlier and hopefully better. Alberto mentioned fetal diagnosis, I mean diagnosis in the womb of patients, potential patients coming out.

So, Alberto, did you want to address what you see in your experience as the major problem?

Dr. Gutierrez: So as I said, I actually put that into my talk. For us typically samples with the ability to get enough samples to test and the ability to actually have banked samples. In many rare diseases, there hasn't been a collaborative effort by either patient groups or groups that are interested in the rare disease, so that the samples tend to be scattered into clinical laboratories all over the country just happen to see a specific sample and test that sample and store it. And so there is no good registry of what is available. The samples tend to be then difficult and expensive for somebody else to get. And without any samples, it is very difficult to actually determine whether a specific assay works or doesn't work.

Dr. Luke: Is Steve still in the audience? I don't see him here. Maybe he stepped out. Is there anyone from the NIH that can talk about registries and whether samples are kept in the registries? Dr. Hirschfeld.

So, in the meantime, I think there might be some collaborative efforts we can work on to pull together samples to help in that environment. And if there is a diagnostic tool, to have phantoms or to have potential libraries of samples to test diagnostics on.

Capt Hirschfeld: Hi, Steven Hirschfeld, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

So, as Dr. Groft noted, there is inconsistency among the various registries. So some of the institutes, for example, National Heart, Lung, and Blood Institute have integration between the samples and patient data and so forth. And others have less degree of integration or less degree of correlation between which sample was from which patient at which time and

so forth.

So the short answer is it is all over the place but there are definitely opportunities. And the trend is to have much better integration. And as Dr. Groft pointed out, everybody uses different vendors and different systems. So, we are trying to consolidate that operationally.

Dr. Luke: I like the optimism of opportunities. So, that is always a good term to use and there are so many opportunities in that environment.

Dr. Rodriguez: I want to share a very --

Dr. Luke: Reintroduce yourself, please.

Dr. Rodriguez: Bill Rodriguez from OPT FDA.

I want to share an experience from my pre-FDA days where NIH, the infectious diseases group and Children's in Washington used to do work on respiratory viruses. And the virus, the samples were stored at minus 70 at Children's inter-catalogue et cetera and NIH ID knew about it. And in fact the reason why I am bringing it up, many, many years after that failure testing -- I mean trying to protect kids with vaccines against RSV and those on the one-year phase did poorly or some of them died, et cetera. We went back to the samples and said what happened there. And in those samples, we find out that there was no antibody being produced by the kids who didn't do well that will keep the virus from spreading from one cell to the other. And it is fascinating that was decades after the studies have been done but they had been kept at minus 70 in collaboration and they both knew about it.

Dr. Luke: Right. These sample collections, I think they raise additional questions about consent and whether -- and ownership of the samples and those kinds of issues.

Did you want to talk a little bit about that or what kind of efforts are underway to look at those?

Dr. Gutierrez: So, I don't really want to get into the consent issues. There are all kinds of issues with consent actually in the area of newborn testing has been a particularly difficult area of consent because many of the states mandated newborn testing and they didn't do a particularly good job of letting parents know that the blood spots, these were mostly blood spots, were being stored and that actually new tests were being -- that were being used to develop new tests. And that resulted, actually, in several lawsuits against several states because of lack of proper consent and proper procedures for determining how long they could, to keep the sample spots and what they could do with them.

So, in general, I do think that the laboratory community has been fairly lax in how they used their samples. They have been used to draw samples from people for regular medical care. And then using the leftover samples for lots of things that they need to do, some of them are essential for running the test. It is things like controls, things like -- but they also have been used for developing new tests or for troubleshooting and for all kinds of things. And what is appropriate consent in all those things I think is still not well worked out.

There is some areas where consent has been better and more people actually have done a better job of storing samples in banks with proper consent, and particularly for

developing new assays. But that is, I think, an area where there is still some need for defining better how we should be doing this across the board.

Dr. Luke: Right. I think you can also read there is numerous articles about the economics of sample collection and the ownership issues that come out with collecting samples of your DNA and what right do you have to that DNA specimen once it is in the hands of a specific laboratory who might try to commercialize, say a certain sequence that might be very individual to you or to a specific disease area or companies, for that matter. I know some of you are out there that are thinking a lot about this. And I think there are some Supreme Court cases and things like federal court cases on this issue, whether it should be decided in courts, that is a different question.

I think we have another audience member and we do have folks in the ethics environment. And if anyone in industry wants to comment on those particular aspects, we have a few minutes in which we can do so.

Dr. Tarachandani: My name is Anil Tarachandani from Usin'Life. Good question about for some of the samples that are ready to get, there is some published data or literature data. Could you just expand upon what is acceptable and what is not acceptable from the literature data?

Dr. Gutierrez: So, it is a little difficult to generalize but there is lots of, we use literature data quite a lot and the specifics matter and the specifics as to whether you can bridge to the literature data matter. But for example, in November of last year, not that long

ago, we actually cleared or down-classified an instrument for sequencing for use in screening for CF and a lot of the mutations that we cleared under that were actually on a very nice registry database that was at the University at Hopkins.

And so really, we have used data if there is enough data and then we have to figure a way for you to bridge to that data. You have to show that you can actually detect that mutation and there are ways for us to do that. But we use literature quite a lot.

Dr. Luke: Anyone else? Comments on diagnostics?

I think we are at the 3:30 mark and --

Operator: Well, we do have one question, if you don't mind.

Dr. Luke: Oh, you do have one more question. Go ahead.

Operator: Yes, this is a question that came through from the webcast. And the question is: If a diagnostic device has been approved for use in adults, what are the regulatory barriers for approval of the same device in children, if the device is unchanged and could be used between the ages of 10 and 12? They are unsure if insurance companies will cover if the device is not approved by the FDA.

Dr. Luke: Is this an in vitro diagnostic? I guess maybe we want to address whether it is an in vitro diagnostic or some other type of diagnostic because there might be different answers, depending on how it is used.

Dr. Gutierrez: So, it depends on a lot of things. There are some devices that are

typically cleared with just -- and there is typically enough data so that you actually don't have to worry. But to clear it, you usually would just samples from adults. But typically, the ranges for pediatrics are similar.

In those cases where they are not, and so for example I can give you a good example, is glucose. Newborns have glucose levels that are much, much lower than adults. We actually clear devices that measure glucose. But if they are going to claim that they can detect glucose at a level that is useful for neonates, then they have to -- they actually have to give us samples within the range that would be required for neonates. And then we would give them the claim. They wouldn't have that claim unless they told us. They would have a cutoff that is too high for use in neonates.

So it depends a little bit on the specific analyte you are using and it depends as to whether the ranges for pediatrics matter. And if they matter, then usually we either exclude them if they haven't tested within the ranges that are required or we include them purposely and intend to use when they have done so.

Operator: Thank you.

Dr. Luke: Alberto, thank you for sharing your expertise and your time with us.

We have next Jackie Ryan, who is going to moderate what could be done, incentives and otherwise. This is, again, in the context of developing pediatric devices for rare diseases. Jackie?



## What Could Be Done? ... Incentives And Otherwise

Ms. Ryan: Hello. I'm Jacqueline Ryan from Office of Device Evaluation in CDRH. We are finally coming down to the end. This is the last session. I want to thank everybody for staying with us. It has been a very productive workshop so far.

This morning we started out with the clinician's view of device development challenges, which was presented by Dr. Geiger. We went on to have some of the agency initiatives and programs explained in detail, including the HDE program and the OOPD grant program, as well as the medical device innovation consortium and CDRH innovation program.

We learned about some of the engineering challenges. We talked about some of the clinical trial considerations, including statistical modeling and using Bayesian methods to account for a limited number of subjects or insufficient data. We talked a little bit about needs access and just recently about in vitro diagnostic considerations.

So our final wrap-up session is to discuss the next steps that we will need to take to facilitate and advance further development of devices for rare pediatric diseases.

We have a panel of experts here who are from industry, regulatory, and policy to consider our further investigation into device development. The first is Tamar Haro. She is assistant director of the AAP Department of Federal Affairs. Dr. Haro handles federal legislative and regulatory initiatives on FDA medical product issues, disaster preparedness, emergency medicine and mental health.

Prior to joining the Academy, Dr. Tamar served as staff director of the U.S.

Senate Subcommittee on Children and Families of the Health, Education, Labor and Pensions Committee chaired by U.S. Senator Christopher Dodd. In that capacity, Dr. Tamar was a lead staffer on the coverage and quality provisions of Healthcare Reform for Acting Chairman Dodd.

In addition to her work on Health Reform, she handled a wide range of healthcare issues for Senator Dodd, including FDA policy, maternal and child health programs, mental health parity, and HIV/AIDS. Before that, she worked on healthcare for Senator Dianne Feinstein as a legislative assistant.

Tamar is a recipient of numerous awards for her work on behalf of children and families. She graduated with honors from Washington University in Saint Louis with a BA in political science and Russian.

#### AAP Perspective

Ms. Haro: Thank you, very much. Quick clarification. I am not a doctor. My parents, I am sure, would be very proud to hear that, as they both are. I have nothing to disclose.

As was mentioned, I work for the American Academy of Pediatrics. The AAP is a nonprofit professional organization of 60,000 pediatricians, pediatric subspecialists and pediatric surgical specialists and we cover pediatricians that focus on any number of child health issues.

I am here today because I work on federal legislative and regulatory initiatives related to pediatric medical devices and drugs and did so when I was on Capitol Hill for almost a

decade working on legislative initiatives, including the Pediatric Medical Device Safety and Improvement Act, which has been discussed at length today.

But what brought the academy to this issue is we have a long history in advocating for medical products for children. I think one of the pivotal points for the academy was for 1977, when our committee on drugs published a policy statement, a seminal statement essentially saying not only is it ethical to study drugs in children, it is unethical not to, if those drugs are going to be used in them.

Fast forward two decades, essentially. We had the first legislative initiative to create an incentive in the drug space to ensure that drug products would be studied in children. And after years of experience with that, we started to think well boy, if we can do it in the drug space, we should be thinking about how to promote pediatric medical devices. And I think a lot of our pediatricians just take for granted the fact that there isn't going to be a device that is approved specifically or designed specifically for children and that is just how it is. It is just the status quo that we should jerry-rig a device for a child because that child needs it. So, we are going to think creatively and do what we need to do for that child's health.

And that is probably not the best way. That is not the best public health answer for children.

So, we got together with a number of other organizations, including NORD and the Elizabeth Glazer Pediatric AIDS Foundation and convened a stakeholder discussion process with industry, with several federal agencies, including the FDA and NIH to start these

discussions on what the problems are, what the barriers are, what the needs are, and how we start addressing those in a meaningful way. And that process began around 2004.

One of the major culminations of that process was, of course, the legislation in 2007 that was reauthorized in 2012. I am not going to talk a lot about it because you have heard about it all day long but it is a success story and Congress saw fit to reauthorize it in 2012. We have seen several new pediatric HDEs, certainly an increased number of devices seeking pediatric or companies seeking HUD designations as a result of the legislation.

And then there is a greater discussion now, a greater awareness of the gaps and the needs, conferences like the one that is happening today and many others that have taken place, spurred on probably indirectly or indirectly from the legislation.

And then the other shining achievement, I think, of the legislation, was the creation of the pediatric device consortia program, which I am not going to go into because you have heard a lot about.

So that is what has been done. I am going to focus now on what needs to be done and then what could be done.

If you leave this talk, my talk today, with nothing else, I hope that you will, I guess for the non-federal participants today, we will take back to your members of Congress that we need to fully fund the pediatric device consortia program. The program is small but mighty. It is receiving \$3 million in federal appropriations. It is authorized to receive \$5.25 million. And just imagine what we can do with an additional \$2 million, based on what the

program has done with its existing \$3 million.

It is absolutely remarkable if I can stand here and put on my hat of when we were negotiating in writing this program, it really was an experiment. We didn't know what was out there. We didn't know would this work. How would it function? Would people be attracted to it? Who would even apply?

We were aware of a couple people out there doing interesting things around this but we didn't really know what the interest level would be and boy, has it proven to be quite a success story. And so we need the full funding. So for those non-feds in the audience, we need your help in making the case to Congress that this program needs to be fully funded, which I hope will be an easier case to make, now that they at least have a short-term -- Congress has passed a short-term proposal on budget and hopefully appropriations soon.

We continue to struggle with payer and insurance issues with more and more devices, which is a good thing, and certainly more pediatric HDEs. We are continuing to get increasingly reports from our pediatrician members about denials of payment from insurance companies, lack of understanding on the payers' side of what an HDE is. This statement was made before and I will underscore it again, that an HDE device is, in fact, approved for marketing in the U.S. So, making that case ensures helping them understand the importance of the devices, whether they are used in an on-label or off-label situation. We need more work in that regard.

We need the extrapolation guidance that was discussed earlier. It was a

requirement. Well, it was an authority granted to the FDA in the 2007 authorization that the FDA could use extrapolation for efficacy, an important point there, that it is for efficacy based on the experience in the drug space. We have about 20 years of experience now of extrapolation of efficacy on the drug side. And if we can prevent or alleviate the need to subject children to clinical trials and utilize extrapolation, boy, we should do that for efficacy.

So, we are excited to hear that draft guidance will be forthcoming and look forward to digesting that and commenting on that.

We still have another completed, I guess, provision from the 2007 reauthorization or authorization that allowed FDA to track potential uses of pediatric devices. And this really generated out of a pretty major study of the institute of medicine on safe medical uses of devices in pediatrics to help the FDA better understand potential pediatric uses of medical devices in the PMA and HDE context.

And then I think we probably need to engage a broader set of stakeholders, many of whom are in the room today. With the pediatric device consortia and others, we have learned that the medical device industry is not a homogeneous industry. And maybe what is attractive to a large company may not be the same motivation factor that is attractive to smaller companies. And so maybe we need to broaden the conversation. And I think the pediatric device consortia program and its experience and the companies that they have been working with may be very instructive in terms of as we look at barriers and overcoming those barriers.

And then as we look at what could be done, I think there is probably some space for some bold thinking but I would caution that we need to think about what is politically feasible. We have heard many folks have proposed ideas and initiatives, many of which would be quite costly. And I think that this is a very difficult and challenging fiscal environment in which we find ourselves and I think we can't be blind to that fact that Congress will have a -- it will be very difficult to bring to Congress those proposals that have a large cost associated with them and that the reality is that there are many competing legislative priorities from the very industries that we are talking about that are before Congress at the moment; everything from this little thing called the medical device tax with the Affordable Care Act, as well as some very tricky issues that I think are resolved in the short-term with the medical device user fee agreement and the impact of sequestration.

And we also need to remember that Congress will continue to, just like we do in medicine in the clinical setting, think about risk versus benefit. Congress, too, will look at it but they look at it from a slightly different lens and so we also need to be cognizant of that. And we have to have willing stakeholders because if we don't go unified and have a common message and a common outcome, we are not going to get very far.

Picking up on some of the themes that Skip talked about, I think it is probably a good time to start thinking about the statutory mandate for IRBs. An IRB review of use of HDE devices, although something that was language that was included in the original HDE, the creation of the HDE pathway and, I think, there is probably reason to think about is that still appropriate. Does the requirement of an IRB approval for an approved device make sense in

this day and age and could that be a barrier that we might think about overcoming?

And I don't want to spend a lot of time talking about the drug laws but I think there are some lessons that we can learn from the experience. We have got more than a decade of experience with the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act and it was beat into me very early on that the drug and device industries are very different and that we have to be mindful of that. But I think some of the challenges that the industries face in pediatrics are very similar and we should learn from that.

The programs work very well as the carrot and stick approach. And increasingly, as we have perfected the programs over the years, have started the conversation about pediatric product development in a much earlier stage in the product development lifecycle. And you have certainly heard, if you were here the last couple of days, heard about the differences between the US and the EU and difference in timing and how that is working or not working in various context.

But I do hear from a lot of folks that starting that starting that conversation early, understanding what the Agency's expectations are going to be, allowing companies to plan and build that into their product development plan can be a good thing, rather than waiting until the very end of the approval stages. So, I think there are some things that we can learn from that.

And then continuing on the other ideas of what could be done, you know, there is always the importance and the need to have pediatric expertise at the table when we are



talking about children. I think we have seen a lot of complications and problems with the advisory committee's ability to find and maintain and keep pediatric expertise. There are a variety of reasons of why that is. I think conflicts of interest are in the rules associated with that, are very challenging. They are there for a reason and an understandable reason but when we are talking about very rare disease situations, pediatric rare diseases, the cadre of experts that exist to review products and to advise the Agency may be very small. So, it would be very hard to recruit and maintain folks without conflicts. And I know that is a controversial issue for a lot of folks but it is impeding, I think, the scientific expertise that is provided to the Agency.

And again, I would say that the Pediatric Device Consortia Program has been a huge success. And let's build upon that. Let's grow it with more funding, broader reach. Let's enable it to do more.

And then finally, I would just say that we have probably reached the time, and this may be a little controversial to say, but it is probably time to shift the paradigm around talking about device needs. I think we have moved past the conversation being about let's define the unmet need. I think you heard very eloquently earlier this morning from Dr. Geiger and certainly from many of the patient advocates that are here today and who spoke over the last couple of days that the need is here. You just need to talk to a family. You just need to talk to a pediatrician, a pediatric surgeon and they could probably spend half a day telling you about all the devices that they wished they had for their patients and they don't currently have.

So, I think it is time to move past the conversation about where the unmet need is. And let's talk about actually getting these devices approved and on the market and that

regulation isn't always a bad thing. And that we can use regulation, hopefully, to promote the pediatric medical devices and the marketing of those devices and that not all regulation is to be opposed and impeded, that we can actually use that to promote what is in the best interests of pediatric patients.

And in the event that you didn't like anything that I had to say, I gratuitously posted a picture of my daughters, BPCA and PREA, they are about seven months here. They are now a year old. But I just had to include that.

Ms. Ryan: Our next speaker is Michael Morton. He is Vice President of Regulatory Affairs for Medtronic, speaking for AdvaMed. Mr. Morton is responsible for public health policy advocacy and internal regulatory policy within corporate regulatory affairs. He has over 20 years of experience in the medical device industry, including quality, clinical, and regulatory affairs.

Before joining Medtronic, Michael worked with CarboMedics, W.L. Gore and Associates, Alcon Labs and Sorin Group.

Michael has been recognized as a fellow of the Regulatory Affairs Professional Association. He is active in industry groups, including the Advanced Medical Technology Association or AdvaMed. He chairs the AdvaMed PMA Working Group and is a member of the 510(k) Working Group and the Heart Valve Task Force.

Michael is a member of the Pediatric Working Group and is active in efforts to increase access to devices for pediatric and other underserved patient populations. He

represented industry within Study Group 1 of the Global Harmonization Task Force. He served as the industry representative to the FDA Circulatory System Devices Advisory Panel from 2001 to 2005.

AdvaMed: Considerations for Pediatric Device Development

Mr. Morton: Thank you for that kind introduction and thank you, Tamar, for a great preceding presentation.

And is there something that I need to do with the slides here? Okay.

Very good. Again, thank you for that nice introduction. Here are some of the things that I would like to talk about today. This session is to kind of go over some of the opportunities that we have. I am going to speak briefly about the current state. Not very much because one of the things you enjoy when you speak late in the afternoon is that you have been preceded by some very knowledgeable people. So, many of these things have been touched on. But we will look at current state and then we will go over some of the proposals that are fairly commonly discussed about reducing barriers to bring devices to children and to rare populations and then also recognize some of the progress that we have made.

I will do a quick reminder for everyone that I am employed by a medical device company. So, we will let that stand as a disclaimer about my presentation today. And I would also like to make some acknowledgments. First of all, a person whom I am sure is going to be familiar to many of our FDA colleagues here in the room, Dr. Susan Alpert, a friend and a mentor to me. Dr. Alpert is my previous boss. She is a pediatrician and a person very

dedicated, very dedicated to children and to ensuring that unmet needs are met.

My colleague Tara Federici who drives the pediatric program within AdvaMed, Tara and I have enjoyed working together for several years in this space.

You know we often think about pediatric devices as being a modification of an adult device and certainly, that has been my experience but it is not always that way. I am going to take a minute to show this photograph and kind of give a little bit of a background. This was taken in 1958. And in 1958, all cardiac pacing was done with alternating current, which of course means it plugs into the wall. When there would be a power outage, then of course there could be an interruption and patients at risk. In 1958, this doctor, Walter Lillehei at the University of Minnesota, in the summer of 1958, a wave of thunderstorms went across the upper Midwest and did knock out power. And there is a sad element to this story. There was an eight-year-old girl who had external pacing, alternating current pacing. The power was interrupted and she died. Dr. Lillehei was very upset about this and in the next day or two, he turned to a skilled technician whom he knew, and that was Earl Bakken, and he said why on earth can't we have DC voltage pacing? Why are we tied to alternating current? And Earl Bakken went back to his garage and actually came back a few days later with external pacers driven by a car battery.

So, here we have a need driven by children. There was adult pacing also but it was a crisis with children that actually drove that.

I am very fond of this photograph which, as you can see, was on the cover of the

Saturday Evening Post. I am remembering Christy's comments earlier this morning about engineering and some of the factors of engineering when you are dealing with pediatric devices. As I have been told anecdotally, one of the first iterations of this device was to change the external controls on it. Because when you look at activity levels of children, one of the first things that they would do, once they were left alone, was adjust the device. So, after their doctor had tweaked it in for them, then they would change it. So, that was one of the first iterations.

The current state, again, we have spent a very productive day talking about this. We, indeed, have unmet needs. That is going to be quantified now and I think that is a great effort. We have talked about how typical it is that there is off-label use of adult devices. We have talked about the jerry-rigging of adult devices. And we have talked about the lack of data. Because if these devices aren't approved, we don't really have a way to know how they are performing.

Let me talk briefly about some of the clinical challenges. Again, very small populations are difficult to study. They are widely dispersed. It is difficult to have an adequately powered study. It is difficult to accrue sufficient numbers. It is difficult to complete a study in a reasonable time frame or to have a manageable number of sites.

So before you even begin to study pediatric devices, you have got some real obstacles in front of you.

If adult devices become the standard of care used off-label, then it may be very

difficult when you are anticipating a study, when you are trying to plan a study, just agreeing on what an appropriate control would be.

So, a lot of clinical challenges. We have talked about informed consent. We have talked about the emotional factor of parents signing their child into a study. We have talked about IRBs sometimes having an even higher standard for pediatric studies than they would for an adult study.

And actually, I participated in the cardiovascular breakout group at lunch. And one of the issues that had come up was that when you are trying to do a study when your test device is a less invasive device but your control is a surgical control, it is very difficult to get parents to randomize their children into a study like that. So, we have seen that historically. That is another reason that RCTs are very difficult to do.

And we have talked about the emotional element of pediatric devices. A personal note from me. When my wife and I moved into our home about nine or ten years ago and we were getting to know the neighbors, the neighbors across the street said well, my son has a heart valve. And I was really interested in that because I have dealt with heart valves. And as I was kind of asking the questions that were important to me, what kind of valve, which valve, and where is it located; and of course, I am thinking is this an approved valve, who made it, what is it made of, things like that and the parents right away kind of brought me back to reality. That none of that was important to them. What was important to them was that their child had a valve and that their child was alive. And it was a great grounding experience for me, certainly a good reminder and one that we -- there is no need to say that to this room but I

think it is a good message.

That particular story has a very good result. As I have lived in the neighborhood with this family, as would anticipate because we know this because technically we are involved in these sorts of things, the child, the patient continued to grow, outgrew the valve, was indicated for another valve and then the parents had to go through the decision of would this be a minimally invasive procedure or would it be surgical. Well, the result is that there was a surgical replacement and this patient is now a late adult -- late adolescent, excuse me, late adolescent and a freshman in college. So really the sort of messages, stories that we want to hear.

Well, let's talk about some of the proposals for increasing access for pediatric devices and I am going to focus on the current framework. I am not necessarily going to talk about legislative changes. I know that certainly there are changes that could be made but I am going to focus really on what is possible now. Here is a list of these and we have got a slide on each one.

Let's start with flexible regulatory models. So, FDA is authorized to use valid scientific evidence other than well-controlled trials. And Dr. Laschinger had a great slide on this regarding the regulation CFR 860 when we talk about the hierarchy of evidence. And actually, we will talk about that in the next slide.

But basically there is, of course, the gold standard, which is the randomized controlled trial but FDA is authorized to consider other types of evidence. And this should be

considered when we have to think about small populations and how we are going to show either probable benefit for an HDE or safety and efficacy with a PMA.

So accessing and using all these sorts of valid scientific evidence can really, I think, help in the development of an approval plan and approval strategy.

And here is a list of some of those other types of valid scientific evidence: literature with an HDE, perhaps off-label experience, registries, retrospective case studies. So by looking at things like this, I think that we can build the evidence that we need to go ahead and get a device approved. Certainly, the use of non-clinical data to support device variants or changes. And we also, during our lunch breakout session, talked about that regarding this recent White Paper for again, pediatric heart valves, that in order to do now a PMA supplement, rather than a PMA, what this new pathway promotes is very heavy on the pre-clinical work, a reasonable clinical trial, and then a PMA supplement. So, I think we have already got a good example of this.

Laura talked about extrapolation. I think that is extremely important, a very important element of this. And then the pre-market/post-market balance.

HDE/HUD program clarifications, certainly there has been a lot of work done. Eric let me recognize that. There has been a lot of improvements in the HDE program just in the past couple of years. I can say from a sponsor's perspective, HDEs are still kind of a difficult sell internally because they are a little bit unknown. We still don't know exactly what it is going to require. We still don't know exactly what probable benefit means. And so when you are



sitting around the table and you say here is a regulatory strategy, that is not popular right off the bat.

Probably, if we were going to ask for one thing it would be even more clarity about what probable benefit does mean.

Dr. Laschinger talked a lot about how important it is to communicate with your FDA team when you are about to embark on an effort to get especially a pediatric device approved. So, some of the proposals that we would have and we are seeing this is that FDA access real experts in these fields, that they access experts both within the FDA and certainly, within the past few years, we have seen pediatric experts brought into the review divisions. I think that is a great step. And there is also access to experts outside the FDA through, for instance, special government employees or arrangements like that.

And certainly to bring that sort of knowledge in so that the FDA has the benefit of that perspective, I think can only help all of us.

Here is an interesting suggestion. From my perspective, the ombudsman program within the FDA has been a pretty positive thing. I think within the Agency and itself and certainly outside the Agency, the ombudsman serves a really good purpose. And if we could have an ombudsman actually dedicated to orphan, rare diseases, and pediatrics, I think that might be a voice within the Agency that would really help these patients.

Again, this third bullet, just reflecting that one of the most important things for sponsors is predictability and transparency.

The next bullet, one of the things that we had talked about during our breakout session was when meeting with the FDA, to be able to sit down and talk about a strategy in which you would say the sponsor is going to identify a population and determine what it is going to take to establish probable benefit and move toward an HDE but, at some point, the goal would be to go to a PMA, either to get rid of that HDE burden so that you could make claims, so that you get rid of the IRB requirement or perhaps and/or to expand populations and to provide a device to a broader population.

But to be able to have that discussion early on could be important and I think what in this room is happening to promote what is now called priority reviews of these devices.

So some of the things that I think are within the current framework that could be done, I am going to make a comment about custom devices. When Dr. Geiger made that presentation today and we saw the examples of the instruments that clearly were the wrong size for pediatrics, I immediately thought, well, what a candidate for custom devices. Yet, the rules regarding custom devices are really pretty unclear. Quite frankly, there is not, at this time, even a guidance on custom devices, even though I understand that that guidance is on a priority for the FDA for next year and it is really important.

But if within the custom device guidance, if there could be special consideration for very small orphan populations or pediatric populations, I think that could only help.

And I will go back to some of the photographs that we saw today, even though Dr. Geiger did not indicate that those were being jerry-rigged, it would probably cut down on

jerry-rigging and would actually put the modifications into the hands of sponsors who are actually set up to do modifications and then to test.

And finally I want to recognize some of the progress that we have made.

Certainly, I know that we are here because we think that there is further work that needs to be done but I think there has been a lot that has been done in the past few years.

On the HDEs now the profit cap are lifted for both peds and for adults. And that is important because it makes a less variable, less unappealing strategy to make devices available. And further, this issue that we have often had with both payers and with IRBs is an HDE an approved device, that has been clarified in the Q and A and I think that is extremely important.

I had referred to this earlier, it is the second bullet. There is a recent publication and the title you can read it there, a new paradigm of obtaining marketing approval for pediatric-sized prosthetic heart valves. There was a question early this morning why is there not work done between companies. Why do manufacturers not get together? Well, as a matter of fact, this is an example through AdvaMed of various valve manufacturers getting together and looking at what it might take to make small-sized valves available. And it was an effort led by AdvaMed and by the FDA, so it included industry. It included the regulatory agency. It included academia and it included the medical community. And Dr. del Nido was very influential in getting this published. So, thanks very much for that.

A couple of other notes that are not on here, benefit-risk. I think the work that

the FDA is doing right now in benefit-risk is going to be extremely important in this area and then again, what Laura had presented on extrapolation is something that is needed now -- is needed. Activities like this workshop, I think deserve an awful lot of credit.

So again, more work to do but let's recognize what has been done.

So, here I have talked about unmet needs, which I think we are all here because we recognize that. We have acknowledged that some of these problems are actually emotional, as well as just regulatory or technical or whatever.

I have talked about existing tools that I think we have within our authority now to use to make these devices available. And we have recognized some of the things that have gone on.

So with that, I will say thank you very much.

Ms. Ryan: Our next presenter is Diane Dorman. Ms. Dorman is the Vice President for Public Policy for the National Organization for Rare Disorders, NORD, and leads NORD efforts in its relationship with the federal government and Congress.

She is the primary D.C. representative for more than 25 million Americans who have one of the 6,000 to 7,000 known rare diseases. Her overriding mission is to improve the plight of patients with rare diseases and increase incentives for the development of orphan drugs, devices, and diagnostics.

Ms. Dorman develops and maintains relationships with other healthcare

voluntary agencies and patient groups. She provides technical assistance and legislative analysis to NORD's member agencies on government-related matters, as well as the training of staff and volunteers of member organizations.

Her leadership efforts have led to the introduction and passage of the Rare Diseases Act and the Rare Diseases Orphan Product Development Act. She was also influential in the introduction of House Current Resolution 147, commemorating the 20th anniversary of the Orphan Drug Act.

#### NORD Perspective

Ms. Dorman: Thank you very much. First of all, I have to thank CDRH and OPD, Gayatri and everybody for an amazing meeting. I mean, this is the most action-oriented, forward-thinking meeting that I have been in the past 14 years since I have been with NORD. So, I want to congratulate the FDA for that.

And I also want to thank the moms and dads who have been here. I think everyone in this room needs to hear what you have to say. And I get choked up when I talk about you guys. Everyone needs to hear the challenges you face every day but I would also want to talk to you about the importance of understanding the regulatory process and the legislative process. And you being here today, I think, is going to go a long way. You have to teach yourself. There are real challenges. So you being here today talking with everybody in this room I think is really critically important. So, I want to thank you for being here as well.

So, NORD has been around since 1983, since the passage of the Orphan Drug

Act. Our goal, our mission has been and continues to be the encouraging of development of orphan products, humanitarian devices. We want to make sure that these incentives contained in that Orphan Drug Act remain strong because we know if those incentives are not in place, we wouldn't be here today and the industry would not be incentivized to develop those drugs. So, it is very, very important for us to protect those incentives that are now in place and to look at ways that we can encourage development of other products as well, and to increase research as well.

So, we really enjoy working with all our stakeholders to protect those incentives. Everyone is aware of all those incentives, so I am not going to go through that.

So this is what we do. We advocate. That's what I do. We do a lot of education and outreach not only to everyone here in this room but also to members of Congress, which is something that I do on a regular basis. We provide connections because talking with one another, I think, is really, really critically important. We have to understand what the challenges are before we can identify the opportunities to address some of those challenges and we need to promote access and we also provide assistance. We have -- I'm not even really sure how many patient assistance programs we have because we recognize that for somebody the orphan products -- when I say orphan products, I also include medical foods and devices. Medical foods are very important for some very rare conditions.

So, we do provide assistance. We help them pay coinsurance or copay or we make sure that they get the free products. So, we do work with humanitarian-minded companies to ensure that patients do get those products, no matter what those circumstances.

And that is one of NORD's primary missions.

There are over 7,000 rare diseases. We have heard all of this before. About 80 percent affect children.

There was an op-ed piece in *Nature* back in 2010. And it said of the 350 most common diseases, 27 percent died before their first birthday. So, that is something that I think about every day.

So there are challenges and that is why we are all here today. We need to identify needs in the pediatric populations. We need to talk about clearance, approval, and reimbursement that is a very, very huge issue. Required IRB review of humanitarian use devices is something we need to think about and I will go into a little bit more detail.

And the coordination between all the Centers and I will talk about that just a little tiny bit, learning everything that Gayatri and everyone is doing right now is so exciting. And I think NORD is really looking forward to working with the Agency on some of these initiatives that you are working on, especially addressing unmet needs. Because as Tamar said, we started talking about this in 2004. We brought everybody together. What are the unmet medical needs? Nobody could reach consensus.

So hopefully, working with everybody in this room, we can identify what those needs are and move forward. So, I am really excited about that initiative as well.

So challenge number one is the needs assessment. And I think Gayatri has gone through a huge amount of detail, so I am not going to go into detail about what are some of the

wonderful things that they are doing. But we were talking about VEPTR, the device that was developed by Dr. Bob Campbell. He was at Corpus Christi Children's at the time. He is a surgeon.

This little boy out of Florida with severe scoliosis was one of the first children that Dr. Campbell worked on. So you can see he identified a need and he fixed the problem. Well not exactly completely fixed the problem but you can see the impact that devices have on children. He's out there playing baseball. I think he is almost in his teens now, I think.

And the second challenge probably for us that we see on a daily basis at NORD is the approval versus reimbursement issues. And what insurers are looking at right now, and I will touch on the IRB issue as well, is that the insurers are saying well, if it has to be reviewed by an IRB, it is experimental. So, we are not going to pay for it. And if they are not going to pay for it, patients are not going to get access and the industry is not going to develop these products. So, this is a really critically important issue that we have been working on.

And labeling may be confusing or unhelpful to payers. I was part of the Entrepreneurs-in-Residence Program at CDRH until this past January. And I was on Team 2 looking at reimbursement issues. And I was really kind of discouraged that some of the folks there at CDRH didn't even know about some of the amazing things that OOPD is doing. They didn't know about the access issues that they are working on. They weren't aware of the research grant program. They weren't aware of the pediatric device consortium. So, I think Gayatri's outreach and the Rare Disease Council working with all the Centers across all of FDA is really critically important. And I have to applaud that office for doing a lot of that outreach.



And there is some lack of transparency. I don't think the IRBs actually really understand what a humanitarian device actually is.

So, challenge number two, I have already talked about that to a very large degree, is the reimbursement issue. And on my team, we are trying to address some of those problems. I was talking with someone earlier today to follow through on some of the things that were worked on, clinical trial design and also reimbursement issues. And CDRH is in the process of implementing a lot of the recommendations that we came up with. So, everyone is moving forward very quickly, which I am very pleased about.

You know, there are small -- most of these companies are really small. Most of them are not the big Medtronic and the Boston Scientific. Most are very, very small companies that may have just one particular device that they are working on. So, they have limited experience about the resources and how to navigate the reimbursement process, as well as the regulatory process. And it is somewhat fragmented for a lot of these small companies. So, I think maybe an ombudsman concept, I think, for pediatrics I think is really a great idea to work with a lot of these small companies to help them move forward in the process.

So, I agree with that idea, and to engage innovators very early in the process. You know, I always hear from people, engage us and engage us often. And it also includes the patients and their families as well. Be involved in what some of the companies are doing. I have found that so many of the patient organizations, the ones that I work with are really very small. And you know they are the ones who get out there and had the bake sales and the bowl-

a-thons, trying to amass maybe just a little bit of money if they had interest, some obscure researcher in some university somewhere to maybe do some of the research on their particular rare disease.

And they have a real stake in research, in basic research and translational research and most of them that I know are really anxious to develop these relationships with industry very early and very often. And I also implore my colleagues in the industry to also think about engaging the patient organizations very early and very often, even long before you have a product that may be coming to market. Because you need to develop that sense of trust with patient organizations because they can be your best friend or they could be your worst enemy. And I can assure you that most of the people in this room would want them to be their best friend, as opposed to their worst enemy.

So they are very anxious to work with you and to advocate for what you want to do.

So, there is some awareness of the differences in potential overlap and evidentiary requirements. But that is somewhat fragmented and I think needs to be really worked on. The FDA approval clearance does not support reimbursement and I have talked about that because there is this real disconnect between what an IRB does and, as has been mentioned, a lot of the IRBs don't even know what a humanitarian device is and why they should be reviewing these devices at all. So, I would agree with Tamar that that is something that really probably needs to be looked at, is an IRB actually necessary to approve the products.

And the coding, when I was with the Entrepreneurs-in-Residence folks for maybe nine months or so, there was real confusion about how to code some of these devices. CMS has no idea how to code them because they are so unique in so many different ways. So how do you code? Because if they are not coded properly, they are not going to be reimbursed. So, that is something that we hope to be working with CMS, with Centers for Medicare and Medicaid Services.

If we talk in acronyms, folks, looking at your guys, please raise your hands. It is a disease in D.C., we have a tendency to talk in acronyms. And my boss, Abbey Meyers used to always tell me, for God's sakes, Diane, they have no idea what you are talking about. So, if I do talk in acronyms, please let me know.

The coverage process is distinct and separate from coding, payment and bundling process but it is key to ensure the patients do get access to the products.

And of course I have already talked about the IRB review process. Manufacturers must submit reports to IRB's record whenever a HUD may have caused or contributed to death or serious injury. Payers view HUDs as experimental, as I have mentioned and access and reimbursement is very often delayed or denied, simply because they do not understand what a humanitarian device is and now it is used.

So, stakeholder coordination, I have learned a lot today from Gayatri about the coordination between all the Centers.

There is the Orphan Product Research Grants Program, which is critically

important, which has been key to the approval of over 40 orphan products and the next will be very, very important. However, the funding for that program has decreased because of budget constraints from \$14.2 million to \$2.9 million. Is that right Gayatri? About -- all the way down to 12?

Dr. Rao: No, \$12.9.

Ms. Dorman: \$12.9 million. Okay, so that is another issue that we have to talk about. There are challenges Tamar talked about. They are all legislative challenges that we all have to talk about but we also have to think that the reauthorization PDUFA and MDUFA are coming up in 2017.

Thoughts and ideas about what to do moving forward, if those conversations have already started, I have already started thinking about it. So, this is everyone's opportunities to start doing the education, reaching out to Energy and Commerce Committee, reaching out to Senate Health Committee, and just saying, these are the problems. I am just here to tell you about the problems. I don't have the solutions yet, but let's partner to figure out what they are. We have time to do that. We have time to do that now.

So, you know it really takes finding a balance. We want to make sure that companies continue to innovate. We want to make sure that the markets continue to be sustained and grow and there is increased research because we want to make sure patients have access to those products. That is why we do what we do, to make sure the patients have products and also that they are products that they can actually afford.

There is one thing I wanted to bring up. We were talking and I have all these scribbled notes because the conversation has been so great over the past day. We were talking about where those numbers come from like the 200,000 and the 4,000 number.

Back in 1983, when they passed the Orphan Drug Act, there was not a real definition of what a rare disease was. So Abbey Meyers, who was the founder of NORD, as well as Woody Guthrie's wife were called to the principal's office, which was Henry Waxman. And they were told okay, you need to come up with a definition of what a rare disease is.

So, Mrs. Guthrie and Abbey went trotting into the bathroom, which is very conveniently located directly outside of Mr. Waxman's office, and said how are we going to define what a rare disease is. And they came up with 200,000 because there were 200,000 people at that time identified with MS. Now of course, we now know that number is much larger because they are being diagnosed properly and treated properly. But back in the day, it was MS 200,000.

They went trotting back into Mr. Waxman's office and that is how the 200,000 number came about. I have to assume that is how they also came up with that number 4,000. I am not really too sure about that. So there has at least been some curiosity about where that 200,000 number comes from.

But these are something that we have looked at. Do we have to look at IRBs? Do we look at that 4,000 number? Do we change 200,000 to a ratio similar to what Europe does? They use a ratio system. NIH, I think, has said in the past that one in ten people in the

U.S. are affected by one of those 7,000 known rare diseases. Do we use a similar ratio of one in ten? That is something we need to look at.

So, I think there are a myriad number of opportunities that we can look at as a community, as everyone in this room. So I am really excited about this opportunity. And again, I want to thank the FDA for putting this great program together. Thank you.

Ms. Ryan: Dr. Hirschfeld will step up to the podium now.

NICHD Perspective

Capt Hirschfeld: So, Linda Ulrich said, you are going to be the last speaker on the last day of a three-day conference during a cold snap and it is going to be dark outside. So, go for it.

And let's see what the trick might be here. Master slide set. So I just keep going advancing. Is that the idea? Keep going from the current slide, go to the next slide? All righty. Holy moly, there it is.

Okay, I am from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. And I can actually say that plus my title on one breath. It takes a little bit of practice.

And what I wanted to leave you with is just a couple of concepts. I don't have answers. We have been hearing challenges. We have been hearing identification of different approaches and different perceived barriers and opportunities most of the day but I will leave

you with a few thoughts to work on.

First is that there is, in every government funding agency, but particularly for the NIH, there are funds that set aside for small businesses to do innovation research and technology transfer. And the thought here is to establish public-private partnerships to do the funding. People always say they need more money and they tend to look at a single source and it is having the glue and the ideas to put all the potential sources together because people love to leverage their money. And there are also multiple grant programs available, where people again, I think, have the opportunity to leverage funding.

The next idea is to think of a device as part of an ecosystem. It is not just patient device but there is a person, not just a patient, it is a whole person. And the person has lots of components to their life, internal and external. The device is going to fit somewhere into that person's ecosystem. And part of the healthcare delivery, healthcare sustainability of that person will be how does that particular device, or intervention, or diagnostic fit in with all the other components? And those devices and diagnostics and components that fit in better with the ecosystem are more likely, and this is just speculation -- we don't have any data because we haven't taken this approach. But they are more likely to be adapted and sustainable in there.

And even with a device, one has to think of all the hands that might touch that device. It is not just in let's say for a surgical implant, the surgeon but it would be who else is taking care of that patient; nurses, physiatrists, mental health professionals, social workers, pediatricians, and so forth. All of them will want to know well what does this device do. How does it fit into the skill set I can offer and so forth?

So providing that context and that information will gain - I would argue not only acceptability for the device but perhaps very rapid improvement because people have an idea of where this device might fit in.

And we discussed needs determination in many ways throughout the course of the day. We do our own set of needs determinations at the NIH in conjunction with the FDA for medicinals. We haven't expanded it to drugs but we would like to. We are having conversations. We started some this afternoon on how we can go from there.

Depending on where you ask someone in the system what are your needs, I had a professor in medical school who was an expert in tuberculosis and said if you left it up to the people who are taking care of the patients, they will say their need would be a smaller, portable iron lung. That would be the need in order to treat tuberculosis. And it took a paradigm shift to go to thinking about antibiotic treatment and other kinds of approaches.

So, depending on whom you ask, you might get different needs identifications. And we need to all work on integrating those various perspectives.

Market size. We could take everybody in this room and put them in the first five rows. I counted the number of people in the room at the beginning of the hour before the talk started and there hasn't much attrition. And then I counted the seats here and it will all fit. But it doesn't work out that way. You don't have all the people who are segregated in one place, unlike the days when tuberculosis was a condition that people put everyone in a sanatorium for. So, people are scattered.



But in this day of easy communication and linkages and so forth, we have to think globally because the market size in the U.S. might be small but in other parts of the world, there might be the opportunities that raise the market size for any effective intervention. And we would have to think not only of where in the planet could an intervention apply and I am part of a group that is trying to coordinate the regulatory approvals for children's products with the World Health Organization, as is Diane Murphy from the FDA and others, but we can find these common denominators. We can identify the partnerships and distribution lines.

We can also think developmentally. If a device is to be used at one age or in one population, can it be used at other ages? Could it just lead to a family of devices or related devices or devices in other types of interventions?

And then in terms of the ecosystem approach, can the device adapt to different roles within that ecosystem?

So, we at the NIH have been partnering with other federal agencies, including Darrell Green from AHRQ who spoke earlier about the different databases that they have and other agencies, HRSA, FDA and so forth. And we have been, ourselves, organizing meeting every other year on pediatric devices. In our last meeting, we discussed the idea of a device map project and that project is underway and we hope to launch that initiative in the coming months.

So, those are the comments and I wanted to thank everyone for sticking it out to now and with the permission of our moderator, I think it is open for discussion. Right?

## Participant Comments

Ms. Ryan: Yes, I just wanted to review very quickly, because I know we have very little time for discussion, the questions from the *Federal Register* for this session. It was to look at the incentives that could help advance the development of diagnostic and therapeutic devices, how to use -- how probable use in pediatric practice could be considered early in the stages of device development. What are the potential private resources that could be tapped to advance the development of medical devices? And I think we did touch on that quite a bit. And what are the potential improvements or changes that could be made to FDA guidance and regulations or current science? And that was definitely discussed.

I am going to leave this open for questions.

Ms. Dorman: If you don't have any questions, I hope you have lots of solutions.

Mr. Bernstein: Hi, I'm Doug Bernstein. I'm from Peca Labs. We are a pediatric device startup. So, private investment is very important to us. I don't think we have talked a lot about how we can incentivize private investment. So I just wanted to sort of comment on a couple of models that I think have been successful in spurring private investment in other fields that are somewhat prohibitive otherwise and could hopefully be applied to pediatrics and rare diseases as well.

The first is the XPRIZE model, which sets aside a prize for something that is successful in reaching the goal. So grants for trials and development are very helpful but if the private investors knew that if their company was successful in bringing this device to market,

there would be somewhat of a return automatically, regardless of the small market size. I think that could be very helpful.

And the other one is the economic development seed funding agencies, which rather than giving out grants evaluate not only the possibility of the product being successful but also the probability of bringing on follow-on funding, and based on that, make an investment which can help to be a sustainable model to keep generating more funding for other diseases. So, I think that could be very helpful.

Ms. Dorman: People might also want to think about looking into other patient organizations who do sometimes have money. Just look at cystic fibrosis and MS and other organizations who have pulled together funding and are very anxious to help in any way they possibly can, not only do the basic and translational research but also product development. So, that is another resource of possible funding. I am not saying it could be a huge amount of money but it may be an opportunity for a researcher to move the needle forward just a little bit further.

Participant: I just wanted to thank you for bringing up the issues regarding reimbursement because that was actually one of my questions.

You know I am working on developing a pediatric medical device and it is, obviously, very challenging. But one of the issues is even if you go through an HUD or an HDE approval process, the device is considered an experimental device and getting reimbursement can be really challenging. And it is very different than, obviously, when you get FDA approval

and kind of Medicare reimbursement tends to follow, fairly consistently lockstep in association with that.

So, I am wondering if there are any efforts with the FDA to incorporate CMS, Medicaid, for instance, since Medicaid, obviously, covers a lot of the pediatric patients in that reimbursement process, because at least if you get Medicaid to agree that this is not quote/unquote "experimental" or at least it can be reimbursed, then you might get more private insurance follow-on and so on and so forth.

Ms. Dorman: When I was involved in the Entrepreneurs-in-Residence Program, we did bring on people from CMS. I don't know if everyone is aware of parallel review, where the FDA and CMS are reviewing the information, although it is different because the FDA is looking at actual data and CMS, historically, is looking at peer review journals and those types of things. So, they are looking at different things but the review is done at the same time, which improves access because if a company goes through the FDA approval to get clearance and then they have to go to CMS and other insurers, that is an additional delay. But if they are doing it at the same time in tandem, that can get products to the patients and the surgeons that much quicker.

Ms. Haro: And you know I am not in a position to talk about what FDA may be doing working with their colleagues at CMS but I can say that at the Academy we have internally a Private Payer Advisory Council and we have pediatric councils in a lot of states, not all states. And their role is really to work with private carriers and again, this is private, on the private side, to work with payers to help them understand medical technologies but a lot of this

is a case-by-case basis.

As I said in my remarks and others have reiterated here, I think there is a real opportunity for additional work. And I think government to government would be extremely helpful in a more robust fashion to help other payers to sort of understand what these technologies are and what they mean for pediatric patients.

Dr. Rao: I could just try to offer some additional thoughts from the FDA perspective. Obviously, you know FDA doesn't directly get involved in terms of reimbursement issues but we do recognize, particularly in the HUD/HDE world, it is an issue.

So to that end, certainly we talked about the HDE guidance and it is currently under review and revision. And one of the things we are trying to do in that guidance, which is sort of a small step forward, is to try to make clear that this is an approval. In spite of sort of the additional burdens placed on HDE-approved devices, once small step is to sort of make very clear that it does actually constitute an approval.

Some of the other issues that were addressed very nicely in these talks is there is, because of some of these burdens, there is some confusion. So for example, requiring IRB review and approval of an HDE-approved device does create some confusion about whether or not it is experimental, for example, even though it isn't. It is an approved device. So, one thing that we are doing is to try to clear up some of that confusion.

Certainly one of the things that we have heard in these conversations is that the idea, the part of the issue is not just the communication and coordination but that the HDE

standard is a probable benefit standard, as opposed to a reasonable assurance of safety and effectiveness and that sort of factors in to whether or not something gets reimbursed, that whole idea of probable benefit.

Having said that, anecdotally, in having spoken to some of the investigators who have gone on to develop devices, you know they do say that initially these are huge challenges in trying to get reimbursement but through greater education and sort of working with regional offices for local coverage determinations and the like, over time with education they have managed to see some success there with reimbursement.

Ms. Dorman: I did want to add something. I'm sorry. I just wanted to add something about the rationale as to why IRB review was included in the legislation. It was felt by some legislators and some advocates that this pathway would be used by industry as an end runner on a PMA. So, aha, we are going to fix you. You have to be reviewed by an IRB. In other words, thinking that would force the companies to go the PMA route and do full blown clinical trials.

And I think the FDA did a really great job of recognizing that there is no way on God's green earth that the industry would be able to amass the clinical data necessary for a full PMA. And that is why they now say okay, you have proved probable benefit, therefore, it is a full approval. But the mindset during negotiations of the humanitarian device legislation was to ensure that the companies did not use this as an end runner on a full PMA.

Ms. Asiello: Hi, Chris Asiello from NHLBI.

First, I would like to thank all of the panelists. I think each of you came up with some very unique concepts of how to innovate and incentivize medical device development. And I was very glad that I stayed to hear Steve's final talk of the day, as well as the discussion that has gone on today.

One thing that I have heard but only in pieces is this concept that it is easier to develop devices in Europe, a CE and a Humanitarian Use Device are sort of similar. Would it totally blow every regulator's mind to consider acceptance of orphan disease products, no matter where they approved?

So, if they are approved in the EU or approved in Australia, approved in Japan, for the U.S. to say, we will accept that and we will allow it to be marketed here in the U.S. and work those relationships with your fellow regulators so that devices that are approved here can also be marketed elsewhere.

I just want to throw it out there as one of those wild crazy ideas that come up occasionally. But I thought I would put it into the atmosphere.

Capt Hirschfeld: I'm certainly not going to speak on behalf of anyone other than me. But that has been a conversation that has been going on to my knowledge, at least for a decade.

And very briefly, there was a history, and they exist in an organization called the International Conference on Harmonization of Medicinal Products for Human Use but they also include devices. And that was part of the goal of that particular organization.

There have ended up being a lot of technical issues that have nothing to do with regulators or scientists. They occur at higher levels. And we could talk about this. But every time you think you have got something solved, there is some other court, or legislative body, or something that appears with another barrier, so to speak.

So, there are people plugging away at the concept. It is not something that seems to be as readily endorsed by people in positions of power and influence across the globe, as it would be by people who are much closer to therapeutics.

Mr. Morton: That's a great summary. What I would follow with that is on the device side we had what was called the Global Harmonization Task Force. That has now evolved into what is called the International Medical Device Regulators Forum, IMDRF. Again, the goal being for jurisdictions such as Europe, Japan, Australia, Canada, which are well-regulated and have a history of regulation, to look at the way they regulate and come up with best proposals.

Now, what happens next? With GHTF, there are guidances which are out on the website and everyone can access them. And they are really good documents to look at and say okay, in a regulatory model, what is a good way to approach one thing or another. So, those are available.

With IMDRF, one of the reasons that GHTF actually was dissolved and IMDRF was formed was there was a recognition that GHTF had moved about as far as they could move and the changes that would need to be made next were going to be legislative changes. And so



that is a pretty steep barrier.

Chairmanship rotates and I believe already now it has rotated to the United States. So, Dr. Shuren is going to be the chair for the next year. So, all of the IMDRF meetings are going to be held in the United States. So, those are going to be very accessible to us and I would encourage everyone who is interested to have a voice.

Ms. Dorman: Steve just walked back into the room. Thank you.

I can't remember the date when we had our first ICORD meeting in Stockholm in February. Why in February in Stockholm, I don't know. I have never been able to figure that out. But during some of the public meetings, there was a conversation between the Europeans in the room, as well as people in the U.S., regulators in the U.S., just talking about the designation process.

And the question was asked by industry and folks in Europe and in the U.S., why can't there be a same form? We recognize that some of the regulatory challenges and issues are very, very different but why can't there be just one form that we can all use?

And Marlene Haffner, who was long-running Director of OOPD, said well, that sounds like a really good idea. And she got together with her colleagues in Europe to develop that similar form, although the regulatory schemes, again, are different, it was a small incremental step. I'm not saying that it is going to move any faster because that was back in 2007. Steve? That long ago? Oh, my God.

So there are those conversations between regulators on both side of the pond. I

am not going to be part of that conversation but I know those conversations are ongoing over time.

Participant: I apologize to hold everybody hostage here when everybody wants to go home but I just had one additional question. And that is not so much in terms of an incentive but rather in removing a disincentive, which is kind of the elephant in the room with pediatric device development, which is liability.

It is a big issue. If you are a medical device startup, you can't afford a bad outcome, let alone in a pediatric patient. And I am curious if there is any efforts involved to try to mitigate some of those risks and some of those issues as well.

Ms. Dorman: You should be talking to the moms and dads in the front of this room.

Participant: I do.

Dr. Francis: I think the short answer is no.

Ms. Haro: The only thing I can add is the one slide I had about political feasibility. In terms of if you are thinking about something that is going to require a statutory change, just giving them -- I am just being honest, this is a pretty controversial issue, talking about liability protection or something that would incentivize or tort reform efforts to move -- tort reform have not been moving at much more than a snail's pace for a decade.

So from that perspective to the extent that it would require a statutory change, I

think that is a pretty high hurdle.

Ms. Ryan: All right, I think that ends our panel and we are going to go to our wrap-up. Thank you.

(Applause.)

#### Wrap-Up/Closing Remarks

Capt Ulrich: Okay, so we would just like to say a first words in wrapping up. It has been a whirlwind day. It has been a whirlwind past three days and I know that people are anxious to get back to doing the good work.

I just wanted to say a few words here. First, I would like to thank everyone for coming out and participating in the meeting today and sticking through to the end here.

I think this is kind of exciting. It is the first time that there has been a meeting specifically for pediatric devices for rare diseases that I know of. And I think we have had a really good turnout and are looking forward to the comments that we received during the conversation today that will be going into a report that hopefully will be coming forward outlining potential steps forward in this area.

I would like to also thank a number of people who have participated in the planning of today's session. We had a team that Jackie and I led that involved folks from CDRH, OOPD, CBER, Office of Pediatric Therapeutics, and it has been a really good, positive experience working together over the course of many months to put this together today.

Also particularly, I would like to thank Carol Krueger who has been wonderful in providing project management support and really keeping us all on task, organizationally, as well as Susan Monahan.

And I also thank Gayatri Rao, my Office Director. Whenever there was a barrier, large or small, she always step forward and came forth with a solution that kind of helped us go forward in making today's meeting, as well as the past two, a success.

So on those notes, I think we can pretty much wrap it up for today.

Thank you.

(Applause.)

(Whereupon, at 5:01 p.m., the foregoing meeting was concluded.)